UAKON 2003

KOLLAM

Souvenir

UROLOGICAL ASSOCIATION OF KERALA

Uakon 2003

Kollam

XVII Annual Conference of
The Urological Association of Kerala

October 11 & 12, 2003

Hosted by
Kollam Urology Club

Souvenir

Contents

Dr. R.P. MADHAVAN M.Ch.
Organising Secretary, UAKON 2003
Consultant Urologist,
Sankar Institute of Medical Sciences,
Kollam

3 October 2003

Editorial

We, the members of the Organising Committee, extend a warm and hearty welcome to UAKON, 2003.

The Urological Association of Kerala is one of the oldest urological associations in India and we have a rich tradition. The meetings of the UAK are usually well organised; the ambience is good and the scientific programme is top-notch. Living up to this lofty standards is no easy task. We have spared no effort in organising this conference in a manner befitting the stature of our association.

Kollam is renowned for its hospitality and we take this reputation very seriously. We are confident that we shall not be found wanting on this score.

Keeping in line with past tradition, this souvenir is being published to mark this special occasion. We have included scientfic articles by some of the finest minds in our speciality. We earnestly hope this would enhance the shelf-life of this publication.

Finally, we wish to express our sincere thanks to all the people who toiled hard to organise UAKON 2003.

UROLOGICAL ASSOCIATION OF KERALA

This Souvenir
is dedicated to
the memory of
our colleague

Dr. Gopakumaran Pillai

who expired on April 5, 2002

Organising Committee UAKON 2003

From right to left Dr. S. Rajendran (Conference Chairman), Dr. R.P. Madhavan (Organising Secretary), Dr. N. Baby Mathew (Treasurer), Dr. A.K. Rajasekharan (Vice Chairman)

PROGRAMME FOR UAKON 2003, KOLLAM

Day1

8.30 am : Registration

9.00-9.30 am : Guest Lecture 1

Chairpersons : Dr. Felix Cardoza, Kozhikode &
Dr. Chandrasenan Nair, Thiruvananthapuram

Newer strategies in the management of sepsis and renal failure in post operative patient
Dr. RAMADAS PISHARODY, KOZHIKODE

9.30 to 10-30 : INAUGURATION

10.30 to 10.45 am : COFFEE BREAK

10.45 to 11.15 am : UAK Annual Oration

Chairpersons : Dr. Vikraman KR, Thiruvananthapuram &
Dr. Krishna Moorthy H, Kochi

MY EXPERIENCE WITH TURP
Dr. Moni VN, Kozhikode

11.15-12.15 pm : Point-Counter Point Session

Chairpersons : Dr. Appu Thomas, Kottayam &
Dr. Suresh Bhat, Kozhikode

DEROOFING IN ADPCKD REVISITED-
ADVISABLE OR NOT?
PGs of Medical College, Thiruvananthapuram Vs
PGs of Medical College, Kottayam

TYPE II SUI
SLING OR RETROPUBIC SURGERY?

PGs of Kasturba Medical College, Manipal Vs
PGs of Medical College, Kozhikode

12.15-1.00 pm : SHORT PAPER 1

Chairpersons : Dr. Biju Mathews, Mavelikkara &
Dr. Venuchandran, Thrissur

MANAGEMENT OF VESICO-
ENTERIC FISTULA-OUR EXPERIENCE
Dr. George P. Abraham,
Dr. Sanel Varghese, Dr. Thamban OS,
Dr. Ramesh H, Dr. Ramesh GN
P.V.S.M. & Lakeshore Hospitals, Kochi

NEWER TRENDS AND DIAGNOSTIC DILEMMAS IN RENAL CELL CARCINOMA-OUR EXPERIENCE

Dr. Vinod KV, Dr. Benny Paul M, Dr. Sivaramakrishnan P, Dr. Venugopal, Dr. Syam K Ramesh, Dr. Albert AS

Department of Urology, Medical College Hospital, Thiruvananthapuram

CONTINENT URINARY DIVERSION AFTER RADICAL CYSTECTOMY

Dr. Krishna Moorthy H, Dr. Pushpangathan VS
Division of Urology, Lourdes Hospital, Kochi

DRINKING WATER AND OXALATE LEVEL

Dr. Jayan Stephen, Dr. Anil Chandran, Dr. YM. Fazil Marickar
Stone Clinic and Urolithiasis Research Wing, Medical College Hospital, Thiruvananthapuram

1.00-2.00 pm : LUNCH

2.00-3.00 pm : CPC

Chairpersons : Dr. Albert AS, Thiruvananthapuram &
Dr. Syam K Ramesh, Thiruvananthapuram

Presentators : Dr. Harigovindan P, Kozhikode
Dr. Joseph Philipraj, Manipal

3.00-3.30 pm : URO QUIZ

Quiz Master: Dr. Vasudevan S, Thrissur

3.30-3.45 pm : TEA BREAK

3.45-4.00 pm : REVIEW PAPER PRESENTATION

Chairpersons : Dr. Mohan P. Sam, Alappuzha &
Dr. Nazer M, Alappuzha

ROLE OF PSA IN THE MANAGMENT OF CARCINOMA PROSTATE
Dr. Vinod, Thiruvananthapuram

4.00-4.30 pm : POSTER PAPER SESSION

Chairpersons : Dr. Hamza Thayyil, Kozhikode &
Dr. Harigovindan P, Kozhikode

UNUSUAL PRESENTATION OF VVF
Dr. Muraleedharan KP, Dr. Chandrasenan Nair, Dr. Venugopal G
Department of Urology, Medical College Hospital, Thiruvananthapuram

POST ESWL RENAL CHANGES MASQUERADING AS A RENAL NEOPLASM-A CASE REPORT
Dr. Manu MK, Dr. Vinod KV, Dr. Santhosh Rollands, Dr. Sankar, Dr. Albert AS
Department of Urology, Medical College Hospital, Thiruvananthapuram

LAPAROSCOPIC SEMINAL VESICLE EXCISION
Dr. George P. Abraham, Dr. Sanel Varghese, Dr. Thamban OS
PVSM Hospital, Kochi

SPONTANEOUS URINOMA
Dr. Muraleedharan KP, Dr. Chandrasenan Nair, Dr. Venugopal G
Department of Urology, Medical COllege Hospital, Thiruvananthapuram

RENAL LYMPHANGIECTASIA-A CASE REPORT
Dr. Shameer Hameed, Dr. Manu MK Dr. Sivaramakrishnan, Dr. Albert AS
Department of Urology, Medical College Hospital, Thiruvananthapuram

RADICAL NEPHRECTOMY WITH EXTRACTION OF RIGHT ATRIAL THROMBUS
Dr. Muraleedharan KP, Dr. Chandrasenan Nair, Dr. Venugopal G
Department of Urology, Medical COllege Hospital, Thiruvananthapuram

RADICAL NEPHRECTOMY WITH EXTRACTION OF RIGHT ATRIAL THROMBUS
Dr. Muraleedharan KP, Dr. Chandrasenan Nair, Dr. Venugopal G
Department of Urology, Medical College Hospital, Thiruvananthapuram

FILARIAL GRANULOMA PRESENTING AS SPERMATIC CORD MASS-A CASE REPORT
Dr. Manu MK, Dr. Vinod KV, Dr. Shameer Hameed, Dr. Harris CH, Dr. Syam K. Ramesh
Department or Urology, Medical COllege Hospital, Thiruvananthapuram

SPINAL CORD REGRESSION SYNDROME-A RARE CAUSE FOR NEUROGENIC BLADDER

Dr. Pushpangathan VS, Dr. Chandrasekhar CS, Dr. Krishna Moorthy H
Division of Urology, Lourdes Hospital, Kochi

TOTAL CORRECTION OF DIPHALLIA WITH TOTAL URETHRA DUPLICATION, DOUBLE SCROTUM AND HYPOSPADIAS
Dr. Bhat HS, Dr. Ginil Kumar P, Dr. Sanjeevan KV, Dr. Sudhir S
Department of Urology, Amrita Institute of Medical Sciences, Kochi

VALVE BLADDER-A NOVEL ANTIREFLUX SURGERY
Dr. Muraleedharan KP, Dr. Chandrasenan Nair, Dr. Venugopal G.
Department of Urology, Medical College Hospital, Thiruvananthapuram

4.30 pm	:	ANNUAL GENERAL BODY MEETING
7.00 PM	:	BANQUET
Venue	:	ATSK Gardens, Olayil Kadavu, Kollam

Day 2

8 a.m. : BREAK FAST

8.30-9.00 am : Dr. P. Subramoniam PG Travel Fellowship Quiz

Quiz Master : Dr. Sivaramakrishnan P. Thiruvananthapuram

9.00-10.00 am : VIDEO SESSION

Chairpersons : Dr. Gopinatha Menon, Thrissur &
Dr. Ashok Pandit, Mangalore

LAPAROSCOPIC RADICAL NEPHRECTOMY
Dr. George P. Abraham, Dr. Sanel Varghese, Dr. Thamban OS
PVSM Hospital, Kochi

LAPAROSCOPIC ADRENALECTOMY: EXPERIENCE WITH OUR INTIAL TEN CASES

Dr. Bhat AS, Dr. Balagopal N, Dr. Sanjeevan KV, Dr. Ginil Kumar P
Department of Urology, Amrita Institute of Medical Sciences, Kochi

LAPAROSCOPIC PYELOPLASTY- ANALYSIS OF 23 CASES

Dr. George. P. Abraham, Dr. Sanel Varghese, Dr. Thamban OS
PVSM Hospital, Kochi

EXPERIENCE WITH INITIAL TWENTY ONE LAPAROSCOPIC DONOR NEPHRECTOMIES

Dr. Bhat AS, Dr. Saheed CSM, Dr. Sanjeevan KV, Dr. Ginil Kumar P
Department of Urology, Amrita Institute of Medical Sciences, Kochi

COST EFFECTIVE LAPAROSCOPIC DONOR NEPHRECTOMY-ANALYSIS OF 65 CASES

Dr. George P. Abraham, Dr. Sanel Varghese, Dr. Thamban OS
PVSM Hospital, Kochi

10.00-10.30 am : GUEST LECTURE II

Chairpersons: Dr. Venugopal, Thiruvananthapuram & Dr. Ajith Bharathan, Pandalam

UROLITHIASIS-PAST, PRESENT AND FUTURE
Dr. Kandasami SV, Coimbatore

10.30-10.45 am : COFFEE BREAK

10.45-11.30 am : SYMPOSIUM

Moderators : Dr. Sulaiman E, Kozhikode & Dr. Joseph Thomas, Manipal

MANAGEMENT OF NEONATAL HYDRONEPHROSIS

: Dr. Pushpangathan VS, Kochi
: Dr. Sanjay Bhat, Kochi

11.30-12.30 pm : SHORT PAPER II

Chairpersons : Dr. Darwin Therattil, Thrissur &
Dr. Sathyendran Nambiar, Kannur

DYNAMIC SUBURETHRAL SLING SUSPENSION VERSUS PUBOVAGINAL SLING IN FEMALE STRESS URINARY INCONTINENCE

Dr. Faizal S, Dr. Sulaiman, Dr. Felix Cardoza, Dr. Suresh Bhat, Dr. Hari Govind, Dr. Mohan Department of Urology, Medical College Hospital, Kozhikode.

ORACLE BASED DIET EVALUATION PROGRAMME FOR UROLOTHIASIS PATIENTS

Fazil Marickar YM, Jayan Stephen, Preetha

Stone Clinic and Urolithiasis Research Wing, Medical College Hospital, Thiruvananthapuram

CHANGING PROFILES IN EMPHYSEMATOUS PYELONEPHRITIS-ROLE OF CONSERVATIVE MANAGEMENT

Dr. Vinod KV, Dr. Shameer P. Hameed, Dr. Albert AS
Department of Urology, Medical College Hospital, Thiruvananthapuram

OUTCOME OF SNODGRASS PROCEDURE FOR HYPOSPADIAS REPAIR

Dr. Faizal S, Dr. Sulaiman, Dr. Felix Cardoza, Dr. Suresh Bhat,
Dr. Harigovind, Dr. Dinesh
Department of Urology, Medical College Hospital, Kozhikode.

