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Lesson 10 Volume 39

Risks for Secondary Malignant Neoplasms: What a Urologist Needs to Know*

Learning Objective: At the conclusion of this continuing medical education activity, the participant should be able to identify pediatric cancer survivors who are at high risk for secondary malignancy and return them to the surveillance protocols that are crucial for their long-term survival.

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INTRODUCTION

Slightly more than 85% of individuals who are diagnosed with pediatric cancer will become a long-term survivor.[1-5] The high probability that the child will survive the malignancy is in major part due to the risk-adjusted stratification of chemo-radiation therapy or, more simply stated, individuals with the most aggressive tumors undergo the most demanding treatment regimens.[4, 6-9] Regrettably, the aggressive chemo-radiation therapies used to improve survival are directly related to the long-term consequences that will significantly impact the quality and duration of life.[4, 5, 7-15] There are currently well-known associations between chemo-radiation therapies and the late onset of cardiovascular disease, pulmonary dysfunction, endocrinopathic conditions (primarily thyroid and gonadal dysfunction) and secondary primary neoplasms, also known as subsequent malignant neoplasms.[4, 5, 7, 11, 13, 15-21]

Regrettably, it is a little known fact that over three-quarters of the patients who have survived childhood cancer for >40 years will have either a severely debilitating, life threatening complication or die as a direct consequence of the treatments they endured.[4, 5, 15, 17-22] When compared to control populations, the excessive death rate of pediatric cancer survivors predominantly involves the major complications of cardiovascular disease and a SMN.[1, 2, 7, 16, 21-24] **The focus of this Update is on patients who survive their pediatric cancer for >30 years. In this patient population a SMN is the primary cause of death in slightly over 50% of the individuals.** [1, 2, 5, 7, 16, 23, 24]

UROLOGICAL MANIFESTATIONS OF COMPLICATIONS SECONDARY TO THE TREATMENT OF CHILDHOOD MALIGNANCIES

The question arises, why should a urologist be interested in the consequences of the treatment of pediatric tumors? To best demonstrate how a urologist can help in the management of this population I will point to our practice of transitional urology patients.[5] Specifically, we have seen an increasing number of childhood cancer survivors who were self-referred due to the late onset of urological complaints. **Characteristically, these patients will present with complaints of infertility, erectile dysfunction, symptoms of androgen deprivation and lower urinary tract symptoms or for urinary diversion follow-up.**[5, 25-30] The patient may or may not recognize that the current urological complaint occurred as a direct result of the treatment for childhood malignancy (Appendix 1). **Unfortunately, of our patients 50% had been lost to or were non-compliant with the recommended follow-up guidelines for childhood cancer survivors.[5] Therefore, the urologist can serve as a unique asset in the care of these patients by having the ability to identify those at risk and recognize the need for continuity of care. Indeed, identification and appropriate referral can be lifesaving events.[5]**

INCIDENCE AND TEMPORAL SIGNIFICANCE OF SECONDARY OR SUBSEQUENT MALIGNANT NEOPLASMS

The incidence of a SMN in childhood cancer survivors is extremely dependent on the length of follow-up, with cumulative data suggesting that 3% of survivors will have a SMN during the first 20 years after the diagnosis of the primary tumor, 10% by year 30 and 15% by year 50.[1, 13-16, 23, 31, 32] Of note is that the risk of a SMN never plateaus with age and continues to rise as the length of follow-up increases.[2, 6, 8, 13, 23, 31, 32]

The likelihood for a childhood cancer survivor to have a second malignancy is unequally expressed among the population at risk. Specifically, the development of a SMN is dependent on the type of initial tumor, intensity and types of multimodal therapies used to treat the initial neoplasm, and patient age at the time of treatment, gender and genetic predispositions to malignancy. The incidence of the development of a SMN may be further modified by exposure to environmental toxins and elective lifestyle factors, such as tobacco use, in adulthood.[1, 8, 14, 24, 31, 33-38]

In general, the risk of a SMN in women is twofold greater than in men with approximately a third of the patients dying of the second malignancy.[34] It is noteworthy that cancer-specific survival of a patient with a SMN ranges from a minimum of 12% to a maximum of 40% lower than a comparable individual with a similar stage of primary malignancy. The decrease in survival following the development of a SMN is hypothesized to be due to the 3 major factors of **1) reduction in the potential types of treatment options available due to the cumulative toxic effects of chemo-radiation, 2) increased incidence of more aggressive tumors that may arise as a consequence of prior cellular exposure to chemotherapy and 3) individual genetic variations that can affect either tumor development, growth or sensitivity to chemo-radiation.[1, 2, 14, 15, 24, 37, 39]** If a SMN develops and the patient does survive, half will have a third malignant neoplasm within the next 20 years, of whom 50% will die of the third malignancy in less than 2 years after its diagnosis.

