Unforeseen Issues of Concern in Pediatric Oncology

FROM THE GUEST EDITOR

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At the 2007 annual Section of Urology meeting of the AAP in San Francisco, I was asked to moderate a panel comprised of: Michael Ritchey, David Joseph, Chris Austin and Jonathon Ross regarding the topic “unforeseen issues of concern” in pediatric oncology. In order to expand this topic Tina Schober has been asked to add fuel to the fire by discussing cancer of the neovagina, and Margaret Shnorhavorian has contributed data on genitourinary outcomes in survivors of pediatric malignancies.

As we make progress in the field of oncology and pediatric urology in general, new questions often arise as a result of our “assumed” successes. When refinements in oncological therapy lead to improved survival in those children who survive childhood neoplasms, what price might they pay down the line as a result? In those with benign conditions, in whom we have attempted to improve the quality of life by creating a neovagina or augmented their bladder for continence and/or renal preservation, have we created a new population at risk for future malignancies? Can we prevent some of the problems that have been brought to our attention and even screen high risk patients at risk of developing neoplasm, hoping to affect the prognosis?

We should be proud of the marked advances made in our field. We must realize, however, that for many conditions which we treat, we do not hold all the answers, and thus long term surveillance and follow up is mandatory. Much of the oncological data is captured in intensive data bases and efforts are continuously ongoing to assure improved outcomes while minimizing short and long term morbidity by multidisciplinary groups such as COG (Children’s Oncology Group). In those patients with non-oncological problems, that in part we may have been partially responsible for creating despite our best knowledge and surgical efforts, or in those who might be at risk of developing neoplasms based on the chromosomal and/or phenotypic ambiguity, we as a specialty have the responsibility to similarly develop such data bases that might allow better tracking of these individuals and ultimately make efforts that might minimize catastrophic outcomes. If we are not ourselves going to continue to follow these patients beyond a certain age, then we also must assure reliable transition of these patients to reliable and interested colleagues in the adult sector when these patients reach adulthood, so that they don’t fall through the cracks.

The message from this issue nearly fits under the category of “No good deed goes unpunished,” but the lessons learned are quite clear. Many of the patients that we see need to be followed long-term and they need to be handed off in a responsible way when these patients reach young adulthood. The long-term consequences, in particular the oncologic potential, of many of the problems that we see are far reaching. In the end, it is indeed our responsibility to educate families as well as other healthcare professionals, including adult urologists, about the long-term consequences of many urologic conditions of childhood.

The exact incidence of these consequences is unclear as in most cases long-term data bases have not been kept. Moving forward, however, the establishment of such databases may not only provide us with better information on true risk but also allow us to track these patients more definitively.

This is an excellent issue which will be referred to often in the future. I congratulate Dr. Koyle and his contributors for assembling this.
Screening for Wilms’ Tumor in High Risk Children

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Wilms’ tumor usually develops sporadically in otherwise healthy young children. However, a small number of cases occur in children with recognized syndromes. The congenital disorders associated with the risk of developing Wilms’ tumor can be classified into overgrowth and non-overgrowth categories (Table 1). The overgrowth syndromes include Beckwith-Wiedemann syndrome (BWS), Perlman syndrome, Sotos syndrome and Simpson-Golabi-Bechmel syndrome. The non-overgrowth syndromes associated with Wilms’ tumor include isolated aniridia, trisomy 18, ambiguous genitalia, Familial Wilms’ Tumor, WAGR syndrome, Bloom’s syndrome and Denys-Drash syndrome.

Although the cause of Wilms’ tumor is unknown, certain genetic factors are implicated. The recognition of Wilms’ tumor risk in WAGR patients led to the discovery of the association with chromosome 11p13 deletions and the identification of the tumor-suppressor gene WT1 at the 11p13 locus. Denys-Drash syndrome and Frasier syndrome are associated with WT1 mutations. Simpson-Golabi-Bechmel syndrome is associated with a mutation in the GPC3 gene. Up to 15% of Wilms’ tumor cases are associated with complex familial inheritance related to alterations in genes at 11p15.