ESWL FOR UPPER URETERIC CLACULUS-OUR EXPERIENCE

Dr. Ginil Kumar P, Dr. Bhat HS, Dr. Sanjeevan KV, Dr. Saheed CSM, Dr. Sudhir S, Dr. Balagopal N. Department of Urology, Amrita Institute of Medical Sciences, Kochi

COMPARISON OF SINGLE SEMINIFEROUS TUBULE (SST) BIOPSY AND OPEN BIOPSY OF TESTIS IN THE EVALUATION OF MALE INFERTILITY
Dr. Reghunath KG, Dr. Suresh Bhat, Dr. Appu Thomas
Department of Urology, Medical College Hospital, Kottayam

12.30-1.00 pm	:	BLACK PEARLS
		Chairpersons: Dr. Thomas AN, Kannur & Dr. Dineshan KM, Kozhikode
Speakers	:	Dr. Murali TR, Madurai Dr. Raja, Tiruchi Dr. Joseph Thomas, Manipal
1.00-1.30 pm	:	VALEDICTORY FUNCTION
1.30 pm	:	LUNCH

The Rich Heritage of Quilon

Dr. M. MARCELES
E.N.T. Surgeon
Benziger Hospital
Kollam

The ancient history of Quilon is something unique and enchanting. No other town in Kerala can claim such an ancient history that is sorich. This town is a little bit of land filled with coconut trees and embraced by the calm and cool waves of the Arabian Sea on one side and the Ashtamudi Lake on the other side.

The serene atmosphere, the enchanting scenic variety, the majestic promontories on the banks of Ashtamudi lake, the crimson red of the setting sun and the coconut trees dancing in the cool breeze. are some of the special gifts of nature, to this most picturesque land of Kerala.

Quilon has been known to the outside world by the time honoured proverb, 'Once you have seen Quilon, you would forget to go back to your very home'. What a wonderful, meaningful and befitting proverb.

The very rich ancient history of Quilon, which can be traced back not only to Ist centuary AD, but to 3000 BC; when the sea port of Quilon town was frequently visited by the travellers of the far off lands-Babylonians, Phoenicians, Persians, Greeks, Romans and Arabs; will explain the significance of the proverb. The foreigners, who came to Quilon, never wanted to leave Quilon and they waged many a war to get control over Quilon. Their main attractions were teak wood, elephant tusks, black pepper and spices. There are enough historical evidences to prove that Quilon had been exporting teak wood and elephant tusks from 3000 BC to Babylonia ie. the present Iraq. In those days Quilon was known to outside world in different names, like Ki-yu-lan, Kollion, Kau-lam, Kollam etc. and the name Quilon came later.

Quilon in Chinese language means Big-Bazar cr a big market place.

It is believed that in 52 AD, St. Thomas visited Quilon and built a church. A Roman traveller, Pleenie (AD 23-79) refers to Quilon in his writings, as a place where one can get the best quality black pepper.

The author of Periplus of the Erythrian Sea' (Ist Century) mentions Quilon. Ptolomy, a Greek author, in his book written in 139 AD also mentions about Quilon. There are enough evidences to establish the very old rich history of Quilon and the fame it had as a trade centre in the world of those years.

Only by the 5th century, the Chinese established trade links with Quilon. A Chinese traveller named Fehiain (AD-414) wrote that the sail ship he travelled, carried many people from Quilon and there were regular marine services, carrying men and materials between China and Quilon. Once the trade was established with the Chinese, the importance of Quilon port grew many fold.

In the book 'Topographica Indica Christiana' written by Induce Pleastus in 522 AD, Quilon is mentioned in many places as an important trade centre of those days.

The Arab Merchant, Sulaiman of Siraf in Persia visited Quilon in 851 AD and he wrote "Quilon is one of the most important ports in India". "The ship that starts from Siraf in Persian Gulf always touched the port of Quilon on their way". The most interesting thing is that Sindbad the Sailor started his journey from Basra port in Persian Gulf, and so the chances of Sindbad the Sailor touching the port of Quilon enroute, can not be ruled out.

Around AD 800, the old Quilon town was destroyed somehow, and in a few years time, it was redesigned and rebuilt by a Syrian Merchant by name Sapir Iso. As a reward for rebuilding the town of Quilon, the King of Quilon (Ayanadikal) made a treaty, known as Theresapally Treaty, permitting Sapir Iso to build a church in Quilon and to enjoy lots of previlages like permission to convert people to Christianity.

Benjamin, a great traveller (1159-1173) using his travel to the East, visited Quilon and wrote that the people in Quilon did worship the Sun God. "The king of Quilon had given the foreigners the freedom of travel and their saftey was guaranteed. There was no cheating, no robbery. The lost property, while travelling, reached safely to the owner. There were street lights and the market places were well lit so that one could do business even at night. The main product of Quilon was pepper and it was dried by sun light.

Towards the end of the 12th Centuary, a Muslim traveller, A1-Quisini has described Quilon as a place where long teak wood trees were grown.

Marco-Polo, the great Venician traveller, who visited Quilon in 1275 wrote that the people of Quilon had their own language. 'There are Hindus, Christians and Jews. Quilon is a hot place and black pepper and ginger are cultivated in large quantities. Traders from Arabia, China etc. come here for trading. The people in Quilon make their own wines. The wine made is very strong and intoxicating in nature. In Quilon, one get what ever is needed, at a very reasonable price. There are very good astrologers and physicians". The descriptions about Quilon goes like that.

In 1324 Friar Jordanus of Sevric who was made the first Bishop of Quilon, wrote "the people of Quilon are very neat and clean in their dressing and food habits. The astrologers and the physicians are well respected".

In 1324 AD Ibu-Batuta wrote that Quilon is one of the five chief ports he had seen in the course of his travel during a period of 24 years, and Quilon town is very big and the rulers of Quilon are just and take much interest in the welfare of the subjkects.

Portuguese were the first Europeans to establish trading centre at Quilon in 1502 and the then King of Quilon Ravi Varma (1484-1512) gave permision to the Portuguese to build a fort in Quilon. In 1516 the MahaRani of Quilon made a treaty and made arrangements to procure any quantity of pepper from Quilon. They were given permission to build churches and to extent the fort, to use Quilon port without any tax, to convert the local people to Christianity. In 1517 AD, again they got the permission to build the St. Thomas Fort in Thangasserry and started the construction, and completed in 1519 September. The Portuguese took by force nearly 5000 bullock cart load of pepper that

was being transported by the local traders. The Maha Rani was very angry on this incident and with the alliance of Nair and Muslim people engulfed the fort and captured the Portuguese. Unneripillai, Balan Pillai and Kollakurup etc. gave the leadership for the blockade. A battalion of Portuguese army from Cochin came to the rescue of the Portuguese army in Quilon and saved them in 1520 August. Following, a treaty was signed by the Maha Rani of Quilon and the Portuguese Governor on 17-11-1520; and slowly the Portuguese tightened their grip and Quilon became under the control of Portuguese upto 1661 December.

In 1588 by the defeat of the Spanish Armeda by the British, the Portuguese became weak in 1658 the Dutch captured Quilon from the Portuguese. The Dutch made a treaty with the Maharani in 1659, January 9th, agreeing to sell all the pepper only to the Dutch and banning the use of the port by the Portuguese. As the Dutch Captain left Quilon, after the agreement, the Portuguese recaptured the fort.

In 1661 a Dutch battalion came and defeated the Portuguese and recaptured the fort. In the confrontation between the Dutch and the Portuguese, the Quilon town was destroyed very much and the Dutch repaired the town.

In 1795 the Dutch became very weak and as the Cochin Fort was captured by the British, the Dutch lost the St. Thomas Fort in Thangassery, in Quilon too. Following that the British kept a battalion of soldiers in Quilon and took control of Quilon. A British garrison was stationed at Quilon in pursuance of a treaty between the British and the King of Travancore.

After the British came in, it is modern history and it is known to everyone.

The rich heritage of Quilon had attracted many people from different parts of the world and those who had come here tried to exploit the natural resources to it's maximum. Still Mother Nature had been very kind to bless this land with the natural resources, including rare earth minerals in abundance.

As the land is in between the Arabian Sea and the Ashtamudi Lake, the natural beauty is something special and unique; with the scenic beauty of the sea coast with the sheltered recess of the calm Arabian Sea with the coconut tree frills, the remanants of the Portuguese and the Dutch Fort and the majestic 144 ft high light house; and of the lake side with the serene, fascinating and enthralling lake surrounded by the coconut trees dancing to the tunes of the breeze passes by, where the special Kerala House Boats, 'Kettuvallams', move to and fro in nature's own lap with the tourists, in the misty moonlight, gazing at the starry sky, exploring the beauty of nature, and... and....

Yes, this ancient town of Quilon is blessed in many ways and the rich heritage stands at its peak.

Overactive bladder in children and its pharmacotherapy-Current and Future

Dr. A.S. ALBERT M.S., M.Ch., D.N.B. (Uro)
Professor and Head
Dept. of Urology, Medical College
Trivandrum

The overactive bladder (OAB) its magnitude and impact, that have received little general medical attention till recently, is now gaining momentum, Is it because of the new drug formulations and its competitions in the pharmaceutical industry, that have stimulated each and every urologist, to think more about this condition?. Researches are going on in the pharmaceutical sector, to bring out newer molecules to compete with the traditional anticholinergic drugs with its crippling side effect. Intravesical therapy and alternative drug delivery methods such as intravesical capsaicin and botulinum to in with special emphasis on approaches to modulate bladder afferent nerve function, are coming out with flying colours, for preventing overactive bladder. There are many advantages to advanced drug delivery system, including long term therapeutic efficacy, decreased side effects and improved patient compliance. Future speculation such as gene therapy holds great promise for overactive bladder because it is possible to access all genitourinary organs via endoscopy and other minimally invasive techinique that are ideally suited for gene therapy.

The overactive bladder (OAB) in children is defined as both involuntary detrusor contraction and urethral instability. The development of urinary control plays a key role in its incidence and our understanding of its pathogenesis. Dysfunctional voiders are most affected by OAB. Urinary infection can be both a cause and effect of OAB.

OAB in children has three origins

1. Neurogenic, 2. Anatomic, 3. Functional

Neurogenic causes: A group of spinal abnormalities collectively called myelodysplasia, which affect lower urinary tract functions, are open spinal canal lesions such as myelomeningocele, lipomeningocele, lipoma of the cauda equina, diastematomyelia or split cord syndrome, thickened film terminale, abberant nerve roots or anterior meningocele. Sacral agenesis can selectively involve the lower urinary tract, but difficult to diagnose clinically.

Anatomic Causes: Posterior urethral valve in children will often result in a hyperactive bladder even if it is treated promptly. Some clinicians even think that vesicoureteral reflux in children is secondary to overactive bladder.

Functional causes: Children with dysfunctional voiding are most affected by OAB. Functional problems such as recurrent urinary infections (UTIs) without an anatomic cause, may result from or actually precipitate a hyperactive bladder, the cause being inflammatory changes in the detrusor wall which trigger premature contractions. Psychosocial developmental abberations of the child can lead to the development of OAB, which once reated results in the resolution of incontinence. Dysfunctional elimination syndrome which include intermittent voiding, incomplete emptying and delayed emptying are associated with residual urine, that can produce recurrent infection and subsequent detrusor overactivity. Detrusor overactivity can even lead to considerable changes in the upper urinary tract and even leading to loss of renal function (Hinman Allen syndrome).

INCIDENCE OF OAB

Incidence of detrusor overactivity depends on the underlying cause. In children with myelomeningocele, the incidence of detrusor hyperreflexia varies with the level of lesions, more with heigher lesions, but it is present even in children with low sacral lesion. 37% of children with sacral agensis have OAB Incidence of overactive bladder in children with posterior urethral valve varies from 15 to 25%. 33% of children with primary vesicoureteral reflux are thought to have detrusor hyperactivity.

EVALUATION OF CHILD WITH OAB

A proper history taking, careful clinical evaluation especially of the spine, external genitalia and nervous system is all that is needed for children with suspected OAB. Sonographic evaluation of the urinary tract is mandatory.

A multichannel urodynamic study is the gold standard investigation for the evaluation of OAB and it helps in defining underlying pathophysiology and in deciding treatment. The information gained at urodynamics, therefore, is not merely diagnostic value ie. in identifying detrusor overactivity, low bladder compliance, urethral obstruction, impaired detrusor contractility, sensory urgency etc, but also prove useful in directing therapy based on the patients degree of awareness, concern and control.