A SMN has a bimodal presentation with a SMN that is due to a blood dyscrasia usually developing within the first 10 years after the diagnosis of the primary malignancy. **These hematopoietic tumors are usually caused by a myelodysplastic syndrome or acute myeloid leukemia with the median time to occurrence of 3 years following initial chemotherapy exposure**.[3, 8, 40, 41] The development of blood dyscrasia is directly related to the use of an alkylating agent or a topoisomerase inhibitor. A list and classification of commonly used chemotherapeutic agents for the treatment of pediatric genitourinary tumors are provided in Appendixes 2 and 3. The risk of developing a hematologic tumor is directly affected by the accumulative dosage of the chemotherapeutic agents and the timing of administration.[3, 40, 41] Classically, this risk is defined as a fivefold to sixfold increase over normal controls. **However, the combination of some chemotherapeutic agents such as cisplatin with any of the topoisomerase inhibitors (eg etoposide) will significantly increase this risk up to 29-fold higher than normal controls.**

A major clinical question that remains unanswered is, does the concurrent use of radiation therapy with chemotherapy increase the risk of secondary blood dyscrasia? We know that radiation therapy alone can induce leukemia, and that its induction is directly related to the dose of radiation received, the regions radiated and the age at which radiation was administered.[13, 40] Unfortunately, in some patients radiation

ABBREVIATIONS: ESRD (end stage renal disease), GU (genitourinary), SMN (secondary malignant neoplasm)

exposure from computerized tomography used for diagnosis and follow-up is considerably greater than that of radiation therapy. In general, univariate analysis suggests that the addition of radiation therapy to the aforementioned chemotherapy regimens increases the risk of secondary leukemia over that of chemotherapy alone by an additional onefold to fivefold.[13,40] However, this increased risk inevitably drops out when multivariate analysis is performed. Therefore, most studies are unable to determine if the addition of radiation therapy to any of the chemotherapy regimens increases the risk of a secondary myelodysplastic or leukemic process.

SMNs that occur more than 10 years after the initial primary tumor are predominately solid tumors and the majority are associated with the use of radiation therapy. In patients exposed to radiation therapy the SMN will most often occur within the radiation portal sites. Median time to occurrence is presently 13 years. However, the interval is perpetually increasing as the length of follow-up of this patient population continues.[3, 8, 35, 36, 40, 41] The bimodal interval related to the onset of a SMN resulted in its traditional classification as a predominantly chemotherapy related myelodysplastic syndrome that occurs during the first 10 years of follow-up or late radiation induced solid SMN. [13, 18, 40-43] However, this classic characterization is erroneous. Indeed, despite a noticeable decrease in the use of radiotherapy in pediatric patients from 1990 to 2001, a subsequent reduction in the incidence of late onset solid SMN in adulthood has not been observed.[15, 43, 44]

RISK OF SMN AFTER TUMORS ROUTINELY SEEN AND EVALUATED BY A PEDIATRIC UROLOGIST

Wilms tumor. Wilms tumor is the etiological cause of 5% of all new pediatric cancers.[2, 45] Approximately 10% of these patients will have associated genetic abnormalities or syndrome that would predispose them to a SMN. **The majority of SMNs in patients with a history of Wilms tumor occur late and are radiation induced.**[2, 23, 45, 46] Specifically, depending on the NWTS (National Wilms Tumor Study) protocol that was used, 33% to 75% of patients received flank, abdominal or chest radiation secondary to either an advanced regional stage at presentation and or the presence of pulmonary metastasis. The use of pulmonary or upper abdominal (flank) radiation results in the most common sites for a SMN following Wilms tumor, which are the breast (chest wall and upper abdominal radiation) and thyroid gland (chest radiation). The risk of these tumors after the routine radiotherapy dosage used for Wilms tumor is approximately 25-fold greater than normal age-matched controls. [1, 2, 23, 46-48]

It is noteworthy that girls who receive chemotherapy alone for a Wilms tumor are still at a fourfold elevated risk above normal for breast cancer compared to a control population.[46,47] The increased risk for breast cancer in patients who did not receive radiation therapy appears to be based on exposure to alkylating agents and anthracycline chemotherapy, and is documented to arise in a chemotherapeutic dose-dependent fashion (Appendix 3).[47]