The current best screening modality for renal masses is abdominal ultrasound. It is widely available, noninvasive, low-cost and does not expose the patient to ionizing radiation. Screening renal ultrasonography in children at risk for Wilms’ tumor should be performed by a pediatric ultrasonographer with significant experience. If the ultrasound demonstrates a suspicious lesion, computed tomography (CT) or magnetic resonance imaging (MRI) should then be performed.

Non-malignant renal lesions do occur at an increased rate in children with BWS and recognition of these is important to avoid unnecessary nephrectomy when new lesions are identified on screening ultrasound. Medullary renal cysts have been noted in 13% of BWS patients. Another challenge when screening patients is to distinguish between nephrogenic rests and Wilms’ tumor. A newly discovered and enlarging solid lesion is concerning in any event, but there is little data on the need for adjuvant chemotherapy if a small hyperplastic rest is removed intact.

There are two potential benefits of screening for Wilms’ tumor in children. The first is improvement in overall survival. Screening ultrasound can theoretically result in the detection of lower stage tumors. This could not only result in improved survival, but also allow a decrease in intensity of therapy and subsequently decrease the morbidity (acute and late effects) associated with chemotherapy and radiation. The other potential benefit of screening is facilitating nephron sparing surgery. These children are at increased risk for bilateral disease. Screening may allow detection of smaller tumors that will allow preservation of the kidney. This has the potential for decreasing the risk for renal failure that occurs at an increased rate in children with bilateral Wilms’ tumor and those with aniridia and Denys-Drash syndrome. However, the latter group of children often progress to renal failure with any treatment.

Overall there is no compelling evidence that screening children at high risk for Wilms’ tumor has improved survival. Three retrospective studies have addressed the role of screening for Wilms’ tumor in patients with aniridia, Beckwith Wiedemann syndrome or hemihypertrophy. Two of these studies demonstrated a difference in stage distribution with unscreened cases having more late-stage disease compared to screened cases. Craft et al. found no difference in outcome or stage distribution among screened and unscreened cases in patients with Beckwith-Wiedemann syndrome, hemihypertrophy or aniridia. Wilms’ tumors with favorable histology have an excellent overall survival, and the small numbers of patients in the reported studies would be too small to detect a significant difference in survival. To date, no prospective randomized study comparing screening to no screening has been conducted.

There have been several published recommendations on the frequency of screening in groups at high risk for developing Wilms’ tumor, although the frequency and maximum age of screening vary. The most recent report from the Wilms’ Tumor Surveillance Working Group from the United Kingdom has recommended renal ultrasound be performed every 3 to 4 months by an experienced renal ultrasonographer. They recommend surveillance continue until 5 years of age for all children except those with Beckwith-Wiedemann syndrome, Simpson-Golabi-Bechmel syndrome and some familial Wilms’ pedigrees in which case surveillance should continue until 7 years of age. They have recommended surveillance in all conditions that have a greater than 5% incidence of Wilms’ tumor development. They also advocate that screening begin at diagnosis and that all children at high risk for developing Wilms’ tumor should be evaluated by a clinical geneticist. Lesions detected through screening should then be referred to a specialist center for management.

Summary of recommendations:
• Children with certain genetic syndromes with at least 5% risk of developing Wilms’ tumor should be screened beginning at the time of diagnosis.
• The goal of screening is to improve survival and decrease morbidity and mortality associated with various forms of treatment. Renal sparing surgery may be a secondary goal for patients prone to develop bilateral disease.
• The current best screening modality is abdominal ultrasound.
• Screening interval should be every 3 to 4 months until 5 or 7 years of age.

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The treatment of pediatric malignancies represents one of the success stories of modern medicine. By 2010, it is projected that 1 in 250 young adults will be survivors of pediatric tumors. The survivors of pediatric malignancies have known secondary malignancies and late effects. As survival has increased, the focus is now on minimizing harmful effects of treatment.

Kidney

Nephropathy, both glomerular and/or tubular damage can occur. Renal damage may be caused by radiation in doses >2000-2500 cGy, but can be seen at lower doses when combined with cisplatin, ifosfamide or in younger children. Hyperrenin hypertension can occur due to renal artery narrowing.14

Bladder

Hematuria, cystitis, fibrosis and dysfunctional voiding and secondary bladder malignancies can occur. Cyclophosphamide is a known risk factor for acute and chronic hemorrhagic cystitis, which is worsened by radiotherapy and can lead to long-term voiding dysfunction.4,5 Radiation effects are related to dose and percentage of bladder wall irradiated. Fibrosis and reduction in bladder capacity and contractility are likely related to vascular ischemia of the muscular wall.

