Recent Advances in Pediatric Urology

Mitra A, Samalad VM, Sripathi V

Department of Pediatric Urology,
Apollo Children’s Hospital, Chennai

Introduction

This article aims to introduce the reader to some interesting innovations in the field of Pediatric Urology over the past few years. The topics are not discussed in detail but are briefly touched upon to stimulate interest. The article is unstructured and each heading may be read independently.

Testes Sparing - enucleation of benign tumours – a norm in children?

Pediatric testicular tumours are uncommon and account for approximately 1% of all pediatric solid tumours. The overall incidence of germ cell tumours is lower in children than in adults. Malignant subtypes like seminoma or embryonal carcinoma are practically never encountered in the pre-pubertal age-group. Teratomas, which are uniformly benign in children, may be malignant in adults (1). In children with bilateral and metachronous lesions, one must endeavour to spare the uninvolved testicular parenchyma and attempt a testicular sparing surgery (TSS). This is aided by the fact that these lesions are quite distinct from normal tissue.

The current European Association of Urology (EAU 2011) Guidelines consider organ-sparing surgery as an alternative to radical orchietomy only for patients with synchronous bilateral testicular tumours, metachronous contralateral tumours, or with a lesion in a solitary testis with normal preoperative testosterone levels, provided that the tumour volume is <30% of testicular volume and surgical rules are respected (2) guidelines for the diagnosis, therapy, and follow-up of testicular cancer were established.

Objective: This article is a short version of the EAU testicular cancer guidelines and summarises the main conclusions from the guidelines on the management of testicular cancer.

Evidence Acquisition: Guidelines were compiled by a multidisciplinary guidelines working group. A systematic review was carried out using Medline and Embase, also taking Cochrane evidence and data from the European Germ Cell Cancer Consensus Group into consideration. A panel of experts weighted the references, and a level of evidence and grade of recommendation were assigned.

Results: There is a paucity of literature especially regarding longer term follow-up, and results from a number of ongoing trials are awaited. The choice of treatment centre is of the utmost importance, and treatment in reference centres within clinical trials, especially for poor-prognosis nonseminomatous germ cell tumours, provides better outcomes. For patients with clinical stage I seminoma, based on recently published data on long-term toxicity, adjuvant radiotherapy is no longer recommended as first-line adjuvant treatment. The TNM classification 2009 is recommended.

Conclusions: These guidelines contain information for the standardised management of patients with testicular cancer based on the latest scientific insights. Cure rates are generally excellent, but because testicular cancer mainly affects men in their third or fourth decade of life, treatment effects on fertility require careful counselling of patients, and treatment must be tailored taking individual circumstances and patient preferences into account.
This appears to be an ‘adult oriented recommendation’. In children most testicular tumors are benign – we would therefore tend towards testicular preservation irrespective of volume of tumor. It has been shown by A Shukla et al that after enucleation, testicular volume restoration is swift and almost complete(1).

The operative technique of enucleation has evolved significantly since it was first described by Stoll et al (3). US-guided needle localization and microsurgical exploration (4) nonpalpable intratesticular tumors are excised using intraoperative ultrasonography and the operating microscope.

MATERIALS AND METHODS: Men with impalpable intratesticular tumors incidentally detected by ultrasonography underwent intraoperative ultrasound guided needle localization and microsurgical exploration of the mass. The testis was delivered through an inguinal incision and placed on ice to minimize warm ischemia. Two rubber shod vascular clamps were placed across the spermatic cord. The tumor was identified by ultrasound and localized with a 30 gauge needle, which was placed adjacent to the tumor. An operating microscope providing 6x to 25x magnification was used to excise the lesion with a 2 to 5 mm margin. Tissue diagnosis was obtained by frozen section. Multiple random biopsies of the remaining parenchyma were done to confirm absent malignancy.

RESULTS: Ultrasound showed incidental, nonpalpable testis tumors in 4 of the 65 men who underwent infertility evaluation and were entered into the microsurgical testis biopsy database between January 1995 and December 2001. All lesions were hypoechoic. Frozen section analysis of the lesions revealed 2 Leydig cell tumors, 1 mass with an inconclusive pathological diagnosis and 1 inflammatory mass. On permanent section the latter allows precise microdissection of the tumour using an operating microscope are recent innovations. The latter allows precise microdissection of the tumour.