TREATMENT OF OAB IN CHILDREN

The basis of treatment for OAB in childhood depends on its presentation, underlying cause, and future effects it may have on the upper and lower urinary tract, as well as the current status of kidneys and bladder. The risk of upper urinary tract deterioration with detrusor hyperactivity, especially in the presence of sphincter dyssynergy in children with myelodysplasia is 80% and the risk is reduced to 10% if prompt treatment is instituted on time. 76% of these children gain continence, as they reach school age, without the need for augmentation cystoplasty. Thus prompt treatment with anticholinergic medication and clean intermittent catheterisation are warranted in children with detrusor hyperactivity and sphincter dyssynergy. Detrusor hyperactivity in children with sacral agensis is managed with anticholinergic medication and clean intermittent catheterisation to ensure

continence and complete bladder emptying. Reflux is likely to resolve in 40% of patients after initiation of treatment. In patients with cerebral palsy and detrusor hyperactivity, the amount of anticholiergic medication must be titrated slowly to empty the bladder completely with each voluntary voidwhite simultaneously minimizing the premature contractions. Patients with detrusor hyperactivity secondary to spinal cord injury and consequent C-fibre stimulation are best managed by direct inhibition of muscle with capsaicin like substance.

Early intervention of posterior urethral valves with ablation of valve leaflets and anticholinerigc medication has improved bladder function and upper urinary tract drainage by 78%. The risk of developing valve bladder is minimal. In the pathogenesis of vesicoureteral reflux, the detrusor hyperactivity is considered a predominant cause. Resolution of vesicoureteral reflux is much quicker if anticholinergic medication is added to the antibiotic regime when therapy is begun.

Detrusor hyperactivity in children with recurrent urinary tract infection has harmful effect to the entire urinary tract. The risk of recurrent urinary tract infection can be reduced substantially, if anticholinergic medication is added to the antibiotic regime and with proper toileting.

Treating a child, who has only incontinence poses a potentially daunting problem. The child may have a hyperreflexic bladder as the cause of incontinence. A careful neurological examination may uncover signs of subtle central nervous system dysfunction or spinal cord abnormality. Proper bowel elimination programme and anticholinergic medication seems warranted in patients who show signs and symptoms of overactive bladder. Behavioural modifications and biofeedback training has shown promise in reducing symptoms and in improving continence on a long term basis in most children.

PHARMACOLOGICAL TREATMENT OF OVERACTIVE BLADDER

1. Anticholinergic agents

Anticholinergic agents that supress muscarinic receptors in bladder smooth muscle are by far the most useful pharmacological agents for managing overactive bladder and urge incontinence. Currently used drugs are:-

a) Oxybutinin hydrochloride: Oxybutinin is an antimuscarinic agent with pronounced muscle relaxant and local anaesthetic activity. Most side effects are related to antimuscarinic action and dry mouth is the most common complaint. A once daily controlled release formulation of oxybutinin namely oxybutinin XL has similar efficacy as that of immediate release oxybutinin, but reduced side effect.

b) Tolterodine: Tolterodine is a new competitive muscarinic receptor antagonist and it has significant beneficial effect for overactive bladder. Tolterodine 4mg appears to be as effective as immediate release oxybutinin 15mg daily, but is significantly better tolerated. Once daily formulation of tolterodine ie. tolterodine LA showed statistically better improved efficacy with less side effects.

c) Propiverine: Propiverine hydrochloride is a benzylic derivative with musculotropic (calcium antagonist) activity and a moderate antimuscarinic effect. It is safe and effective for OAB.

d) Trospium: Trospium is quarternary ammonium derivative with mainly antimuscarinic action. With 40mg daily dose, clinical efficacy is as good as 15mg oxybutinin, but with fewer severe side effect.

e) Propantheline: Propantheline hydrochloride was the first classically described oral antimuscarinic drug for overactive bladder, but significant side effect made it a less attractive choice.

FUTURE DIRECTIONS OF ANTICHOLINERGIC AGENTS

Pharmacologically defined subtype selective drugs have been developed recently. Darifenacin and Vamicamide are subtype selective antimuscarinic drugs. They have high affinity for M3 muscarinic receptor. But it has adverse effect on the central nervous system via supression of M1 muscarinic receptor, leading to impairment of memory and affect learning.

Future anticholinergic agents may not only be receptor selective, but also organ selective. A truly blader selective antimuscarinic drug with no associated dry mouth or central nervous system effects, would be the ideal drug for overactive bladder.

2. Direct Bladder Bladder Smooth Muscle Suppressant:

Flavoxate: Flavoxate hydrochloride has a direct inhibitory action on smooth muscles in vitro. It has favourable effect in patients with overactive bladder.

Imipramine: Many clinician have observed that tricyclic antidepressants particularly imipramine hydrochloride, are useful for facilitating urine storage, by decreasing bladder contraction and increasing outlet resistance. The disadvantage of tricyclic antidepressant is the narrow safety profile and significant side effects. Combination therapy using antimuscarinics and imipramine may have sinergistic benefits.

K+ channel openers: A promising class of drugs that a number of pharmaceutical companies are considering for overactive bladder is Pottassium channel openers. Drugs such as Cromakalim and pinacidil open ATP sensitive K+ channels and supress bladder muscle contraction. The drug act not only on bladder smooth muscles, but also on capsaicin sensitive bladder afferents to decrease afferent firing induced by bladder distension or chemical moucosal irritation.

Desmopressin: Desmopressin is a synthetic vasopressin analogue with strong antidiuretic effects. The drug is commonly administered in children with nocturnal enuresis. Giving desmopressin at bed time for bother some nocturia is becoming more popular.

3. Centrally Acting Drugs for OAB:

Currently there are no clinically proved pharmacotherapies that act in the central nervous system to treat overactive bladder. However recent advances in animal studies have revealed potential targets in the brain and spinal cord for treating overactive bladder.

Duloxetine is a selective serotonin and nor epinephrine reuptake inhibitor and it is undergoing FDA clinical trial for overactive bladder. In animal models, duloxetine has been shown to increase

significantly bladder capacity and sphineter tone without interfering with the normal voiding cycle.

4. Intravesical Therapy and Advanced Drug Delivery

The success of intravesical anticholinergic drug treatment for overactive bladder and detrusor hyperreflexia is well documented. But this is not widely used because of the cumbersome methods of drug delivery and the need for repeated catheterisation. Intravesical therapy would be widely adopted if we had drugs that could last weeks to months after a single instillation or if we could design a convenient and non irritating intravesical drug pump.

(i) Intravesical local anaesthetics:

Intravesical application of lidocaine has been effective for supressing overactive bladder. But the effect is short lived and not suitable for long term management of overactive bladder.

(ii) Intravesical Oxybutinin:

Intravesical oxybutinin has been efficacious in patients with overactive bladder in whom oral oxybutynin failed. The rate of symptomatic improvement is 55 to 90%. Side effect is less than that of oral medication. Side effect is mainly due to the metabolite of oxybutinin ie. desethyl-oxybutinin that enter the systemic circulation. Metabolite formation is more with oral delivery of the drug than intravesical and transdermal delivery.

(iii) Transdermal Oxybutynin:

It is logical that transcutaneous application of anticholinergic drugs can further decrease side effect, while still maintaining efficacy. Transdermal oxybutinin achieved a similar decrease in urge incontinence episodes but with significantly fewer episodes of dry mouth than oral immediate release oxybutinin.

A NOVEL INRAVESICAL DRUG DELIVERY SYSTEM-PROMISE OF THE FUTURE

The key to this intravesical regime is a long lasting intravesical pump to deliver the desired drug dose. This technology is not available today, but it is currently under development. The concept involves a reserviour that can be easily inserted into the bladder and filled with desired drug. Reserviour size must be balanced, so that it is not too small to be voided and yet not too large to cause bladder irritation or obstruction. The reserviour should constantly release a precise quantity of drug into the bladder. When the reserviour is empty, after some days or months, flexible cystoscope can be used to retrieve the empty reserviour and a new reserviour can be inserted.

(iv) Intravesical Peppers

Vanilloids such as capsaicin and resiniferatoxin activate nonciceptive sensory nerve fibres through an ion channel known as vanilloid receptor subtype 1. vanilloid receptors are located predominantly on C-fibre afferents and activating the receptor initially excites and subsequently desensitizes C-fibre. C-fibre bladder afferents are not essential for normal voluntary voiding. However, various pathoogical conditions such as spinal cord injury or chronic bladder irritation, induces sensitization

and or recruitment of C-fibres, resulting in overall increase in the C-fibre contribution to mechanotransduction and bladder activity.

a) Intravesical capsaicin: Intravesical capsaicin decreases significant bladder hyperactivity. The use of capsaicin is still experimental. The effect of capsaicin on clinical and urodynamic parameters may be long lasting, exceeding one year in select patients.

b) Intravesical Resiniferatoxin:

Resiniferatoxin is a much more potent sensory antagoinst than capsaicin. The key advantage of resiniferatoxin is that it is at least as effective as capsaicin without many of the local side effects such a spain and inflammatory neuropeptisde release. It is very effective in detrusor hyperreflexia and incontinence.

c) Intravesical Botulinum Injection:

Urologically botulinum toxin has been used to treat spinal cord injured patients with detrusor sphincter dyssynergy. Botulinum A toxin injection produce reversible chemical sphincterotomy, which avoids a major surgical procedure with it attendant risk ie. bleeding, stricture and fistula formation. Botulinum toxin represents a viable option for treating detrusor sphincter dyssynergy. Many questions remain regarding the botulinum effect on neural pathways of the lower urinary tract. However one cannot deny human ingenuity in transforming the lethal toxin of clostridium botulinum into a modern day therapeutic medicine.

FUTURE THERAPIES

During the last few years research has stimulated the development of new therapeutic approaches for incontinence and overactive bladder. The drug industry should be encouraged to develop a truly bladder specific and effective anticholinergic drug with no'dry mouth' side effects. Selective serotonin and norepinephrine reuptake inhibitors such as Duloxetine that are specific for reflexes that control the bladder and urethra, are promising for treating not only overactive bladder but also stress incontinence. Intravesical resiniferatoxin and botulinum toxin should be evaluated to determine whether they may be potentially be effective for bladder hyperreflexia and overactive bladder. Single instillation of liquid resiniferatoxin or bladder injection of botulinum toxin that can last 3 to 6 months without any systemic side effects would be useful. K+channel openers may alleviate overactive and sensitive bladder without dry mouth or without increasing post void residual urine and it may become the gold standard treatment for overactive bladder in the future.

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The Management of Female Urinary Stress Incontinence

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The prevalence of urinary incontinence (UI) depends on the population under survey and the definition of incontinence. However, it is the elderly who predominantly have UI. The overall prevalence in elderly (above 60 years) is about 30%. The etiology in women is SUI in 27%, urge in 9%, and mixed in 56%. Continence in women is under control of different factors: an intact sphincter mechanism, an adequate support for the bladder neck and proximal urethra and compensatory mechanisms occurring during stress manouevres and increase in intra abdominal pressure.

Diagnostic evaluation includes a detailed history, a thorough physical examination which should focus on anatomic and neurologic abnormalities, a micturition diary, pad test, uroflowmetry, urodynamic evaluation and cystoscopy. Particular attention should be paid to any concomitant genital prolapse.

In general, surgical treatment of SUI is more effective than non surgical treatment.

NONSURGICAL TREATMENT

Medical treatment largely includes alfa agonists and estrogens. A high concentration of estrogen receptors are present in the urethra. Estrogens increase the alfa adrenergic receptor density and sensitivity, enhances neuronal sensitivity and transmitter metabolism, exerts trophic effects on the urethral mucosa, submucosa, and pelvic floor. Oral and topical preparations are available. These are indicated in pre and postmenopausal women.

Alfa adrenergic drugs include ephedrine 25-50mg 4 times daily, psuedoephedrine 30-60mg 4 times daily. Phenylpropanolamine in doses of 50mg tid was used earlier. However recent reports indicate increased incidence of hemorrhagic strokes as a complication of this drug.

Pelvic floor exercises (PFE), biofeedback, electric stimulation (ES) and behavioral modification are empirical rehabilitative therapies used singly or in combination. Many patients are unwilling or unable to comply with established treatment regimens. However for motivated patients, who are willing to pursue the rigors of long term treatment, a reasonable degree of improvement can be expected.

Vaginal cones offer a cure rate of 17-84%. Estradiol releasing pessaries have been used with a success uf 60%. Minidevices like the Danish urethral plug, the reliance urethral plug etc. have been given up because of the difficulty in handling these.

SURGICAL TREATMENT

A wide variety of surgical treatments are available to treat female SUI. These consists of periurethral injections, transvaginal suspensions, retropublic suspensions, slings and sphincter prostheses.

The choice of procedure depends on a no. of factors but the most important caviet is that the surgeon should be experienced enough with whatever surgery she chooses to ensure that it is done competently. No matter what the purported benefits of a particular operation are, if the surgeon doesnot possess adequate skill and experience, the outcome will be uncertain and serious complications might ensure. The following factors whould be considered when deciding on the type of surgery :

a) the relative contributions of hypermobility and ISD (i.e. Q tip angle and VLPP)

b) urodynamic findings

c) the need for concomitant surgery eg. repair of genital prolapse, hysterectomy etc.

d) the patients life style

e) the age and overall medical condition of the patient.