The most conclusive data in the literature regarding the dose-response relationship between cyclophosphamide (CPM) and bladder cancer was reported in a National Cancer Institute (NCI) study of 6,171 survivors of non-Hodgkin Lymphoma (NHL) in which 48 of the patients developed urinary tract cancer of which 31 were bladder cancer.6 Radiation effects are more resistant to radiation injury than older ones.11

Testicular or ovarian damage may be caused by radiation therapy or alkylating agents. The degree of gonadal impairment is related to the age and dose of chemotherapy and the age of, dose of and fractionation schedule for radiation therapy. Infertility and germ cell damage are common in boys. Greater than 3 Gy in boys usually produces irreversible azosperma and with less than 12 Gy Leydig function is usually spared in prepubertal boys. Greater than 20Gy produces ovarian failure in most girls, however, the ovaries of younger female patients are more resistant to radiation injury than older ones.11

National Wilms’ Tumor Study Group

In a study of 5,278 patients entered in the National Wilms’ Tumor Study Group from 1969 through 1991 with follow-up data through 1993, 43 were identified who developed a secondary malignant neoplasm (SMN). This was 8.4 times the number expected based on national cancer incidence rates. The cumulative incidence was 1.6% after 15 years and continued to increase steadily. Abdominal radiation increased the risk of an SMN and doxorubicin potentiated the radiation effect.12

The incidence of end stage renal disease (ESRD) is low for the majority of patients with Wilms’ tumor, but patients with Denys-Drash syndrome, WAGR or other genitourinary anomalies are at higher risk for ESRD.13

Congestive heart failure is a risk of treatment with doxorubicin. In a case-control study of patients in NWTS, the cumulative frequency of congestive heart failure was 4.4% at 20 years after diagnosis among patients treated initially with doxorubicin and 17.4% at 20 years after diagnosis among those treated with doxorubicin for their first or subsequent relapse of Wilms’ tumor. The relative risk of congestive heart failure was increased in females and by cumulative doxorubicin dose, lung irradiation, and left abdominal irradiation.14

Pregnancy outcomes in women who received flank radiation therapy as part of their treatment for Wilms’ tumor demonstrated an increased risk of fetal malposition and premature labor. The offspring of these women are at risk for low birthweight, prematurity (< 36 weeks gestation) birth, and the occurrence of congenital malformations.15

References
Childhood Cancer Survivor Study

In the largest study of SMNs to date, secondary genitourinary neoplasms was determined in 13,136 participants of the Childhood Cancer Survivor Study (CCSS), a multi-institutional retrospective cohort of survivors of childhood cancer designed to study the late effects of cancer therapy among 5-year survivors of childhood cancer (funded by the National Institutes of Health and the Children’s Cancer Research Fund). Of SMNs other than breast, thyroid, and skin, 35% (25/71) occurred in the genitourinary system. Survivors of neuroblastoma had the greatest risk of carcinoma largely because of their elevated risk of developing a kidney tumor (Standardized Incidence Ratio (SIR), 329), all of which were renal cell carcinomas. Women had a higher risk of developing SMNs of the kidney and bladder. The risk of subsequent carcinoma of the kidney in individuals diagnosed at younger than 1 year old was particularly elevated (SIR, 94.8). Three of four patients in this age category had neuroblastoma. Platinum therapy resulted in significantly elevated SIR estimates for subsequent kidney (SIR, 48.7) carcinomas. Twenty-five percent (2/8) of renal cell carcinomas and 20% (1/5) of the bladder carcinomas arose within a region of previous radiation.

Renal cell carcinoma was the most common SMN diagnosed in neuroblastoma survivors in this cohort. Two of five renal cell carcinomas following neuroblastoma arose from the radiation field, and four of the five patients received cyclophosphamide. Others have also reported a possible association between renal cell carcinoma and neuroblastoma. Wilms’ tumor survivors and neuroblastoma survivors were significantly more likely than sibling controls to have any chronic health condition, a severe or life-threatening condition, or multiple chronic health conditions.