CONCLUSIONS: Intraoperative ultrasound guided needle localization with microsurgical exploration is a safe and effective approach to even small impalpable testicular masses. This technique provides the opportunity to identify and remove benign and malignant lesions, and preserve the testis when the lesion is benign. In cases of a solitary testis or bilateral synchronous lesions the technique allows a potentially testis sparing operation for small malignancies.

Corpora sparing clitoral recession in feminising genitoplasty

This procedure should be part of the arsenal of every reconstructive urologist. In children with Congenital Virilising Adrenal Hyperplasia, clitoridectomy (the removal of both the corpora and the glans) was done till the late 1980s as it was wrongly believed that it would have no great long-term effect on sexual function.

As the understanding of the clitoral anatomy, its physiology and its unique role in sexual gratification improved, techniques to preserve the blood and nerve supply to the clitoris were developed. The paired clitoral corpora were removed (thereby reducing its size) but the glans and its innervation was preserved(5).

Pippe Salle et al have described a technique of corpora sparing dismembered clitoroplasty(8) such as recession or partial resection. However, these techniques risk decreasing clitoral sensation or causing painful erections. Moreover, irreversibility continues to be the principal problem that fuels patient, surgeon and societal anxiety in the management of this challenging developmental issue. We describe a new technique, corporeal sparing dismembered clitoroplasty, that dismembers the corporeal bodies and preserves all clitoral structures.

MATERIALS AND METHODS: After obtaining full informed consent and institutional review board approval 8 consecutive patients with clitoral enlargement underwent corporeal sparing dismembered clitoroplasty. Five girls had congenital adrenal hyperplasia (Prader IV and V in 4 and 1,
respectively which involves retaining the corporal bodies rather than excision at their bifurcation. Corpora preserving clitoroplasty demonstrated that cosmetically acceptable feminizing genitoplasty can be performed in children with disorders of sexual differentiation (DSD) but still be potentially reversible at puberty or thereafter.

**Minimally Invasive Surgery (MIS) in Pediatric Urology**

The term “Minimally invasive techniques” has now come to encompass a large number of modalities in pediatric urology, from sub-ureteral injection for abolishing vesicoureteric reflux to robot-assisted laparoscopic pyeloplasty. There is no doubt a dearth of well-planned randomized studies comparing the relative benefits of MIS over standard open techniques. While there are enough publications detailing the evolution of MIS and techniques in our field, a few points which are rarely brought to the fore are worth mentioning. Firstly the pursuance of MIS should not be at the cost of open surgical training for residents especially in index cases. Simulators and wet labs may help circumvent this particular problem. However the ethics of operating for the first time on a live patient using a technique practised on a simulator is an unanswered question. The medico-legal implications of such training and surgery should be seriously questioned. Secondly, blind persistence with a MIS technique in reconstructive procedures while keeping the child under anaesthesia for a prolonged period of time should be strongly discouraged.

Single-Incision Laparoscopic surgery (SILS) and Natural Orifice Transluminal Surgery (NOTES) are not applicable in children as the perceived advantages are small when compared to the risks of an adverse / inadequate outcome.

**Role of robotics – revolutionised minimal invasive management**

Robotic-assisted laparoscopic surgery offers the benefits of laparoscopy with reduced anesthesia time and ease of suturing. This has led to its widespread use for many common pediatric urological conditions. The day is not far off when it may become the MIS procedure of choice even in infants.

**Robotic Assisted Laparoscopic Pyeloplasty (RALP)**

Conventionally, the gold standard surgical method for the treatment of pelviureteric junction obstruction (PUJO) is open dismembered pyeloplasty. The steps of surgery have been successfully translated into the minimally invasive approach and RALP is the natural extension of laproscopic pyeloplasty. It is the most commonly reported robotic procedure in children to date. A transperitoneal or retroperitoneal approach can be used depending on the surgeon’s preference.