SURGERY

The basic principles of surgery are to prevent the abnormal descent of the urethra and to provide a backboard against which the urethra is compressed during increase is abdominal pressure.

As a general rule an autologous fascial pubovaginal sling is appropriate and effective for both simple and complex sphincter incontinence, whereas Burch colposuspension is most effective for those with simple sphincter incontinence associated with urethral hypermobility. A sphincer prosthesis has excellent results in the hands of an experienced surgeon, but has high complication rate in patients who have had multiple surgeries.

Of late we have been doing the modified suburethral sling procedure using the external oblique aponeurosis. In a series of 30 patients only I patient had voiding difficulty which required catheterisation for 7 days, another patient de novo developed urgency.

In cases of mixed incontinence treatment depends on which component is more troublesome. If SUI is more then a sling will be beneficial, if the urge is more, medical treatment is indicated.

Complications of Urologic Laparoscopy

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"Diseases that harm require treatments that harm less". William Osler once said. For decades this statement remained ignored by the Urologists. Now we have modified this statement and often say "diseases that harm require treatment with laparoscopy". Enthusiasm in the field of laparoscopic surgery has reached a point that almost all incisional procedures can be replaced by laparoscopic techniques. This minimally invasive, maximally effective technique has to be weighed against the lethal complications associated with it. The benefits highlighted for the procedure are shorter hospitalization, less post operative pain, better cosmesis and more rapid convalescence. The overall complication rate for an experienced surgeon in the latest reported series ranges from 4-5% with a mortality rate of 0.03%. These low complication rates quoted are for the surgeons who had immense training in animal labs.

Complication rates depends on the experience and exposure of the surgeon. Early complication rates were approximating to 15%. So in my opinion, all urologists trying for a metamorphosis to a skilled laparoscopic surgeon should have a proper home work on the possible complications.

INCIDENCE:

Ever since Cortessi reported the 1st urologic use of laparoscopy in 1976, the no. of ablative and reconstructive procedures have increased as also the complication rates. In 1993, urologists entered the retroperitoneum taking along with them the added complications.

The various reported series are as shown in Table-1.

TABLE-1

Author	No. of Cases	Overall complications	Specific complications	Conversion rate
Dirk Fahlenkemp et al (1999)	2407	4.4%	1.7% Vascular 1.1% Visceral 0.8% Healing 0.2% Access	0.8%
Vallaneien G et al (2002)	1311	0.7% Major 1.8% Intermediate 1.1% Minor	0.5% Vascular 1.2% Bowel 0.8% Ureteric	2.4%
Fahlenkemp D et al (2001)	741	1.9%		
Cadeddu JA et al (2001) (Training Centre)	738	11.9%		1.1%
Rass Weder et al (1998)	482	6%		10%
Es Posto C et al (1997) (pediatric cases)	430	1.8%		
Soulie M et al (2001)	350	5.4%		1.1%

The documented complications are:

-Vascular injury : 1.7%

-Visceral injury : 1.1%

-Healing and Infection : 0.8%

-Access techniques : 0.2%

-During dissection : 2.9%

Studies have shown that the rate of complication and conversion rate rapidly decreases after 30-50 procedures.

The complications may be discussed under the following headings.

1. Intraoperative complications
2. Postoperative complications
3. Complications related to specific procedures
4. Complications related to retroperitoneoscopy
5. Complications related to pediatric laparoscopy
6. Preventions and precautions

The entire complications may be summarised as in Table: 2

TABLE-2

PATIENT POSITIONING	:	Neuromuscular Injury
ACCESS	:	Intraperitoneal Vs Retroperitoneal Primary port - Open Vs Closed technique
BALLOON DISSECTION	:	Loss of Orientation Abdominal muscle injury Peritoneal rupture Balloon rupture
PNEUMOPERITONEUM	:	Surgical - Subcutaneous emphysema Pneumothorax Pneumomediastinum Pneumopericardium Gas embolism
		Cardiovascular
		Pulmonary
INSERTION OF SECONDARY PORT:		
	:	Pneumothrax
	:	Visceral injury
	:	Abd. wall hematoma & bleeding

Disection: INJURY

- Vascular
- Peritoneal
- Retroperitoneal nerves & vessels
- Hollow organs & solid organ
- Thermal

Closure related complications:
Complications of prolonged surgery:

- Pneumonitis
- DVT
- Nerve palsy
- Paralytic ileus

Post Operative Complications:

Early:

- General : Pain, Nausea, Vomiting
- Local : Wound infection & peritonitis
- Vascular : Delayed haemorrhage
- Pulmonary
- Renal-Azotemia

Late:

- Hernia
- Port site metastasis
- Intraperitoneal adhesion

INTRAOPERATIVE COMPLICATIONS:

Improper patient positioning can result in abnormal compression of a nerve leading to neuropathy. For example brachial plexus injuries are the most common abduction injury of arms ($>90^0$). During renal surgery, a flank position can lead to abnormal flexion of axial skeleton.

Access related problems are less in retroperitoneoscopic approach. Retroperitoneoscopy can be applied in patients with multiple prior surgeries with lesser risk of injury to intraperitoneal organs. This approach has no risk of spillage of infected urine into the peritoneal cavity later leading to intraperitoneal adhesions. The demerits are less working space, longer learning curve and increased incidence of pneumothorax and pneumomediastinum (37% vs 3%).

Balloon rupture can lead to air embolism if inflated with air. So liquid medium is preferable nowadays. Picking the residual fragments of the balloon should be done immediately. Silicon balloons are stronger but they are more expensive. Balloons with double latex is another alternative.

Pneumoperitoneum creation can lead to complications in the form of improper placement of Veres needle leading to subcutaneous emphysema. Sudden development of creptius over abdominal wall, excessive changes in airway pressure etc. are the indicators of development of emphysema. Significant hypercapnoea, pneumomediastinum and pneumothorax are the other consequences. Application of Hasson's technique, Drop test, Saline injection may reduce these complication rates.

Hemodynamic disturbances due to penumoperitoneum are challenging problems for the anaesthesiologist. There will be increase in systemic vascular resistance and arterial blood pressure. Alterations in blood pressure may be the first manifestation of this eventuality. Dysarrhythmia (25-43%), cardiac arrest etc. are the final consequences. The immediate treatment options include keeping the intra abdominal pressure <15 mm of Hg, release of pneumoperitoneum and administration of anticholinergic drugs.

Hypoxemia may occur as a result of reduction in lung volumes, increase in peak airway pressure and decrease in pulmonary compliance. Pulmonary vasoconstriction from hypercapnia may be lethal in patients with pulmonary hypertension.

Secondary port insertion complication can be reduced by insertion under vision. Many series have reported incidence of peritoneal and visceral injury during insertion of secondary port. The epigastric vessels are at risk during port placement. Identifying the significant vessels by transillumination, through the abdominal wall with laparoscope and placing the trocars lateral to the rectus abdominis muscle can reduce the vascular injuries.

Dissection and instrumentation can lead to vascular, peritoneal, hollow and solid organ injury. Retroperitoneoscopy can lead to damage to femoral nerve, obturator nerve, ileo hypogastric nerve and lumbar sympathetic chain. The incidence of vescular injury in 0.017%-0.05%, with a mortality rate of 8.8%-13%. Aortic bifurcation and iliac vessels are at risk during the insertion of ports. Retroperitoneoscopy should be avoided in patients with portal H.T. due to increased incidence of vascular injury arising from the collaterals of portocaval anastomosis.

The reported incidence of hollow organ injury (Bowel and Bladder) is 0.06-0.14%. Many of these are trocar or tissue dissection injuries. Sudden deflation of abdomen, CO^2 in the urosac, hematuria etc are indicators of bladder injury. Bladder perforation may present as peritonitis, azotemia, ascitis and hyponatremia in the postoperative period.

Nasogastric tube and Foley's catheter insertion will reduce the rate of these complications.

Ureteric injuries in retroperitoneoscopy is reduced by preplacement of ureteric catheters. The principles of management are as in open surgery.

Thermal injuries are created by electrocautery and lasers. Improperly grounded unipolar device can cause thermal damage to ureter, bladder, duodenum, gall bladder, colon etc.

Closure related complications are reduced by checking the hemostasis at low intraabdominal case pressure (,5mm of Hg.).

Pulmonary impairment is the worst ***postoperative*** problem after a laparoscopic surgery. This may be due to diaphragmatic dysfunction & inadequate pain relief. Co_2 concentration commonly return to normal with in 45 minutes of delfation of abdomen. The other post operative problems like

DVT & pulmonary embolism are precipitated by the lithotomy and Trendelenberg position and pneumoperitoneum.

Postoperative azotemia may be due to prerenal, renal and postrenal or an unrecognized bladder performation.

Very late complication like portsite metastasis from ***malignancy*** has to be further evaluated. The incidence of incisional hernia at trocar site is 0.1% approximately.

The important results of ***specific urologic*** laparoscopic surgery are as shown in Table: 3.

TABLE-3

Surgery		
Donor Nephrectomy	Conversion rate: 6-17%	Reoperation rate: 1-5%
Pyeloplasty	Intra op. compli: 3.8-15% Success : 80-100%	

Radical Nephrectomy	<u>Transperitoneal:</u> (Janetschek et al; 73 cases) Time : 2-4 hr Minor : 8% Major : 4% Open : 4% Retroperitoneal: (Gill et al; 47 cases) Time: 2.9 hrs Minor : 16% Major : 5% Conversion : 5%
Adrenalectomy	32% complication rate (Suzuki et al)

PREVENTIONS AND PRECAUTIONS:

Preoperative evaluation of cardiopulmonary status is a crucial stemp, as impaired function will predispose to fluid overload & Co_2 retention. Proper padding during procedure, Hassons's approach, placement of secondary Trocars under laparoscopy visualization will reduce the complication.

The insensible fluid losses and third spacing are minimal in laparoscopic surgery. Further more prolonged massive increase in intraabdominal pressure during pneumoperitoneum causes oligoanuria. Failure to limit intraoperative fluid administration will lead to fluid overload and failures.

As a conclusion ramark learning the complications of laparoscopic surgery is the first step of learning curve. This steep learning curve is a consequence of the special skills to perform laparoscopy, including appreciation of anatomy, altered hand-eye co-ordination, loss of tactile feedback, visualization of a 2D monitor, decreased working space and dependence on a team effort. So it is prudent for Urologist to initiate this carrier with simpler procedures like renal cyst decortication before proceeding to more complicated ablative & reconstructive surgery. Besides this meticulous selection of patients include avoiding patients with hemopoeitic disorders, active retroperitoneal infection, aortic aneurysm, abdominal wall infection etc. Caution to be taken in patient with decreased cardiopulmonary reserve, portal hypertension and massive ascites.

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Role of PSA in the Management of Carcinoma of Prostate

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INTRODUCTION

Many advances have occurred during the last decade in the clinical use of prostate specific antigen (PSA) for detecting, staging and monitoring prostate cancer. It was Wang et al who purified and characterised tissue specific antigen from the prostate and called it PSA in 1979. Later in 1980, Papsidero developed a serologic test allowing PSA to be measured in the serum. The prostate specific antigen test was approved by the U.S. Food and Drug Administration in 1986 to monitor the disease status in patients with prostate cancer and, in 1994, to aid in prostate cancer detection. The widespread use of PSA has resulted in significant changes in the detection and management of carcinoma prostate and this period is often referred to as 'PSA era'.

PSA is a serine protease encoded by the human Kallikrein gene family located in the chromosome 19. It is a 33 kD protein primarily synthesized in the prostatic epithelium and the epithelial lining of the periurethral glands. The plasma level of PSA is very low when compared to its high concentration in the semen. The exact mechanism by which it gains access to the circulation remains unknown. PSA and of PSA gene expression has been detected at low concentrations in the endometrium, normal breast tissue, breast tumors, breast milk, adrenal neoplasms and renal cell carcinomas!. But for practical and clinical purposes PSA is organ specific to the prostate gland.

There are over 20 immunoassays available in the market for the detection of the PSA. The wide variances between PSA values for various assays and the demonstration that many of these differences are due to calibration differences has resulted in efforts to develop standards for PSA. The Second Stanford PSA Conference proposed a mixture of 90% PSA-ACT and 10% PSA (90:10 standard) with a biochemically defined concentration to calibrate total PSA assays. Significant improvements in agreement between assays was observed with the 90:10 standrad as compared to results with kit calibrators. The National Committee for Clinical Laboratory Standards (NCCLS) has reviewed and adopted the 90:10 proposal.'