Pregnancy outcomes were also studied in the CCSS. Compared with siblings, survivors were less likely to have live births, more likely to have medical abortions and more likely to have low birthweight babies.

Conclusion

Survivors of childhood malignancies are at increased risk of late toxicities. There continue to be late toxicities of the GU system for childhood cancer survivors related to the specific therapeutic exposures. A more systematic approach to follow-up is important and partnerships between pediatric oncologists, primary care providers and urologists are essential.

References

Cancer of the neovagina has been said to be rare. Creation of a neovagina is an infrequently done procedure with no established long-term follow-up. Tissues used in neovaginal construction are varied (bowel, skin graft, vulvar skin flaps, rectus abdominus myocutaneous flaps, inverted penile skin, traction and cleavage techniques without tissue transplantation, as well as a number of others), and the pathological criteria of abnormality are not well established. When exogenous tissue is used, tissue dysplasia may be expected since tissue is suddenly subjected to new contacts or stresses. Epithelium transplanted to a vaginal location assumes the anatomic and physiologic characteristics of a normal vagina, including normal vaginal pH, and normal vaginal flora. Skin grafted to form vagina loses hair follicles, and sweat glands. A reduction in the number of elastic fibers, and hyperplasia of epithelial cells occurs. Grafts accumulate large amounts of glycogen, which is typical of vaginal mucosa, but almost never occurs in normal skin. Such tissue is changed by cyclic estrogen environments. Specific to split thickness skin grafts, cytologic specimens from vaginal smears showed anucleated and keratinized squamous epithelial cells. Squamous cell maturation shows a shift to the right with a preponderance of superficial and intermediate squamous epithelial cells. Although the neovagina is modified cytologically in the direction of the normal vagina, it never loses certain characteristics of the original skin, such as keratinization.

Transplanted colon or bowel retains the basic properties of bowel, including genetic factors such as oncogene activation for the development of cancer, chronic inflammatory bowel disease, or any type of polyposis syndrome. The isolation of bowel, as a segment for vaginal use, excludes two factors for cancer development, exposure to bile acids and the direct carcinogenic influences of certain foods. Sexually transmitted influences to bowel from human papilloma type related DNA, and c-myc oncogene alterations in colon cell lines has been reported. Tumors associated with exogenous tissue still have the potential to express the expected tumor or inflammatory change (as in natural environment of the tissue). Such problems must be anticipated and monitored in long-term follow-up of patients with feminizing genitoplasty.

There are many possibilities for neovaginal tissues to become subject to unexpected stresses. Recurrent dilatation to keep the vagina open, persistent granulation tissue, chronic infection and inflammation secondary to dampness may cause dysplastic surface change and pseudopolyps. Microabnormal and trauma from intercourse, and alteration of the donor surface by exogenous noxious agents (reaction to semen and urine exposure, and stool if a fistula occurs) may also be the etiologic cause of dysplasia. Insipidation of secretions that do not drain and harden, forming calcifications that abrade the surface, can also cause inflammatory changes. Other initiators of inflammation include colonization by bacteria that neovaginal tissues are usually not exposed to, inflammation from stents left in place to prevent vaginal shrinkage, and sexually transmitted HPV.

Though carcinoma of the neovagina is a rare malignancy, many cases have been reported and continue to accumulate.1 Cancer types appear to be related to the type of transplanted tissue. All recorded cases of squamous cell carcinoma are related to split-thickness skin graft or McIndoe variations, and all adenocarcinomas to intestinal grafts. No malignancies have been reported in vaginas made from amnion or peritoneum.

Development of these tumors varies from 18 months to 30 years, reflecting a younger age range than carcinoma of the natural vagina. Peak incidence for carcinoma of natural vagina is 65 years of age, while carcinoma of the neovagina is documented in patients between the ages of 25 and 53 years.

In almost every case, cancer of the neovagina presents with a bloody or clear vaginal discharge or postcoital bleeding. As is common with primary vaginal carcinomas, all lesions occur in the posterior vaginal vault. Invasive vaginal cancer tends to be undifferentiated, and development of squamous pearls is unusual. In contrast, cancer of the neovagina presents with squamous lesions that typically represent mature squamous cell carcinoma, with pearl formation. Carcinoma of the neovagina is distinct in its occurrence in a young population and histopathologic cell type, but the risk of development after reconstruction is not known to be greater than the reported incidence of primary vaginal cancer.