The advantages of robotic surgery have become increasingly apparent, especially with regard to intra corporeal suturing and a shortened learning curve. A growing body of evidence suggests that RALP is appropriate for small infants and reoperation after a failed pyeloplasty. The bottom line is that robotic technology has allowed more surgeons to offer a minimally invasive approach to their patients, compared to the limited number of surgeons able to perform a pure laparoscopic pyeloplasty.

**Extravesical ureteric reimplantation**

While open surgery remains the gold standard definitive therapy for VUR, there has been increased interest in minimally invasive therapy for VUR, including endoscopic subureteral injections and minimally invasive surgery. Extravesical ureteric reimplantation and the recent development of robotic assistance, laparoscopic treatment of vesicoureteral reflux has gained popularity. We sought to evaluate our initial experience with pediatric robotic assisted laparoscopic intravesical and extravesical ureteral reimplantation, and to compare outcomes with the open technique.

**PURPOSE:** Surgical treatment may be required in some patients with vesicoureteral reflux. With the recent development of robotic assistance, laparoscopic treatment of vesicoureteral reflux has gained popularity. We sought to evaluate our initial experience with pediatric robotic assisted laparoscopic intravesical and extravesical ureteral reimplantation, and to compare outcomes with the open technique.

**MATERIALS AND METHODS:** A retrospective chart review was performed on all patients who underwent robotic assisted laparoscopic ureteral reimplantation between 2007 and 2010. Comparisons were made with a case matched cohort of patients who underwent the open technique. The groups were compared using t tests for numerical variables and chi-square comparisons or Fisher’s exact test for categorical variables. A Kaplan-Meier model was used to compare success rates.

**RESULTS:** A total of 19 patients underwent intravesical and 20 underwent extra vesical robotic assisted laparoscopic ureteral reimplantation during
the study period. They were compared to 22 patients undergoing intravesical and 17 undergoing extra vesical open ureteral reimplantation. Although the robotic assisted approach was associated with a longer operative time (p < 0.001. The laparoscopic approach, though as effective as open surgery, has not been widely adopted due to increased technical complexity. Robot assisted laparoscopic extravascular ureteric reimplantation (RALEUR) has sparked a renewed interest in minimally invasive surgery for the correction of VUR (13) 20 open and 20 RALUR procedures were completed by a single surgeon at our institution. Gender and VUR grade were similar in both cohorts. Operative times were longer in the RALUR group, but postoperative opioid use (morphine equivalents).

A recent comparative analysis of postoperative outcomes in a cohort of 92 patients – 57 and 35 unilateral and bilateral RALUR, respectively reported no significant differences in terms of postoperative complications including incidence of UTIs, presence of new voiding dysfunction or urinary retention. It was concluded that RALEUR is a safe technique to use in the surgical correction of unilateral VUR and that bilateral extravascular RALUR is not associated with an increased risk of postoperative morbidity when compared with unilateral surgery (14). Preoperative characteristics, and postoperative outcomes were analyzed. Patients with postoperative febrile urinary tract infection (UTI. If tapering is required this can be done in-situ or by exteriorisation via a lower abdominal port site.

Robotic assisted nephrectomy and heminephrectomy

Partial and total nephrectomy have both been performed by transperitoneal and retroperitoneal approaches using the robotic system. No comparative studies of robotic and laparoscopic or open nephrectomy in children had been conducted until recently. Performing a robot-assisted total nephrectomy has been debated, as the procedure is excessively expensive and does not offer any added advantages over conventional laparoscopy (18) the unique and delicate movements generated by the robotic system make this technology ideal for children who often require reconstructive procedures. We critically review the current role of RALS in paediatric urology and to analyse the published data, with a special emphasis on the most common applications. We also propose a structured plan to expedite training and the surgical ‘learning curve’.