MOLECULAR FORMS OF PSA

PSA is initially synthesized in the cell as enzymatically inactive forms called as prepro PSA and

pro PSA. PSA within sera circulates in both bound and unbound forms. Most PSA in sera is bound to the antiproteases Al-antichymotrypsin (ACT) and a 2-macroglobulin (AMG). Binding of PSA by AMG still allows some proteolytic activity but renders the PSA-MG complex undetectable by current assays as all the five epitopes of PSA are hidden by it. Free PSA without proteolytic activity is probably rendered inactive within the prostatic epithelial cell before release into the sera. This free inactive PSA does not form complexes with antiproteases, circulates unbound in sera, and is immunodetectable by current assays. Thus, most detectable PSA in sera (65% to 90%) is bound to ACT, whereas 10% to 35% of detectable PSA is unbound or free.

Free PSA is a mixture of different molecular forms of PSA. The PSA produced by the transitional zone epithelium of prostates with nodular BPH has a high percentage of PSA molecules that have been clipped at amino acid residues Lys 145-146 and Lys 182-183[4]. This enzymatically inactive form of PSA has been named BPSA. BPSA is not elevated in prostate cancer. BPSA is a significant percentage of the free PSA in BPH serum but not in control serum. Prostate cancer producers PSA with either two (-2pPSA) or four (-4PSA) unclipped amino acids from its leader sequence. These molecular forms of PSA are, for the most part, not present in transitional zone epithelium, where BPH occurs. The fraction of -2pPSA in prostate cancer patients ranged from 25% to 95%, whereas that of the biopsy-negative patients was between 6% and 19%. Recent studies analyzing the free PSA content of prostate cancer patients with very high concentrations of total PSA have detected -1, -5 and -7p PSA the clinical relevance of which is is unknown.

FACTORS AFFECTING THE PSA LEVELS

Finasteride will lower PSA by an average of 50%. The reduction in PSA of malignant origin appears to be no greater than that in PSA of benign origin. So in men treated with finasteride, multiplying PSA by two and using norma ranges for untreated men preserves the usefulness of PSA for prostate cancer detection.. But the heterogencity of PSA response to finasteride may make monitoring patients for the development of prostate cancer problematic. The decrease in total PSA after finasteride treatment results from a proportional reduction in free PSA and PSA-ACT. So the percent free PSA and percent complement PSA do not show significant change with finasteride. Surgical or medical castration will lower PSA. often dramatically. Herbal medicines like Saw palmeto (Serenoa repens) and PC SPES may also affect PSA. But in one large randomized trial using Saw palmetto, no impact on PSA was noted[5].

Stenner et al showed no clinically significant change of serum PSA levels after ejaculation in a population screened for carcinoma prostate[6]. Similar results were obtained in both young and old age groups. But Tchetgen et al reported a significant increase in the serum PSA concentration after ejaculation[7]. This change correlated with age and baseline PSA. They recommended that men should abstain from ejaculation for 48 hours prior to having a serum PSA determination. The mean total, free, and percent free serum PSA increased one hour after ejaculation[8]. Mean total PSA levels remained significantly increased 24 hours after ejaculation. Free PSA and percent free PSA decreased to baseline levels by six hours after ejaculation. Chybowski et al found that after digital rectal examination though there was a statistically significant change in the serum PSA level the median change in the serum PSA level (0.4 ng./ml) produced very little alterations in the management decisions[9]. The increase of PSA was mainly due to the increase of free PSA. Complexed PSA seems less sensitive to digital rectal examination (DRE). So free PSA measurement should be done before DRE. The change of percent free PSA after DRE depended on the initial percentage of free PSA. Increases in PSA were significantly great in men whose initial PSA concentrations were less than 4.0 ng./ml.

Total and free PSA values were significantly increased after biopsy and returned to baseline 30 days after biopsy[10]. Immediately after biopsy serum PSA level showed a median increase of 7.9 ng/mL". The free/total PSA ratio was significantly increased one hour after biopsy and significantly decreased eight days after biopsy[11]. Age, prostate volume, number of cores, and digital rectal examination and histoogic finding were not significantly associated with variation in percent free PSA. Prostate size and the presence of cancer had no influence on the duration of PSA elevation following biopsy. Increases in percentage of free PSA were greater in men with malignancy. There was no statistically significant increase in cPSA level after prostate biopsy in patients with prostate cancer although there was a statistically significant but minimal rise in cPSA level in patients with benign histology [12]. *It is recommended that a serum PSA determination should not be obtained at least six weeks after a prostate biopsy"*. Cystoscopy did not produce significant change in total PSA but caused increase in free PSA and thereby changed percent free PSA[13]. Flexible cystoscopy did not produce any change in total and cPSA [12]. The median increase in serum PSA concentration following transrectal ultrasound was 0.3 microgram/L.

Transurethral resection of bladder tumours resulted in a variable rise in serum PSA, with a median increase of 2.6 ng/mL after I day, which returned to normal over 7-14 days. The median increase in serum PSA following transurethral resection of the prostate (TURP) was 13 ng/mL. Inserting a urethral catheter and maintaining it for several days does not result in any clinically or statistically significant change in PSA levels.

There is no statistically or clinically significant increase in PSA after bicycle riding. However, the few participants with an initially elevated PSA had an increase after bicycle riding. Flexible colonoscopy does not adversely affect serum PSA levels. Serum free PSA as well as total PSA is not eliminated by hemodialysis and the slightly elevated levels of free PSA and the free-to-total PSA ratio in uremic patients after hemodialysis may be caused by the concomitant decrease in binding problems[14].

Subclinical prostatitis seen in many of the benign prostatatic hyperplasias can cause PSA elevation. Histologically defined acute inflammation within the prostate is a significant contibutor to elevated serum PSA levels, especially in patients with small prostates. (<25g)[15]. The PSA level does not correlate with the extent of inflammation but with the disruption of epithelial integrity caused by the inflammatory infiltrate. It causes reduction in percent free PSA as in malignancy. After treatment with antibiotics the PSA level returns to normal level. Morote et al reported that histological inflammation had no significant influence on total and percent free serum PSA 16.

PSA FOR PROSTATE CANCER DETECTION

The likelihood of having prostate cancer in an average man older than 50 years is 27%, 20 to 30% and 42 to 64% if his PSA levels are 2.5-4,>4 and> 10 ng/mL respectively. [1-17] PSA is currently the best single test for early prostate cancer detection. Combination of PSA and digital rectal examination improves the overall rate of prostate cancer detection when compared with either test alone. Transrectal ultrasonography adds little to the combination of PSA and DRE[17].

Optimal PSA Cut-Points To detect prostate cancer with reliability at an early stage, a low serum PSA cut-off level of 4 ng/mL is used during screening. Use of this low cut-off value, however, s associated with an appreciable risk (65%) of false-positive results, thus diminishing its predictive value and resulting in unnecessary biopsies for those with benign conditions. Approximately 25% to 30% of men with BPH and 80% with proven prostate cancer have serum PSA concentrations below

4 ng/mL18. Between 13 and 20% of men with normal serum PSA levels (2.6 to 4ng/ml) will have clinically detectable prostate cancer within a 3 to 5 year period. Since 30 to 509% of men with serum PSA levels between 4 and 10 ng/ml have extraprostatic disease at surgery identifying these early nonpalpable cancers would likely result in improved cure rates. More study is needed to determine whether lowering of the PSA cut-point would improve long term survival and to determine how many extra biopsies would be required to do so.

Optimal Screening Protocol American Urological Association recommends that PSA be done in all men 50 years of age and older as part of an annual prostate examination and that PSA screening should begin at the age of 40 in men at high risk. African-American men have a substantially increased incidence of prostate cancer compred to age matched white men. In addition, African-American men tend to present with higher grade and stage tumors and have a high mortality. So screening should begin at the age of 40 in these groups. Studies have shown that a man's relative risk of prostate cacer diagnosis is 2-3 fold higher if he has a first degree relative with prostate cancer. Screening of such individuals should also begin before 50 years.

Longitudinal screening studies has shown that a man's PSA level at the time of entry into a study is a strong predictor of his risk of eventually being diagnosed with prostate cancer[19]. For example, men with a total PSA <2.5 ng/ml has a 1.0 percent chance of being diagnosed with prostate cancer[19]. For example, men with a total PSA <2.5 ng/ml has a 1.0 percent chance of being diagnosed with prostate cancer within four years of follow up compared to 12.7 percent for men with PSA levels between 2.6 and 4.0 ng/ml and 38.4% for men with PSA levels between 4.1 and 10.0 ng/ml. A 2 years PSA testing interval is not likely to miss a currable prostate cancer when the initial PSA level is less than 2.0 ng/mL. Serial PSA determinations lead to a decrease in detection of pathologically advanced disease.

Changing Trends in the 'PSA Era' In USA where prostate cancer incidence rates increased greatly between 1988 and 1922, declined sharply between 1992 and 1995, and leveled off from 1995 to 1999[20]. This trend reflects extensive use of prostate-specific antigen (PSA) screening in a previously unscreened population and the subsequent increase in diagnosis of early stage cancers[21]. The decline in incidence from the years 1992 to 1995 may be the result of a cull phenomenon whereby repeat screening in a relatively cancer-depleted population resulted in lower prostate cancer case yields. The new baseline incidence for the year 1995 to 1997 is higher than the incidence before the PSA era and raises questions about increases in overdiagnosis and overtreatment of prostate cancer[22].

Most of the tumors (80%) detected in the PSA era belongs to the moderately differentiated group[22]. The decline in the rate of distant stage cancer along with substantial increases in local and regional stage disease demonstrate a powerful stage migration effect during the PSA era. The mean age at diagnosis has dropped substantially in the PSA era. The average lead time resulting from a PSA-based diagnosis is approximately 3 years when compared with pre-PSA detection methods. The relative mix of clinically beneficial lead time and undesirable lead-time bias in the PSA era will be reflected in the steepness of changes seen in future mortality rates. But a 5 year cutoff window is probably too narrow to detect changes in mortality rates owng to localized disease because few localized cancers would have resulted in death. Unfortunately, wider cutoff windows would prevent presentation of mortality data for PSA-era cases alone. there is an abrupt upward trend in prostate cancer mortality from 1987 through 1991, consistent with an increase in attribution bias. Fewer men are dying of prostate cancer as a result of PSA-mediated early detection and enhanced treatment. Nevertheless, the declines in mortality are small when compared with the large increase seen in the number of men with prostate cancer who are diagnosed and treated. This comparison of

the large magnitude of change in incidence versus the relatively small change in mortality is additional evidence of a substantial increase in the overdiagnosis and overtreatment of prostate cancer.

Does Screening do more good than harm? Some studies have found that a large proportion of patients diagnosed with clinically localized prostate cancer who did not recive early aggressive treatment still had favorable clinical outcomes and normal life expectancies[23]. Several reports show that a very large proportion of cancers detected through PSA testing are likely to be clinically important, but that PSA testing is unlikely to detect many of the more prevalent small-volume histologic cancers [24,25,18]. Only a small proportion of prostate tumors detected by PSA and treated with radical prostatectomy are subsequently found to be clinically insignificant [18,25,26,27]. There is currently no universally accepted definition of what is clinically significant or insignificant prostate cancer[17].

There is no evidence in the form of a randomized control trial supporting the managemenent of early prostate cancer. Randomized trial by the Scandinavian Prostatic Cancer Group Found a statistically significant difference in the risk of death due to prostate cancer after radical prostatectomy as compared with watchful waiting, yet there was no significant difference between the two groups in the overall survival rate[28]. The result of PIVOT (Prostate Intervention Versus Observation Trial) study is awaited. American Cancer Society and American Urological Association recommends screening for prostate cancer but recommendations against PSA screening have been issued by the U.S. Preventive Services Task Force, the Canadian Task Force on the Periodic Health Examination and the Canadian Urologic Association.

Thus a conclusive risk-benefit analysis for prostate cancer screening is not available at this time. The screening, and management of subsequently diagnosed prostate cancer can be harmful to the individuals. So there is an obvious need to provide conclusive information before the application of screening tests to men who wish to be screened. Patient should be conuselled without any bias and an informed consent may be obtained.