ESRD is a relatively rare occurrence in children presenting with a non-syndromic Wilms tumor, approaching a 2% incidence at 20 years of survivorship, with the majority of patients having had either synchronous or metachronous bilateral Wilms tumors.[49, 50] The incidence of ESRD is significantly increased in children with the WAGR (Wilms tumor, aniridia, genitourinary malformations and mental retardation) syndrome or Deny-Drash syndrome (gonadal dysgenesis, glomerular nephropathy and Wilms tumor) for whom the 20-year risk of renal failure following diagnosis of the primary tumor will reach 40% and 80%, respectively.[49, 50]

The development of ESRD in both patient populations will significantly increase the risk of a SMN regardless of transplantation status. Specifically, a fourfold increased risk for a bladder, renal or hepatic malignancy is present in survivors of Wilms tumor with ESRD.[14, 34, 50] The risk of these tumors is organ-specific and impacted by gender, and duration of dialysis, immunosuppression and follow-up.

Rhabdomyosarcoma of the lower genitourinary tract and spermatic cord. **Although the risk for a SMN is predominantly attributed to the treatment received, there appears to be an inherent predisposition for a SMN in patients with a history of rhabdomyosarcoma.** Survivors of this tumor will have a fivefold to sixfold increased risk of a SMN over the general population, with the development of a delayed solid tumor dramatically predominating over myelodysplastic syndromes by approximately 9:1.[6, 51] This risk of a SMN following successful treatment of a rhabdomyosarcoma is significantly increased in children younger than 2 years old at the time of initial treatment.[6, 48]

Two-thirds of the individuals who have a SMN following a genitourinary rhabdomyosarcoma received radiation therapy, and half of the tumors occurred within the radiated field.[6] However, it is noteworthy that due to the routine use of alkylating agents, ie cyclophosphamide and ifosfamide, a third of the SMNs are associated with chemotherapy alone, with a documented dose-dependent related risk for developing the SMN.[3, 48, 51, 52] Classically, the type of SMN that develops in patients surviving rhabdomyosarcoma is any type of sarcoma, followed by thyroid, renal, colorectal and breast carcinomas.[6, 48, 51]

Germ cell neoplasia. Within the first 25 years following treatment of a primary germ cell tumor, approximately 5% of patients will have a SMN. In the current era of cisplatin based chemotherapeutic regimens, standard doses of cisplatin and etoposide are associated with a threefold increased risk of leukemia over normal controls.[48, 53-55] **When patients with germ cell tumors treated with surgery alone are compared to those who underwent surgery and received cisplatin based chemotherapy, patients receiving chemotherapy have a threefold to sevenfold increased risk of a late onset SMN, especially renal cell, colon or thyroid cancer.**[53-55] These findings strongly suggest a mutagenic effect related to cisplatin based chemotherapy.[48, 53-55]

GUIDELINES FOR SURVEILLANCE/ SURVIVORSHIP SCREENING FOR SMN

Recommended surveillance protocols to screen for the presence of a SMN are based on the principle that the probability of development is unequally expressed among the population at risk.[17] Specifically, the development of a SMN is bimodal, and lifelong screening is recommended for only high risk patients for whom benefits of the screening tests outweigh their harm and costs.[1, 2, 7, 16, 17, 19, 21, 22, 39]

Chemotherapy induced hematologic malignancy. A minimal 10-year follow-up period is recommended for patients who received alkylating agents (eg cyclophosphamide, ifosfamide), alkylating-like agents (eg cisplatin, carboplatin) or topoisomerase inhibitors (eg etoposide, mitoxantrone, doxorubicin). These

agents primarily induce hematologic based malignancies (eg acute myelogenous leukemia, myelodysplastic syndrome) with a median time to occurrence of 3 years and with minimal risk of development after 10 years.[1, 3, 56] Therefore, it is recommended to screen for hematologic based SMN for only the first 10 years after use of alkylating agents, alkylating-like agents and topoisomerase inhibitors.