OBJECTIVES: To critically review the current role of robot-assisted laparoscopic surgery (RALS). The robotic approach could be more valuable for partial nephrectomy, which is technically more difficult and the enhanced visualization and dexterity of a robotic
Other procedures that have been performed routinely include bladder diverticulectomy, uretero-ureterostomy, ureterocalycostomy, ureterolithotomy and procedures on the bladder neck. Robotic paediatric procedures are evolving. Available literature and results have been encouraging and the advantages of this approach are quite obvious. But further large randomised studies are required to compare the operating times and outcomes in comparison to the laparoscopic approach (15), three-dimensional operating view and an improved degree of freedom. Robotic surgery is performed for a wide range of surgeries in urology, which include radical prostatectomy, radical cystectomy, and ureteric reimplantation. Robotic paediatric urology is evolving. The major hindrance in the development of paediatric robotics is, first, the differences in practice patterns in paediatric urology compared with adult urology thereby making development of expertise difficult and secondly it is challenging to conduct proper studies in the paediatric population because of the paucity of cases. The difficulties in conducting these studies include difficulty in designing a proper randomised study, difficulties with blinding, and finally, the ethical issues involved, finally the instruments although in the phase of evolution require a lot of improvement. In this article, we review the relevant articles for paediatric robotic surgery. We emphasise on the technical aspects and results in contemporary paediatric robotic case series. DOI: 10.4103/0972-9941.147689, ISSN: 0972-9941, note: PMID: 25598599, nPMCID: PMC4290118, shortTitle: "How small is small enough?", journalAbbreviation: "J Mínim Access Surg", language: "eng", author: [{"family": "Ganpule", "given": "Arvind P."}, {"family": "Sripathi", "given": "Venkat"}], issued: {"date-parts": [{"2015", 3}]}, schema: "https://github.com/citation-style-language/schema/raw/master/csl-citation.json".

Pediatric Surgical Uro-Oncology

Radical excision of tumour in Neuroblastoma (NB)

Neuroblastoma (NB) is the most common solid tumour of childhood and the most common malignancy in the first year of life. The median age at onset is 2 years, and one-third of the patients are <1 year of age. During the last few decades, the combination of multi-agent chemotherapy, radiotherapy and radical surgery has improved the prognosis for children with neuroblastoma. Despite the advances in multidrug therapy, surgery is still important in the treatment of neuroblastoma. There is no doubt that complete surgical resection in locally confined tumours is the treatment of choice. There is, however, an ongoing discussion about the value of radical surgery for extended (stage 3) and disseminated (stages 4 and 4s) neuroblastomas. Some studies have shown improved survival rates after radical excision and various protocols of chemotherapy (19), while others have questioned the role of extensive radical surgeries especially with recent advances in intensive preoperative and postoperative chemotherapy regimens (20). A recent study by von Schweinitz et al, showed a significant correlation between the radicality of extirpation of the primary tumour and prognosis during the early follow-up. However there was no difference in outcome between complete or partial resection during the later follow-up (>5 years). Zwaveling et al found four studies that explicitly compared survival between patients undergoing either complete total resection (CR) or gross total resection (GTR). A significant survival benefit (for CR) was shown in one case only (21), complete tumour resection (CR, macroscopic total tumour removal.

Despite recent advances, 50 to 60% of patients with high-risk neuroblastoma have a relapse, and to date there are no salvage treatment regimens known to be curative. Over the past decade, several highly active agents have been identified that may help such patients. The issue of survival after relapse is a delicate one for clinicians who treat patients with neuroblastoma. It is necessary to offer hope for a cure but also to acknowledge that, at least until recently, long-term disease-free survival after a relapse was rarely seen, if ever. Recent advances in our understanding of the molecular basis of high-risk neuroblastoma have identified therapeutic tumortargets that may respond to novel agents with unprecedented anti-tumour activity (22).

Rhabdomyosarcoma (RMS)

Although the outcomes for children with low- or intermediate risk disease seems to have plateaued in recent years, those with metastatic or refractory/relapsed disease continue to have a poor prognosis (25). Great strides have been taken in the area of genetics with the elucidation of many important genes such as MYOD1. A mutation in this may be responsible for treatment failure in those with sclerosing/spindle cell variant of RMS (11). The knowledge of these genes and of the oncogenic fusion proteins which are the
products of chromosomal translocations in alveolar RMS may assist with risk stratification and application of chemotherapeutic protocols.