The investigation, staging, and follow up of vaginal malignancies may be improved by radiologic advances. Transvaginal sonography has been suggested and is being considered as a screening tool.3 MR imaging of vaginal carcinomas have noted signal intensity characteristics that correlate with histologic subtypes. Location of the posterior wall in the upper third of the vagina with ulceration, fungating, or annular constricting lesion is confirmed.3 MRI identified 95% of primary vaginal tumors and enabled staging that correlated with outcome.4 Such information may assist in treatment choices and planning.

Cytology findings have been reported only for the neovagina created by the Vecchietti technique. This neovagina is created by traction on the interlabial space and does not insert new tissue. Neovaginal smears done after the period of cicatrization (after the period of healing during which one might expect inflammatory and parakeratotic cells) following construction of the type of neovagina show eosinophilic superficial cells that responded to hormonal variation similar to natural vaginal tissue as well as a normal vaginal flora (regional environment). None of these smears showed nuclear atypia at 2-12 years after vaginal construction. Noted were infection with G vaginalis and HPV. The documented presence of HPV suggests the possibility of generation of carcinoma from HPV lesions. Cancer has been reported in a neovagina created by epithelialization over a prosthesis.

Disease survival is significantly related to the stage of disease at diagnosis, just as with carcinoma in a natural vagina. The first four

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reported patients with cancer of the neovagina were treated with primary radiation therapy. Three developed recurrence, suggesting a high percentage of failure with radiation as a primary treatment modality. More recent reports of the use of intracavitary high-dose brachytherapy using a vaginal cylinder (HDRB) for primary or recurrent vaginal cancer have better results, with crude local control of 100% in those without prior radiation, 67% for those with recurrence and prior radiation.\textsuperscript{3} External Beam RT (EBRT) in combination with interstitial template brachytherapy achieved local control in 64% of those with locally advanced disease.\textsuperscript{4} Hyperthermia has also been suggested to be beneficial in the treatment of tumors $>$ 4cm in diameter in cases of primary vaginal carcinoma.\textsuperscript{7} Use and outcomes of these specific modalities in cancer of the neovagina is yet to be reported.

Squamous cell carcinoma of the neovagina has been reported with infiltration of the urethra and bladder neck.\textsuperscript{8} Complete excision without nodal involvement was reported. The ten most recent cases of cancer of the neovagina were treated with primary surgical therapy; one recurrence has been noted.

Follow-up pelvic exams are necessary on a regular basis after the creation of a neovagina though gross pelvic exam and even colposcopy or endoscopy may be insensitive for screening. Biopsies of abnormal tissue is used for diagnosis. Better methods for histopathologic collection of surface cells are needed. Though no established screening cytology method has been developed for the bowel or skin graft vagina, typical PAP surface smears in the case of the Vecchietti vagina appear reliable for diagnostics purposes. A novel self sampling device that mimics a tampon, and is based on the central role of HPV as a precursor lesion, is currently being tested as an adjunct to typical cytology in typical vaginal/cervical situations.\textsuperscript{8} This may be of future value for cytology collection in the neovagina. The role of tumor markers is yet to be determined.

Risk factors for neovaginal cancer appear to be ulcerative colitis in a bowel vagina, granulation tissue formation, persistent inflammatory pseudoplyps, infection and mechanical irritation by continued use of a prosthesis or dilators and viral infection with HPV.

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References
Gonadal Tumors in Disorders of Sex Development

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Treatment options in children with Disorders of Sex Development (DSD) are complex, subjective, and not often supported by evidence based medicine. When helping families determine the sex identity of their child, it is critical to provide information allowing them to make an informed consent. Information regarding the potential to maintain gonads based on tumor development plays an important role in the decision-making process. What follows is a brief review of gonadal tumors in DSD highlighting WHO is at risk, WHY they are at risk, and WHAT are the treatment options.

There is a “male” factor responsible for the increased risk of a gonadal tumor not related to hormonal production. Exposure to elevated levels of testosterone does not increase the risk for a gonadal tumor. However, individuals with a component of a Y chromosome are at risk for malignant gonadal degeneration.