PSA Density Benson et al introduced the term PSA density in 1992 to correct PSA for prostate volume since prostate cancer releases more PSA per volume unit into the circulation than BPH. PSA density is defined as the total serum PSA level (ng/ml) divided by the prostate volume (c.c). In Benson's study PSA density for prostate cancer was 0.581 while that for BPH was 0.004. Estimation of PSA density need accurate assessment of prostate volume by TRUS which is relatively expensive and less accurate. Moreover the epithelium-to-stroma ratio varies considerably between individuals and only the epithelium produces PSA. So the estimated BPH volume does not necessarily correlate with serum PSA levels.

Seaman et al successfully used a cut off PSA density of 0.15 to discriminate between cancer and benign prostatic hyperplasia[29]. But Catalona et showed that approximately 50% of prostate cancers would have been missed if cut off of 0.15 is used[30]. However, Catalona et al has proved the usefulness of PSA density for predicting prostate cancer in men who had had a prior negative biopsy, a serum PSA level of 4.1 to 10.0 ng./ml. and benign findings on prostate examination[31].

Since the majority of prostatic enlargement is the result of growth in the transition zone, adjusting for transition zone volume (Transition zone PSA density) may be a more valuable method of calculating PSA density. In patients with PSA levels of 4.0 to 10.0 ng/ml and a normal digital rectal examination, a cut off of 0.3 avoided 51% of biopsies missing only 12 percent of the cancers [32]. Due to the lack of reproducibility between centers and inherent inter examiner difficulties for accurately determining prostate volume using transrectal ultrasonography, transition zone PSA remains an investigative tool for detecting prostate cancer[1].

PSA Velocity PSA velocity is determined by the equation$^{1}/_{2}$* (PSA2-PSA1/Time^{1} in years)+(PSA3-PSA^{2}/time2 in years). At least three PSA measurements should be obtained during a 2-year period or at least 12 to 18 months apart to obtain maximal benefit using velocity measurements. A PSA velocity of 0.75 ng/ml. per year or greater was strongly suggestive of cancer. The limitations of PSA velocity are that it is difficult to calculate, PSA is not cancer specific, and PSA varies significantly with time and different assays.

Age specific Range and Racial Variations A lower PSA cut off in younger men could result in additional unnecessary negative biopsies and greater health care costs. But it detection of cancer in younger men with early, organ confined tumors who would benefit from definitive local therapy. Raising the PSA cut off level in older men could result in fewer cancers being detected but avoids unnecessary negative biopsies. On using the age specific range there was an 8% increase in the number of positive biopsies in men younger than 59 years''. In men older than 60 years this resulted in 21% fewer biopsies while missing 4% organ confined tumors. But Catalona et al has noted the standard PSA cut off (0-4 ng/ml) to optimal for all age groups[34].

PSA levels are higher in blackmen when compred to the whites. Age specific PSA vary slightly in the Asians when compared to the blacks and white men. Additional studies are needed to characterize further differences in age specific reference ranges demonstrated between racial groups and the clinical usefulness of these ranges for early detection of prostate cancer1.

Free PSA Men with prostate cancer has a lower percentage of free PSA when compared with men without prostate cancer. Although not completely understood, it is thought that the loss of tissue architecture that results from disorganized cancer growth leads to the release of enzymatically active forms of PSA directly into the bloodstream. This in turn, is thought to facilitate the binding of protease inhibitors such as PSA-ACT and PSA-AMG to PSA. PSA that is produced by BPH, on the other hand, is secreted into the seminal spaces from where it must leak back through the intercellular space to reach the circulation. This exposes BPH-produced PSA to proteases. Cleaved forms of PSA are not able to bind to proteas inhibitors such as PSA-ACT or PSA-AMG[35].

The probability of having prostate cancer increases as the percentage of free PSA decreases[1]. In men with intermediate PSA values (4-10ng/ml) the main goal has been to decrease the number of inappropriate biopsies for detecting prostate cancer. Sesveral authors have recommended the use of different cut off values of percent free PSA ranging from 14% to 28% as indication for biopsy. High cut off vlues increase sensitivity but reduce specificity and increase the number of negative biopsies. Lower cut off values almost certainly result in some missed cancers. So optimal cut off has to be identified. However, it appears that cancers missed by percent free PSA measurements are more likely to be indolent tumors as several studies has shown a strong inverse correlation between percent free PSA and tumor aggressiveness. Percent free PSA measurements may be particularly useful in determining the need for repeat biopsy in a man who has had one negative prostate bbiopsy but has a persistently elevated total PSA level.

Several investigators has studies the role of percent free PSA in improving the sensitivity of cancer detection in cases with PSA levels between 2.6 and 4 ng/ml by using different percent free PSA cut off values. Studies have shown that percent free PSA declines in men with prostate cancer several years before diagnosis and may be able to detect cancer earlier thatn total PSA[37].

Catalona et al has recommended using a single cutoff (25% free PSA) in detection of prostate

cancer regardless of prostate size[38]. But Percent free PSA density is found to be more specific than percent free PSA in distinguishing benign from malignant disease in men with a normal digital rectal examination and an intermediate PSA level[39]. Catalona et al demonstrated that percent free PSA was effective in detecting cancers in both white and black subjects with serum PSA levels between 4 and 10 ng/ml[40]. But fowler et al found that on evaluating men with total PSA ranges of 2.5 of 10ng/ml diagnostic performance of percent free PSA in black men was significantly worse [41].

There is a significant variability when various combinations of free and total PSA assays from different manufacturers are used. Serum sample handling is important in preserving the immunoreactivity of free PSA. Therefore the serum should be processed and refrigerated within 3 hours of blood collection. Also serum should be kept at 70 degrees C for long term storage to preserve the immunoreactivity of free PSA Repeat freeze-thaw cycles did not decrease the immunoreactivity of free PSA significantly.

Complexed PSA (cPSA) Complexed PSA (cPSA) showed an increase in specificity in the detection of prostate cancer without loss of sensitivity when used in patients with normal and abnormal ranges of PSA. Cutpoint of 2.1 ng/mL for cPSA provided a specificity of 34.2% and sensitivity of 86%. Fourteen percent of biopsies would have been avoided without altering the sensitivity when compared with total PSA with a cut point of 2.5ng/mL[42]. complexed PSA density has been found to modestly enhance the usefulness of cPSA in detecting prostatic cancer in patients with serum PSA level from 4-10 ng/mL. But in the 2.5-4ng/mL range of serum PSA, percent cPSA performed better than other indices of cPSA.

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) for PSA The application of RT-PCR to clinical urology has focused on prostate cancer staging primarily to detect hematogenous extraprostatic disease. Circulating PSA message has been detected by RT-PCR in as many as 88% of men with known prostate metastases. Until further study defines its clinical usefulness RT-PCR should remain a research endeavour and not be used for decision making.

ProstAsure Index The values from four variables, (patient age, serum PSA concentration; serum prostatic acid phosphatase (PAP) level, serum creatine kinase concentration) which are biologically and medically independent, are analysed in an interrelated way, using a very sophisticated biostatistical-mathematical method known as 'neural networks. The ProstAsure ™ Index values can range from less than 0.00 t greater than 1.0, with the reference range (normal) being a value of 0.5 or less. In general, the ProstAsure ™ Index values are divided into four zone: Zone 1: <0.0 Zone 2: 00-0.5; Zone 3: 0-5-1.0 Zone 4:> 1.0. The risk of prostate cancer increases the higher the zone: from 2% for Zone 1, 16% for Zone 2, 33% for Zone 3, to 90% for Zone 4. Individuals with a ProstAsure TM Index value in Zone 3 or 4 (>0.5) should be considered for a transrectal) ultrasound guided biopsy of the prostate to determise whether the gland is harbouring a cancer.

In men with normal PSA ProstAsure™ Index could indentify prostage cancer with a sensitivity of 71% and specificity of 86%[44]. The ProstAsure ™ Index appears to be able to detect prostate cancers that are associated with low PSA value-tumors that are likely to be of low volume, organ confined and curable by today's treatments. ProstAsure ™ Indexcan detect small cancers as readily as the larger cancers. It has a 92% senstivity for detecting cancers <4cc in volume[45]. Babaian et al found that ProstAsure™ Index could identify prostate cancer with a sensitivity of 93% and specificity of 81% which was higher than that shown by free. PSA [46]. ProstAsure left fewer cancers undetected (7%) compared to free PSA at the 15% cutoff (20%)

ROLE OF PSA IN PRETREATMENT STAGING

Based on immunohistochemical studies, PSA expression decreases with increasing Gleason grade. Serum PSA level per gram of tumor decreased with increasing Gleason score. But serum PSA concentration has been shown to be proportional to the volume, Gleason score, and stage of prostate cancer. This paradox may be explained by the increased release of PSA into the serum that occurs with the increased disorganization of epithelium associated with higher-grade cancers. Larger tumor volume at the time of presentation in patients with higher-grade cancers also account for this.

PSA levels show a linear relation with tumor stage[47]. (Partin AW97) In patients with PSA levels greater than 50 ng/mL. only 9% had organ-confined desease while 27% had positive lymph nodes. But in patients with a PSA level of less than 4 ng/mL64% had organ-confined disease while less than 1% of patients had positive lymph nodes. Thus PSA is an excellent predictor of pathologic stage when very high or low values are considered. But it is a poor marker for the prediction of prostate cancer stage and prognosis when applied to patients with PSA concentrations below 10 ng/mL[48]. PSA has concordance index of 0.55 to 0.66 when used alone to discriminate preoperatively between pathologic T1 and T2 disease[49]. Furthermore, when analyzed on an individual basis, PSA is able to predict ECE, seminar vesicle invasion, or lymph node involvement only 50% to 55% of the time[48].

PSA-based nomograms In 1993, Partin et al introduced "Partin Tables'' which predict the probability of organ confined disease, ECE, seminal vesicle involvement, and pelvic lymph node status based on Gleason score, clinical stage, and serum PSA[47]. This nomogram was found to have a concordance index of 0.84 for the prediction of node positive disease and 0.76 for the prediction of organ-confined disease. In 2001, the tables were updated to reflect the shift toward lower grade, stage, and PSA at the time of presentation[50]. The Baylor College of Medicine group developed a preoperative nomogram that predicts 5-year biochemical recurrence with a concordance index of 0.79[51]. Kattan et al produced nomogram based on all the prognostic factors- pretreatment serum prostate-specific antigen level, specimen Gleason sum, prostatic capsular invasion, surgical margin status, seminal vesicle invasion, and lymph node status 52. Using this model one can approximate the 7 year biochemical recurrence-free rte probability after radical prostatectomy.

Percentage free PSA was a stronger predictor of postoperative pathologic outcome than was Gleason score. A value of 15% (PSA was found to discriminate between favourable and unfavourable pathologic outcome[53]. Nevertheless, two later studies [49,54] showed that percent free PSA had a predictive value in univariate analyses that was similar to that of total PSA and Gleason score. In multivariate analyses using PSA, Gleason score, and clinical stage, however, %fPSA failed to provide additional staging or prognostic data. These divergent results may be due to the fact that staging utility of percent free PSA is highly dependent on multiple parameters of the study population including age, race, and distribution of total PSA levels.

CT or MRI scans are generally not indicated in the staging of men with clinically localized prostate cancer when the PSA is <25.0ng/ml[12]. The risk of nodal disease is generally so low when PSA is less than 25ng/ml and these iunvestigations are not very sensitive to identify the early changes. Patients with PSA concentrations of <10.0ng/ml. 10.1-15.0ng/ml and 15-1-20.0ng/ml showed an incidence of 0.8%, 0.6% and 2.6% positive bone scan respectively'. Bone scans are generally not necessary in patients with prostate cancer who have a PSA less than 20.0 ng/ml unless the history or clinical examination suggests bony involvement. As some high-grade prostate cancers are PSA-negative, it is reasonable to consider bone scans at the time of diagnosis when the patient has poorly differentated or high-grade, stage> T3 prostate cancer, even if the PSA is <10.0 ng/ml.

In patients with PSA of less than 4.0 ng/ml, although only 1% had lymph node involvement and 3% had seminal vesicle involvement, 32% had evidence of capsular penetration and thus were at greater risk of disease reccurrence following treatment[36%]. Elevations in PSA between 4.0 and 10.0 ng/mL, as compared with PSA levels of less than 4.0 ng/mL. Increase the odds of clinically significant, intracapsular prostate cancer with preoperative PSA levels of 4.0 to 10.0 ng/mL were found to be extraprostatic[47]. More than 80% of men whose preoperative serum PSA exceeded 20.0 ng/mL had cancers that were not organ-confined. Approximately 5% of men with PSA levels of 4.0-10.0 ng/mL had either seminal vesicle or lymph node involvement increasing to approximately 15% for men whose PSA was between 20.0 and 30.0 ng/mL.