In terms of imaging, Positron Emission Tomography (PET) imaging has made staging more accurate. In a recent study (25) MRI, bone scintigraphy, histological analysis and bone marrow biopsy. Advanced functional imaging (FI, the sensitivity and specificity of PET-CT or PET for lymph node involvement and also for the detection of distant metastasis was found to be far higher than conventional imaging.

There has been a significant shift in the treatment paradigm from radical surgery advocated till the eighties to organ preservation in the current era. Advances in chemotherapy and radiation therapy have allowed oncologists to even consider forgoing primary excision if local control has been achieved. The current outcomes include a 90% FFS (Failure Free Survival) rate for low-risk patients and an approximately 70% 4-year FFS for intermediate-risk patients. High-risk RMS patients still have poor overall survival with a 3-year OS of approximately 30%.

Wilms Tumour

The most common primary renal malignancy in children has been written about extensively. Its management has evolved considerably over the years and is especially interesting because of the ideological differences between the two major treatment groups, the National Wilms Tumour Study Group (NWTS) and the International Society of Pediatric Oncology (SIOP). While a discussion about the treatment protocols is beyond the scope of this article, a few new concepts (some controversial) will be touched upon.

Radical nephrectomy usually encompasses the ipsilateral adrenal gland as well but two recent studies have shown enough evidence for sparing the adrenal unless there is a high degree of suspicion (26), (27). There is a growing body of work with minimally invasive modalities including laparoscopy and robot-assisted laparoscopy, and it can be expected that these will be used more frequently not just for those tumours downsized by chemotherapy but for upfront nephrectomy as well (28). This becomes even more exciting when considered with advances in hemostatic agents and intra-operative ultrasonography.

There is a lot of work underway to discover a tumour marker for Wilms tumour and MicroRNAs seem promising in this regard. Salvage chemotherapy with a combination of irinotecan, vincristine, bevacizumab and temozolomide has shown good results in relapsed Wilms tumour (29).

Recent developments in neuropsychological research in Disorders of Sexual Differentiation (DSD)

This area of study is fraught with controversy and multiple opinions have muddied the waters. Multidisciplinary management is the key with a therapeutic protocol customized to every individual patient. A consensus statement on the management of intersex disorders put forth by Hughes, Houk, Ahmed and Lee in 2006 (30), identified a major shortcoming in terms of lack of information regarding long-term outcomes. It also advocated the need to amalgamate hard-core science with in-depth psychosocial studies in order to provide the best management outcomes.

Most of the current knowledge about the behavioural differences between the sexes has been derived from studies in patients with DSD as well as animal experiments. This has provided the foundation for therapeutic options which are now being offered to these children. The creation of a normal genital appearance became synonymous with a “good outcome”. This approach has been challenged in a recent publication (31). It now appears that we weren’t asking the appropriate questions. There is currently no evidence that corrective surgery at the youngest possible age leads to better psychological development especially in cases like hypospadias (32). It is painfully obvious that we need better tools to assess psychological development in order to do the best for our patients.

Recent advances in the field of Bladder Exstrophy/Epispadias Complex (BEEC)

One can expect the outcomes of this condition to be impacted positively by advances in four key areas including pathophysiology (and genetics), radiology, psychological aspects of gender identity and regenerative medicine. An example of this is the finding that the bony pelvis in exstrophy has the same potential for growth as a normal pelvis (33).

The gene p63 probably has an important role in the ventrocaudal formation of the urogenital tract. There is an increased apoptotic activity of the ventral urothelium if it is under-expressed and this appears to be important in the etiology of BEEC (34). The elucidation of such
Recent Advances in Pediatric Urology

Key players in organ development pave the way for the development of gene therapies. As Tourchi et al (35) surmised, the identification of the genes associated with key cellular structures will eventually allow for “re-engineering” of the diseased tissue of the bladder into healthy tissues. This can be done by targeting the under-expressed genes and inhibiting the overexpressed genes. It may eventually be possible to do this when bladder exstrophy (or the OEIS complex) is identified antenatally.