TART

Testicular adrenal rest tumors (TART) are exclusive to boys with CAH and have been reported to occur from 0 – 47% of boys. The tumors are bulky and often bilateral. Interestingly, 18% occur in men with undiagnosed CAH. Histologically the TART resembles a Leydig cell tumor, but do not contain Reinke crystalloids pathognomonic for a Leydig cell tumor. TARTs arise in the mediastinum of the testis and obstruct seminiferous tubules. Treatment of TARTs is with high dose glucocorticoids. Unfortunately, this does not restore testicular function and that has prompted investigation of testis sparing tumor enucleation. There is no documented support to show conservative surgery is of value.

Germ Cell

Individuals with DSD are at risk for malignant type II germ cells tumors; seminoma in a testis and dysgerminoma in an ovary. Germ cell tumors are preceded by in situ neoplasia in the form of either gonadoblastoma or intratubular germ cell neoplasia (ITGCN) also referred to as carcinoma in situ (CIS). Gonadoblastoma is most often associated with undifferentiated gonadal tissue. ITGCN typically occurs in under virilized disorders (androgen insensitivity) with well differentiated testes.

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The potential for malignant transformation occurs due to overgrowth of germinal cells and the risk factor is a “signal” that lies somewhere on the Y chromosome. This is referred to as the GBY oncogene. This gene is not related to SRY. There is thought that the GBY oncogene is either consistent with, or influenced by the TSPY (testis-specific-protein-Y) gene or protein. The TSPY hypothesis suggests an association of abnormal testicular development by increasing the presence of immature fetal type cells and decreasing apoptosis. This results in an overpopulation of fetal germ cells and a higher risk for in situ neoplasia.

Because of the significance of the Y chromosome, it is critical that it is detected in all cases of DSD. This is especially true for girls reported to have Turner syndrome (45 XO). Routine karyotyping has a limited ability to recover small fragments of the Y chromosome, therefore PCR or FISH analysis is necessary.

Risk

The risk of developing a germ cell tumor is not founded in strong scientific evidence and the reported percent risks for the various disorders are of limited value. Given that limitation, Table 1 reflects the best guesstimates of risk. A few specific points: older literature reports the incidence of germ cell tumors in girls with androgen insensitivity approaches 22%. Contemporary studies have downgraded this risk to 5 – 15%. It is interesting that there does appear to be a significant difference between complete (CAIS) and partial androgen insensitivity (PAIS). ITGCN is reported to occur less than 1% in CAIS and 15% PAIS.

Markers

Tumor markers may play an important future role in determining “at risk” individuals with DSD. Markers under investigation include PLAP (placenta like alkaline phosphatase), TSPY, OCT3/4 (octamer binding transcription factor), C-kit (CD117), and VASA. These markers show variable expression by gonadoblastoma, IGTCN, and malignant germ cells. However, their expression is also reported to occur with normal primordial germ cells, and, therefore, an elevation of these markers may simply reflect an increased number of primordial germ cells due to maturation delay and not necessarily in situ neoplasia.

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References

Pediatric Risk Factors for the Later Development of Testicular Tumors

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Several risk factors for the future development of testicular cancers have been identified in the literature (Table 1). The most relevant to pediatric urologists are gonadal dysgenesis (discussed elsewhere in this issue) and cryptorchidism (UDT). Historically the risk of future testicular cancer in patients with a history of UDT has been reported to be 10-40 fold that of the general population. These estimates were based on retrospective analyses of the incidence of a history of UDT in men with cancer, combined with the incidence of UDT in the studied population. However, flaws in the determination of the incidence of UDT in the general population led to an overestimate of the risk. More recent, better controlled studies have found the risk to be closer to 4-6 fold that of the general population. This suggests a life-time risk of testicular cancer for a patient with a history of UDT of 1-2%. A recent report by Petterson et al. suggests that prepubertal orchidopexy may ameliorate the risk of testicular cancer in these patients.2 Beyond early orchidopexy, which is standard practice in any case, it is unclear what other intervention is warranted for boys and men with a history of UDT. While of unproven benefit, instructing these patients to perform regular testicular self-examination commencing at puberty seems prudent.