PSA level often help in taking appropriate therapeutic dicisions. Patients with serum PSA levels of less than 10.0 ng/ml are most likely to respond to local therapy. Pelvic lymphadenectomy for T1-2 prostate cancer may not be necessary if PSA< 10.0 ng/ml or if PSA<20ng/ml and Gleason score is <6. As pelvic lymph node dissectin does add cost and morbidity when performed in association with radical retropublic prostatectomy, it is wholly appropriate to omit lymphadenectomy in such patients.

Patients with cancer with higher percent free PSA values (> 15%) or lower PSA density values (0.15 or less) tended to have less aggressive disease[40]. PSA-transition zone levels were significantly higher in extracapsular disease than organ confined cancers[56]. Complexed PSA was equivalent to tal PSA in predicting organ-confined disease[57]. Complexed PSA density and total PSA density provides good staging accuracy[58].

ROLE OF PSA IN MONITORING AFTER THERAPY

Longitudinal measurement of serum PSA levels has been shown to be the most sensitive method of detecting and monotoring cancer persistence, relapse and progression following radical prostatectomy. It is generally accepted that radical prostatectomy should remove all prostatic tissue and the serum PSA should drop to an undetectable level within a month of surgery if the disease has been eradicated. The clinical evidence of local or distant disease is preceeded by months to years with biochemical evidence (detectable PSA) of cancer return.

Using the original Tandem R PSA Assay it was established that the residual cancer detection limit (RCDL) of this assay was 0.4ng/ml (0.2-0.6 ng/ml), because all patients who reached this value following prostatectomy subsequently developed continued biochemical progression. The combination of ultrasensitive Tosoh assay with serum concentration techniques lowered the RCDL to 0.02 ng/mL allowing lead time recognition of biochemical failure following prostatectomy by approximately 2 years over the standard commercial PSA assays with RCDLs of 0.3ng/mL. Use of more sensitive assays allows earlier calculation of PSA and presumably tumor doubling times which can influence decisions regarding further aggressive local therapy. When using these very sensitive assays the serum PSA may not nadir for upto three months following surgery. Urinary PSA has been examineed as a means of detecging locally recurrent cancer following prostatectomy. Unfortunately local secretion of PSA by the periorethral glands prevents urinary PSA levels from becoming trul undetectable even in patients felt to be cured by radical prostatectomy and in cystoprostatectomy controls.

Partin et al has showed that 50% of men developing distant metastasis have a detectable PSA <I year following surgery and no patient who developed a local recurrence alone had a detectable PSA

within 6 months of surgery[59]. 94% of men who developed local cancer recurrence had a PSAV <0.75 ng/ml/yr at one year following surgery comared to 46% developing distant disease. In patients with post prostatectomy doubling times of <6 months. 33% developed clinical distant disease. 3% clinical local recurrence, and 64% no evidence of clinical recurrence. Conversely, of patients with post-prostatectomy PSA doubling times of >6 months, 2% developed clinical distant disease, 18% clinical local recurrence, and no clinical disease in 80%. They used multivariate analysis and found that PSA doubling time was a better indicator of site and time to clinical recurrence than was preoperative PSA level, sugical specimen Gleason score, or pathologic stage. The Stanfod group has concluded that in post-prostatectomy biochemical failures, the PSA doubling time represeents the aggressiveness of the original tumor cells, wheras the time to PSA detectability reflects the extent of residual disease following surgery[60].

The effect of prostatic bed massage on both serum and urinary PSA levels in post-prostatectomy biochemical failures has been examined. Answer reported that only 5% of biochemical failures patients with vigorous anastamotic massage had an ensuing rise in serum PSA levels five minutes post massage eventhough 83% had recurrent cancer. A ratio of post massage urinary PSA/pre massage urinary PSA of ?2.5 accurately predicted all patients with biopsy confirmed local recurrence following prostatectomy.

In patients with increasing serum PSA after radical prostatectomy current serum PSA is the best predictor of the bone scintigram result. The probability of a positive bone scintigram was less than 5% until PSA increased to 40 to 45 ng/ml. The median length of time between PSA recurrence and death from prostate cancer ranges between 5 to 12 years depending upon the initial Gleason score.

Following radiation, PSA falls slowly reaching a nadir value at a median of 17 months. What constitutes an acceptable serum PSA after radiotherapy is a matter of debate. American Society for Therepeutic Radiology and Oncology (Astro) has produced guidelines in 1997 which defines biochemical recurrence on the basis of three consecutive rises in serum PSA above nadir. 89% of patients with this pattern go on to have a fourth increase. No absolute level of PSA was found to separate failure from success. This group recommends that PSA be measured no more often than every 3 to 4 months during the first two years and semiannually therafter to detect meaningful rises beyond the intrinsic variability of the assay. The date of failure should be the midpoint between the post irradiation nadir PSA value and the first of the three consecutive increases.

PSA bounce was defined as an initial increase in serum PSA of at least 0.5 ng/mL, followed by a decrease to pre-bounce baseline serum PSA values no more than 60 months after external beam radiation therapy. PSA bounce was unrelated to age, race, pretreatment PSA. Gleason score, clinical T stage or radiation dose. Of men with prostate cancer treated with external beam radiation therapy 12% experienced a transient increase in PSA (PSA bounce) followed by a return to pre-bounce levels after radiation. The PSA bounce phenomenon was not predictive of time to biochemical recurrence.

Serum PSA levels in patients with metastatic prostate cancer who receive and rogen deprivation should decline. Both nadir PSA and the percent decline at 3 and 6 months predict progrression free survival. Patients whose serum PSA level becomes undetectable and those whose PSA decreases by 90% or more at 3 and 6 months are more likely to experience a prolonged progression-free survival[17]. Similarly, patients who achieve a 50% or greater fll in PSA following second line therapy have improved survival[61].

The pre-RT PSA is the most important single parameter determining the success of salvage RT[62]. A PSA level less than 2 ng/mL correlated with a 74%4-year second biochemical relapse-free rate

versus only 22% if the pre-RT PSA was greater than 2 ng/mL. Patients with positive seminal vesicle invasion had a 50% chance of being free of a second PSA relapse if the pre-RT PSA was less than 2 ng/mL.

Conclusions

When PSA was introduced clinically in 1986 the impact that this tumor marker would have on detecting, staging and monitoring prostate cancer was not fully understood. This has become the most commonly used tumor marker in oncology due to its organ specificity. The developments in research has always been to make this molecule as cancer specific as possible. But interestingly the importance of detecting and early prostatic cancer has not been convincingly proved by randomized studies till now. The results of these ongoing studies may alter the future of this wonder molecule.

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Asymptomatic microscopic hematuria in adults-Guidelines for evaluation

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There are guidelines regarding the evaluation and management of gross hematuria. However there is controversy regarding the diagnosis, evaluation and treatment of asymptomatic microscopic hematuria (AMH). The American Urological Association has brought out a best practice policy to address these issues and the recommendations are summarised in this article.

There is no general consenus about when to test for asymptomatic microscopic hematuria in the primary care set up. The presence of the risk factors for significant underlying diseases should guide the physician. These include greater than 40 years, tobacco use, analgesic abuse, pelvic irradiation and exposure to occupational toxins like benzenes and aromatic amines. Of the patients who undergo full urologic evaluation for asymptomatic hematuria, a cause can be determined in 32-100%, depending on the population studies. Although bladder cancer is the most common malignancy detected in patients with microscopic hematuria, no major organisations recommend the screening for bladder cancer in asymptomatic patients.

Definition and detection: The degree of hematuria can be measured by determining the number of RBC's/ml of urine (chamber count), by direct examination of the centrifuged sediment (sediment count) and by dipstick examination of the urine. Though the chamber count is more precise and sensitive, the sediment count is preferred as it is less time consuming and easier to perform. Though these counts correlated with acceptable sensitivity, the fact remains that the sediment count is a semi quantitative method and cannot replace chamber count. Urinary dipstricks detect AMH with a sensitivity of over 90%. However the specificity reduced with lower number of red cells. Fase positive results could be due to myoglobin, free hemoglobin or oxidising contaminants like Betadine. Hence a positive dipstick finding should be confirmed by microscopic examination before a full urologic evaluation is done. In patients with low specific gravity, as majority of RBC's lyse, dipstricks may be a more accurate reflection of hematuria than microscopic examination of the urinary sediment.

A freshly voided, clean catch, mid stream sample should be used and the initial determination regarding the presence of hematuria should be based on microscopic examination of the urinary sediment. The standard technique is to centrifuge 10 ml of urine for 5 minutes at 2000 rpm, the sediment is re suspended in 0.5-1 ml of the remaining urine and a drop is examined under high

power. The most commonly accepted definition of microscopic hematuria is> =3 RBC/hpf from 2 or 3 properly collected urinalysis specimens.

PATIENT EVALUATION

Patients with AMH associated with significant proteinuria, RBC cast, dysmorphic RBCs or elevated renal parameters should undergo evaluation for primary renal diseases. The other patients undergo urological evaluation. It is important to get a good history and conduct a proper local examination looking for local causes to explain blood in urine. A catherized sample is taken if it not possible to collect a clean catch without contamination. A comprehensive lab evaluation includes looking for number of RBCs/hpf, presence of dysmorphic RBCs and casts. Presence of proteinuria is noted. Urinary infection indicated by pus cells require culture and appropriate treatment and re-evaluation for hematuria after 6 weeks. Patients with identifiable benign diseases like menstruation, vigorous exercise, sexual intercourse, viral ilness or trauma should have a repeated evaluation after 48 hours and further evaluation is not required if urinalysis is negative for hematuria.

CYTOLOGY

Urothelial cancers are the most commonly detected malignancies with hematuria. All patients with hematuria with or without irritative symptoms having positive cytology or atypical and suspicious cytology require complete evaluation. Voiding cytology is recommended for all patients with risk of transitional cell carcinoma. However in an assymptomatic low risk patient who chooses to undergo a cystoscopy, cytology is optional as the sensitivity is limited in these patients.

IMAGINGS

Imaging is an important component in the initial evaluation of patients with AMH. IVU is still considered by many as the imaging modality of choice for evaluating microscopic hematuria. IVU may have limited sensitivity and most of the times warrant further charecterisation of the lesion. Ultrasonography is an excellent modality for the initial evaluation to guide further imagings and is increasingly used instead of IVU as the initial modality. CY is more widely available and less expensive than MRI and therefore MRI is considered for problem solving in patients who require additional imaging following CT or US. There are no data on the impact of IVU, US, CT or MRI on the management of patients with AMH. In patients with normal renal function and no contraindication to iodinated agents, IVU or CT scan should be the initial imaging modality. Spiral CT is preferred. In low risk patients an alternative is KUB and US. MRI remains a second line test due to its higher cost and limited availability.

CYSTOSCOPY

The role of diagnostic imagings in the detection of bladder pathology is limited. So cystoscopy should be a part of the initial office evaluation of AMH for all adults over 40 years and those under 40 years with risk factors for development of bladder cancer like smoking history, occupational exposure and history of irritative voiding symptoms. Initial cystoscopy may be deferred in those with a low risk for bladder cancer.

ISOLATED HEMATURIA.

These are cases with microscopic hematuria with a negative urologic evaluation and there is absence of systemic disease, significant proteinuria, red cell casts or other evidences of glomerular bleeding. These cases may have stuctural abnormalities on histologic examination of which majority have IgA nephropathy or thin basement membrane disease. The prognosis is excellent in relation to the development of renal failure. As there is no specific therapy in these situations there is a very limited role for renal biopsy in isolated hematuria. However it is necessary to follow these patients for the early detection of develpment of hypertension, renal insufficiency or proteinuria.

FOLLOWUP

At least 8-10% of cases no cause for hematuria is revealed during the initial evaluation. There are studies to show that urologic malignancy is diagnosed in one to three percent these cases of AMH and most of these lesions are discovered within three years of the initial negative evaluation. This evidence suggests that some form of follow up is required. It is important for high risk patients, including those over 40 years of age and patients who use tobacco or have occupational exposures. There is no fixed protocol as most of the recommendations were not rigidly tested. In patients with negative initial evaluation urinalysis, voided urine cytology and blood pressure determination should be done at 6, 12, 24 and 36 months. Immediate urological revaluation is required if patient develops irritative voiding symptoms without infection, hematuria or a positive urine cytology. If none of these occurs within three years, the patient does not require urologic monitoring. Further evaluation for renal parenchymal disease should be considered if hematuria persists and either hypertension, proteinuria, red cell casts or dysmorphic RBCs develop.