3D Printing and tissue engineering in Urological Practice

The ability to print in three dimensional space is proving to be a game-changer in the field of medicine. The usefulness of this technology in the manufacturing of surgical prostheses, fabricated biomaterials and models for education and pre-operative planning has been established (36). However applications in pediatric urology are evolving.

The technology was introduced in the late 1980s and was aimed at the creation of three dimensional (3D) objects from two-dimensional slices of a computer-aided design template. 3D printed ureteric stents and laparoscopic trocars have been successfully tried in porcine and human cadaver models (37). Materials and Methods: We created computer-aided designs for ureteral stents and laparoscopic trocars using SolidWorks. We developed three generations of stents, which were printed with an Objet 500 Connex printer, and a fourth generation was printed with an EOSINT P395 printer. The trocars were printed with an Objet30 Pro printer. We deployed the printed stents and trocars in a female cadaver and in vivo porcine model. We compared the printed trocars to two standard trocars for defect area and length using a digital caliper. Paired T-tests and ANOVA were used to test for statistical difference. Results: The first two generations of stents (7F and 9F. This means it is now possible to customize the surgical device to the patient which will be enormously useful in children. However Limitations low tensile strength of the materials prevents adequate sterilisation and long term durability is a concern.

The pinnacle of 3D printing application will be the creation of transplantable organs (38), otherwise known as three-dimensional (3D). The challenges are many and include the arrangement of cells and extracellular matrix in a functional form and enabling this biological material to withstand the mechanical stress of the bioprinting process. In addition the cells must also retain their proliferative potential. Once these problems are overcome the current shortage of transplantable organs will be completely eliminated. In fact the very shape of surgery will be altered forever.

Sacral neuromodulation: Therapy of the future?

Sacral neuromodulation (SNM), which received FDA approval in 1997, is gradually gaining acceptance as the standard of care in patients with refractory overactive bladder and non-obstructive urinary retention (39). Such patients have an imbalance of inhibitory and excitatory signals on the voiding reflex. The same treatment may be effective for both voiding and retentive issues. Thus, this therapy may act by modulating responses at a central nervous system level.

Schmidt and Tanagho’s elegant canine experiments uncovered the response to sacral stimulation. The key finding was that stimulation-induced contraction of the urethral sphincter abolished detrusor contractions. The primitive voiding reflex is orchestrated by the pudendal nerve and has a significant role to play in SNM which seems to work by coordinating the bladder, sphincter and pelvic floor (40).

The recent advances in this field have been the production of the tined permanent lead, routine use of fluoroscopy and a smaller implantable pulse generator (IPG) (39). A prospective worldwide study on the outcomes of SNM have throw up favourable results in selected patients. With the advent of these advances, the field is set to grow in leaps and bounds.

The percutaneous, self-anchored tined permanent leads do not need large incisions to insert and can be placed even under conscious sedation hence allowing one to utilize the patient’s response to sensory stimulation as a guide to placement. Further, the use of fluoroscopy has made placement even more accurate. The smaller IPG makes pediatric use even more appealing.

In the pediatric context, those with dysfunctional elimination syndrome may be specifically benefitted. Reinberg et al used SNM in those refractory to medical therapy and found resolution or improvements in urinary incontinence (88%), frequency and urgency (89%), nocturnal enuresis (69%) and constipation (71%) with a median 27 months follow-up in a group of 20 patients (41).
PURPOSE: Recent advances in neuromodulation have demonstrated promise in treating children with the dysfunctional elimination syndrome refractory to medical management. Sacral nerve stimulation with the InterStim implantable device has been used in adults for management of chronic urinary complaints. However, there are few data regarding the usefulness of sacral nerve stimulation in children. We report our experience with sacral nerve stimulation for severe dysfunctional elimination syndrome.

MATERIALS AND METHODS: A total of 20 patients 8 to 17 years old with the dysfunctional elimination syndrome refractory to maximum medical treatment underwent sacral nerve stimulation at our institution. Patients were followed prospectively for a median of 27 months after the procedure.

RESULTS: Urinary incontinence, urgency and frequency, nocturnal enuresis and constipation were improved or resolved in 88% (14 of 16).

References