More troublesome, primarily because of a paucity of data, is the recent concern about incidentally detected testicular microlithiasis (TM) in children as a risk factor for testicular cancer. The concern about TM arises from the observation that approximately 25% of testicles harboring cancer in adults are found to have TM.3 The median incidence of TM in asymptomatic men was found to be 2.4% and 5.6%.3,5 These incidences of TM are roughly 1,000-fold the incidence of cancer in these populations suggesting that TM is a very non-specific predictor, if at all, of future cancer development. Most relevant are 6 small series with a total of 152 patients (including 2 prospective studies) that report on the development of testicular cancer in patients initially identified with TM.7,12 Of the patients in these series, 1.8% developed testicular cancer with a median follow-up of 41 months. None of the 81 patients in the 2 prospective studies developed tumors. Of the 3 patients in the retrospective studies that developed cancer, 1 had testicular atrophy and another was infertile. Indeed, TM seems to be most significant when found in association with other testicular cancer risk factors. In a study of 263 sub-fertile men, 20% of those with TM had carcinoma in situ biopsy compared to only 1 of 210 sub-fertile men without TM.13 Similarly, in a group of 64 men with a history of orchietomy for testicular cancer, 78% with TM in the remaining testes were found to have CIS compared to only 11% of those without TM.14

In summary, while there is a high incidence of TM in adults with testicular cancer, the prospective development of cancer in asymptomatic men with TM seems uncommon. The presence of TM may be most important in men who have another risk factor for cancer. The vast majority of these data describe testicular cancer occurring in men who were found during adulthood to have TM. The implications for children with TM are even less well-defined. Since TM does not appear to spontaneously resolve, children with TM will most likely become adults with TM and be subject to whatever risk, if any, pertains to adults. Given the apparent frequency of incidental TM in children and the rarity of pre-pubertal testis tumors, it seems that the presence of TM portends, at the most, a very small risk for the development of a pre-pubertal tumor. So what to do with the child noted incidentally to have testicular microlithiasis? In truth, the risk is probably so low that it could be ignored. But this is difficult for both physicians and families, particularly since the risk of TM is not well-defined. At present it seems prudent to follow these children with periodic ultrasound and instruct them in TSE at puberty. Hopefully, over time, the risk and resultant recommendations for follow-up can be clarified. Young adults with microlithiasis and another risk factor – particularly a history of contralateral tumor – may require more aggressive follow-up including, in some cases, testicular biopsy for CIS.

References

Introduction

Over the last several years, there have been several publications reporting bladder cancer in young adults with pediatric bladder dysfunction. Most of these patients have had spina bifida, but others have been reported in patients with bladder extrophy and posterior urethral valves. This is disturbing as most of these patients had advanced, aggressive disease with poor survival. Publications have predominantly focused on tumors in patients following bladder augmentation. While most of these publications indicate that patients are at an increased risk for bladder cancer after bladder augmentation, there has not been any conclusive study demonstrating that bladder augmentation is an independent risk factor for the development of bladder cancer. Indeed, many of these patients have other potential risk factors including chronic bacteriuria and repetitive trauma due to intermittent catheterization. Next to bladder perforation, development of bladder cancer would be considered one of the most worrisome complications associated with bladder augmentation surgery. While the concern of malignancy and bladder augmentation was raised over a decade ago, the problem regained our attention in 2004 when Sorgel et al. from Indiana University reported three spina bifida patients with transitional cell cancer after bladder augmentation. None of the patients survived their cancer. The authors recommended yearly cystoscopy and screening for bladder cancer starting 10 years after bladder augmentation. A second study by Castellan et al. from the University of Miami reported three spina bifida patients who developed gastric carcinomas of their augmentation segment after gastrocystoplasty. The authors recommended screening for bladder cancer with annual ultrasound and cystoscopy beginning 10 years after gastrocystoplasty.