Reference:

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Renal artery stenosis-surgical perspective

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Renal artery stenosis (RAS) is a frequently overlooked clinical entity that can cause uncontrolled hypertension and lead to a progressive deterioration of renal function. Increasing awareness of the presentation of different forms of RAS and improved diagnostic techniques has led to much interest in this condition in recent years.

CAUSES OF RENAL ARTERY STENOSIS (RAS)

* Atherosclerostic RAS and Fibromuscular dysplasis (FMD) form the major types of RAS and this review will try to concentrate on the management aspect of these entities.

FMD is made up of a rare group of non-atherosclerotic occlusive conditions that affect different segments of the arterial wall and can cause secondary hypertension.

Revascularization can lead to cure of hypertension or a significant improvement in blood pressure control in most affected patients.

Atherosclerotic RAS, on the other hand is a common disease particularly in association with the presence of atherosclerosis elsewhere. Between 30 and 50% of patients undergoing either coronary or femoral angiography will be found to have atherosclerotic RAS if the renal arteries are imaged. Distringuishing between RAS and renovascular hypertension is important because the former does not always result in hypertension or hypertension may not be related to RAS.

The other rarer causes of RAS are:

* Takayasu's arteritis
* Aortic or renal artery dissection
* Thrombotic or cholesterol embolization
* Collagen vascular disease
* Post renal transplantation stenosis
* Post radiation

PHYSIOLOGY

Unilateral RAS with two functioning kidneys leads to increased renin secretion by the affected kidney and suppression of its secretion by the contralateral kidney. Renin moderates the conversion of angiotensinogen to angiotensin I, which then converts to angiotensin II with the angiotensin-converting enzyme (ACE). Angiotensin II causes vasoconstriction, which leads to hypertension and enhances the adrenal synthesis of aldosterone. Aldosterone causes sodium and fluid retention, which also promote the development of hypertension. The contralateral kidney responds with diuresis leading to sodium and water excretion to restore plasma volume to normal.

In bilateral RAS, renin secretion is increased by both kidneys. Subsequently, plasma volume expands rapidly because of the lack of a healthy kidney that can initiate diuresis. With plasma volume expansion, renin secretion will ultimately decrease. If a renal artery has a stenosis of 60% or greater then the kidneys will progressively shrink in size due to replacement of glomeruli with fibrous tissue. This process is irreversible and gradually leads to renal failure. Reported rates of renal failure in atherosclerotic RAS is usually less than 5% at two years for unilateral stenosis, increasing to 20% for bilateral stenosis and 55% for unilateral occlusion with stenosis on the opposite side.

CLINICAL FEATURES

A high index of clinical suspicion is paramount in the diagnosis of RAS. Patients with general hypertension have a low prevalence of renovascular hypertension. Hints suggestive of renovascular hypertension are

* onset of hypertension before age 30 years or after 55 years
* malignant or accelerated hypertension
* sudden onset of uncontrolled hypertension that was previously well controlled
* evidence of diffuse atherosclerosis
* epigastric bruit
* 'ACE inhibitor kidney' is an interesting clinical phenomenon in RAS.

Angiotensin converting enzyme (ACE) inhibitors are commonly used as first line treatment for hypertension or heart failure. However, these agents may precipitate renal failure in patients with renal artery stenosis. A common scenario in recent years is for elderly patients with hypertension to be statrted on an ACE inhibitor and subsequently present in renal failure.

* unexplained azotaemia
* 'Flash pulmonary edema' in the presence of hypertension and normal left ventricular function.

DIAGNOSTIC METHODS

Numerous invasive and noninvasive tests are available to screen for RAS in appropriate patients. Intravenous urography is no longer used because of poor sensitivity and specificity. Measurement of plasma renin activity is influenced by multiple medications and also has a poor sensitivity and specificity. Several other noninvasive screening tests are available that provide better screening for RAS. The following methods are used widely and offer various levels of benefit.

Duplex ultrasonography

This is the simplest noninvasive screening tests and provides an assessment of the kidney size and structure as well as a functional evaluation of the severity of stenosis. The length of the kidneys by ultrasound can be an indication of the amount of renal parenchyma present. Generally a renal lenght less than 8cm is a contraindication to intervention since there will not be sufficient renal parenchyma left to provide useful function. Sensitivity and specificity is operator dependent but usually exceed 90% in dedicated laboratories. The test is safe in all age groups and in patients will impaired rend function. It is also useful for serial follow-up examination after revascularization.

Captopril renography

This is a highly sensitive and specific nuclear imaging test that can be used to identify critical RAS. However, the test lacks anatomic information about the renal arteries, and its accuracy is reduced in patients with impaired renal function. The test is based on the effect of an ACE inhibitor in decreasing perfusion of glomeruli downstream from a renal stenosis. Essentially the ACE inhibitor blocks contraction of the efferent glomerular arteriole. This arteriolar contraction is a natural response to renal hypoperfusion which normally maintains sufficient perfusion pressure in the presence of decreased inflow from the afferent arteriole by raising the postglomerular resistance. Therefore a renogram performed before and after a dose of captopril will show marked diminution in renal excretion following the administration of the ACE inhibitor. This test has a high sensitivity and specificity but only for high grade renal artery stenosis greater than 50%.

Magnetic resonance angiography

It is entirely a noninvasive technique and has no specific contraindications. Major disadvantages are related to costs, and false-positive artefacts are related to respiration, peristalsis, and tortuous vessels.

Spiral computed tomography with angiography

Spiral computed tomographic (CT) scanning is of value since it provides information about the status of the kidneys and produces a three-dimensional reconstruction of the visceral vessels. Sensitivity of 90% and a specificity of 80% have been reported from using CT spiral angiography when compared to intra-arterial angiography. However, the need for contrast and its related complications limits its usefulness in patients with impaired renal function.

Renal angiography

Contrast angiography is the current diagnostic gold standard and is needed to demonstrate the exact site of the stenosis or occlusion, any polar vessels or segmental artery disease and to plan appropriate revascularization strategies. Angiography must be obtained in two planes including lateral and oblique views because of the common posterolateral origin of the renal arteries. In the patient with renal compromise it is important to maintain adequate intravenous hydration and, if indicated, the use of renal inotropes because of the risk of acute renal failure from contrast load or cholesterol embolisation.

TREATMENT

Medical therapy.

In patients with atherosclerotic RAS medical therapy is an important part of the management process. Aggressive risk factor modification including treatment of hypertension, lipid-lowering therapy and antiplatelet therapy is essential.

Indications for revascularisation:

The timing and strategy of revascularization of patients with RAS is controversioal.

* In general, a stenosis becomes hemodynamically significant when it occludes 70% or more of the renal artery diameter. Revascularization of these patients is associated with preservation of renal function and better control of hypertension, unstable angina, and congestive cardiac failure.
* Patients with bilateral RAS or with stenosed renal artery in a solitary kidney are unlikely to tolerate medical therapy without renal function deterioration and are candidates for revascularisation.
* Likewise, significant deterioration of renal function after starting medications should prompt revascularisation.,
* Frequent flash pulmonary oedema responds well to revascularisation.

Percutaneous revascularization

Percutaneous transluminal renal angioplasty (PTRA) is currently the treatment of choice for patients with FMD. Stenting is usually not necessary and successful PTRA in these patients is expected to result in cure of hypertension or significant improvement in blood pressure control. Recurrence of stenosis and loss of renal function is less than 5%. Atherosclerotic RAS usually involves the proximal renal artery, particularly the ostium, and extends into the aorta. Angioplasty in this group of patients is usually limited by recoil and high rates of restenosis (50%) that could limit the clinical benefit of revascularization. On the contrary, stenting of atherosclerotic renal arteries has a high rate of procedural success and a low rate of restenosis. Renal artery stenting has been associated with better control of hypertension and preservation of renal function and is currently the procedure of choice for patients with atherosclerotic RAS that requires intervention.

Surgical revascularization

The decision to proceed to surgery and indeed the type of surgery to be performed is dependent on several factors. These include

* whether one or both kidneys are involved
* amount of renal parenchymal loss or fibrosis that has occurred.
* The nature of the lesion. Is it directly at the renal ostium or further out along the renal artery or in the subdivided segmental branch vessels?
* condition of the native aorta
* if an extra anatomic bypass is considered, the state of the other visceral vessels must be optimal
* cardiorespiratory fitness of the patient. This is an important consideration if aortic cross clamp ing and direct aortic surgery is planned.

Nephrectomy is the oldest surgical procedure used to treat renovascular hypertension. It remains the option of choice where there is a normal kidney and renal artery on one side with a shrunken (i.e. less than 8 cm) kidney on the other producing large quantities of renin. Nephrectomy may often be required as part of a procedure of revascularisation of a viable kidney on the other side. In this situation measurement of renal vein renin levels is of value with nephrectomy indicated when the ratio of renal vein renin is greater than I. The range of other surgical options include:

Simultaneous aortic graft and renal revascularisation is associated with much higher mortality rates than renal revascularisation alone and should only be undertaken where there is a significant abdominal aortic aneurysm or aortic occlusive disease requiring treatment.

Transaortic renal endarterectomy is an attractive surgical option where the aorta does not need to be replaced. The disadvantage of this approach is that it requires extensive dissection of the visceral aorta and complete aortic cross-clamping with its attendant problems of left ventricular strain and distal embolisation. Most commonly renal endarterectomy is performed using a partial aortic clamping technique with an incision made from the aorta across the origin of the renal artery, careful endarterectomy and inspection of the end point and patch closure. Five-year patencies in the order of 90% can be achieved for renal artery endarterectomy in experienced hands.

Extra-anatomical bypass graft is an attractive option in high risk patients, avoiding any aortic dissection or cross-clamping with access obtained via a simple subcostal incision. The right kidney can be revascularised from the common hepatic artery via the gastroduodenal branch. Where this is not possible use of an interposition saphenous vein graft can be used. On the left side the splenic artery is mobilised at its mid point from the pacreas. Taking care to divide the multiple small branches, careful proximal dissection is made, sufficient to mobilise enough length to reach the divided renal artery for an end-to-end anastomosis. The spleen does not need to be removed since there is sufficient blood supply form splenic collaterals and the short gastric arteries.

Direct aorto-renal bypassing is a commonly used technique using long saphenous vein, PTFE, Dacron or rarely internal iliac artery. The choice of inflow site will depend very much on the condition of the infrarenal aorta which is to be preferred if it is sufficiently disease free. If not the supracoeliac aorta is usually suitable and can be approached via a rooftop abdominal incision. Where more than one renal or visceral artery has to be revascularised simultaneously a bifurcated 12 x 7mm Dacron graft will provide two limbs for subsequent anastomosis onto the stenosed vessels.

Extracorporeal or bench surgery is required for patients with disease in the branch renal arteries since multiple small anastomoses need to be made. Fibrous dysplasis, renal aneurysm, arteriovenous fistulae, dissection, atheroma and arteritis form the bulk of conditions involving these arteries. Removal of the kidney, cooling and preservation exactly as in a renal transplant harvest procedure will allow multiple micro-vascular anastomoses to be performed in safety before autotransplantation of the reconstructed kidney back onto the iliac vessels.

ശ്രീനാരായണ ട്രസ്റ്റ് മെഡിക്കൽ മിഷൻ

കൊല്ലം

സിംസ് ഹോസ്പിറ്റലിൽ NICU

നവജാത ശിശുക്കൾക്കുവേണ്ടിയുള്ള തീവ്രപരിചരണവിഭാഗം

- പ്രത്യേക പരിശീലനം സിദ്ധിച്ച വിദഗ്ദ്ധ ഡോക്ടർമാർ
- വെന്റിലേറ്റർ കെയർ
- എക്സ്ചേഞ്ച് ട്രാൻസ്ഫ്യൂഷൻ
- സർഫാക്ടന്റ് തെറാപ്പി
- 24 മണിക്കൂറും പ്രവർത്തിക്കുന്നു.
- എല്ലാവിധ ജനനവൈകല്യങ്ങളും ശസ്ത്രക്രിയ മുഖേന പരിഹരിക്കാനുള്ള ശിശു സർജറി വിഭാഗവും ഇവിടെ പ്രവർത്തിക്കുന്നു.

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(Rtd. Prof. from SATH)
Paediatric and Neonatal Surgery)

Dr. SHAJI JOSE MD

Dr. AJITHA RAGHAVAN MBBS DCH

Dr. ASWATHY PAVITHRAN MD

Dr. AMBILI N. DCH Dip NB

സെക്രട്ടറി
ഡോ. ജി. ജയദേവൻ

ചെയർമാൻ
വെള്ളാപ്പള്ളി നടേശൻ

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