University of Iowa Experience with Spina Bifida and Bladder Cancer

In 2007, we published a series of eight patients with spina bifida and bladder cancer. Since that time, an additional two patients have been added to our series. These 10 patients were treated over a period of 11 years. Eight patients were female and two male. The median age was 37 years (range 20-60). The presentation varied, but predominantly was characterized by gross hematuria in approximately 75% of patients. All patients underwent transurethral resection and ultimately 80% underwent radical cystectomy. One patient died at presentation. Most concerning is that only 1 of 10 patients (10%) had organ-confined disease. Most had locally invasive disease (stage T3 or T4) or lymph node metastases at diagnosis. Histopathology revealed transitional cell carcinoma in only 60% with adenocarcinoma and squamous cell carcinoma accounting for 20% of cases each. Median survival was 15 months and only one patient with pT2N0 is alive and free of disease at 20 months. Notably, 6 of 10 of these patients had regular yearly visits with a urologist, and were typically followed with urinalyses, labs, and occasional upper tract imaging with ultrasound. None had been undergoing active surveillance for bladder cancer or bladder surveillance. Only 2 or these 10 patients (20%) had undergone bladder augmentation. The interval from bladder augmentation and developing cancer was 8 and 14 years in our two patients. This series demonstrates a low number of patients with bladder cancer who had previously undergone augmentation surgery.

Review of Prior Published Cases

Reviewing all previously published case of spina bifida and bladder cancer, an additional 13 patients can be identified. Combining these patients with ours reveals a similar median age (35 years) and augmentation cystoplasty had been performed in 10 of 23 patients (43%). Of these 10 patients, three were colonic, three ileal and four were gastric augmentations. Histological findings were similar with the majority being transitional cell carcinoma (57%) with a smaller portion comprising squamous cell and adenocarcinoma. Interestingly, gastric carcinoma arising from the gastric patch occurred in 3 of 4 patients with tumors following gastrocystoplasty. The development of gastric carcinoma in the bowel segment is dramatically different from what has typically been seen in patients with augmentations using small or large bowel, where the development of malignancies in these bowel segments is extremely rare. The development of gastric carcinoma after gastrocystoplasty may become a more frequent finding in the future. Tumors stages were typically advanced, with only 1 patient with a gastric carcinoma having T1 disease. These pathological and histological findings are markedly different than the typical adult with bladder cancer where transitional cell carcinoma makes up greater than 90% of the histopathology and 75% have non-invasive disease. Additionally, the median age (35 years) is significantly younger than the typical adult with bladder carcinoma. Of the 10 patients who had undergone bladder augmentation, the median time from augmentation to diagnosis of bladder cancer was 13 years (range of 8 to 21). Median survival for all patients was 15 months.

Is Screening Going to Help?

Fortunately, the incidence of these bladder malignancies appears to be low. There are no prior published studies on screening pediatric neurogenic bladder patients for bladder cancer. Studies have been performed in spinal cord injury patients for early detection of bladder cancer. The majority of studies showed no significant benefit and that screening was not cost-effective. There was a single study which reported a non-statistically significant trend toward lower stage and better survival in those patients who were screened. Given the aggressive nature and poor survival of the tumors seen in these patients, it may be that yearly screening may not catch the tumors in time to alter the outcome. With bowel augmentation, bladder cancer rates between 1-3.8% have been estimated. No conclusive epidemiologic studies have been performed in this area. With gastrocystoplasty, reported rates have varied between 1% and 10%. Due to the poor outcome of adult patients with pediatric neurogenic bladder dysfunction and bladder cancer, we have adopted a follow-up program which includes yearly cystoscopy, renal and bladder ultrasound, and urine cytology. We have also been educating our patients regarding a possible risk of bladder cancer and if they would develop any new symptoms such as gross hematuria, increased urinary tract infections, difficulty catheterizing or changes in their continence status to return sooner for evaluation.

Summary

Patients with spina bifida and bladder cancer present at a younger age than typical. Their symptoms are most commonly gross hema-
turia, but they may have atypical symptoms in presentation. It is important for urologists to suspect the diagnosis in young adults with neurogenic bladder dysfunction as these are typically aggressive tumors which present in advanced stage. Patients have had poor survival. Bladder augmentation has been associated in a significant percentage of patients who have developed bladder cancer; however, it has not been conclusively proven to be an independent risk factor. Neurogenic bladder patients can develop bladder cancer at a young age without a history of bladder augmentation. The development of this late complication in patients with neurogenic bladder dysfunction emphasizes the need for lifelong follow-up and care. The role for screening is currently being evaluated. In the next 5-10 years, hopefully an effective strategy to identify and follow at-risk patients and methods for early detection will be available.

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