Follow-up should consist of yearly history and physical examination. Routine performance of laboratory or radiographic studies is not indicated.[11, 16, 19, 36, 45] Laboratory tests are recommended only if the history or physical examination findings are positive for chronic fatigue, bruising, pallor or petechiae (Appendix 4). Lifelong screening for the development of a late occurring SMN is not beneficial for this population unless other risk factors are present. However, the physician should be aware that long-term follow-up for other chemotherapeutic complications, such as the increased risk of cardiovascular disease and congestive heart failure after treatment with anthracycline therapy (eg doxorubicin), is recommended. Therefore, referral to a long-term cancer survival clinic for follow-up for this possible chemotherapy complication may be considered.[11, 16, 19, 36, 41, 45]

Late onset secondary malignancy. **Lifelong follow-up to assess for the development of a SMN should be limited to the high risk patient population characterized by the presence of 1) inherent genetic abnormalities or syndromes that predispose to tumor growth, 2) a persistent non-malignant mass after successful treatment of the primary tumor, 3) a type of primary neoplasm that is known to have a high risk for SMN (eg retinoblastoma, any type of sarcoma or Hodgkin's disease), 4) prior chemotherapy at age <2 years or 5) treatment protocol that includes radiation therapy.[3, 15, 16, 36, 39, 41] Individuals with any of these 5 characteristics should undergo a yearly history and physical examination, and non-ionizing radiographic evaluations (either magnetic resonance imaging or ultrasonography) should be performed to rule out new growth in those with a persistent mass after initial treatment. Otherwise no additional studies are beneficial (Appendix 4).**[5, 16, 39]

Inherent Genotype Abnormalities: **An abnormality in either a tumor suppressor gene or DNA reparative gene and genetic syndromes are highly suggestive of an underlying hereditary predisposition for cancer, placing patients with these characteristics at the highest risk for a SMN.**[1, 6, 14, 16, 39, 56] Current studies suggest that up to 15% of childhood cancer survivors are in this category.[1, 2, 6, 9] There is intense interest in identifying and targeting these genetic abnormalities to guide treatment of the primary tumor and establish monitoring protocols for the at risk patient population.[1, 6, 9, 38]

Persistent Non-Malignant Masses after Chemotherapy: There is a significantly increased risk for a SMN when residual masses persist after successful treatment, which classically occurs in patients surviving childhood neuroblastoma or rhabdomyosarcoma.[3] A SMN may arise within persistent masses after they have been stable for decades, and where prior biopsies, sometimes multiple, revealed benign or fibrotic components. These findings suggest that the residual cells within these persistent masses may have either an inherent or acquired DNA defect induced by the chemo-radiation which can predispose to their malignant degeneration.

Chemotherapy or Radiation Therapy at Age Less than 2 Years: A high risk of a SMN exists in children who receive chemotherapy or radiation therapy before age 2 years. It is believed that the high rate of normal cell proliferation in this age range renders the normal non-involved cells more susceptible to chemo-radiation induced DNA damage.[1, 14, 36, 56] The induced mutagenesis combined with the long-term survival results in multiple cellular replications that amplify the induced DNA abnormalities as the patient matures.

Primary Tumor Type: The primary tumor type plays a major role in subsequent tumor development. Specifically, retinoblastoma, Hodgkin's lymphoma and any type of sarcoma place the patient at a substantially increased risk for a SMN, irrespective of the treatment modalities used. This finding suggests that individuals with these tumors may have inherent mutagenesis or an as yet unidentified gene that promotes tumor development.[1, 6, 7, 16, 36, 56]

Radiation Induced Malignancies: Two-thirds of the patients with a late occurring SMN received radiation therapy, and 50% of the SMNs occurred within the radiation therapy portal (Appendix 3).[1, 3, 18] However, approximately a third of late occurring SMNs develop in patients who were never exposed to radiation therapy. This finding suggests that the late onset of solid malignant neoplasms is not just radiotherapy related but instead could be due to either genetic susceptibility to tumor development, chemotherapeutic induced DNA damage or a combination of both.[43, 47]

RADIATION THERAPY FOR CHILDHOOD GENITOURINARY MALIGNANCIES AND ITS IMPACT ON BREAST AND COLON CANCER DEVELOPMENT

Radiation therapy is frequently part of the multimodal treatment protocol for childhood genitourinary malignancies, especially advanced Wilms tumor and pelvic rhabdomyosarcoma. Specifically, in the last 40 years, depending on the NWTS protocol that was used, 33% to 75% of patients with a history Wilms tumor received either abdominal, flank or chest radiation for treatment of advanced regional stages of a tumor and pulmonary metastasis.[23, 45, 46] In addition, two-thirds of individuals with a history of pelvic rhabdomyosarcoma received radiation therapy to the lower abdomen.[6]

The induction of either breast or colon cancer by radiation therapy is significant. Indeed, approximately 50% of SMN deaths are due to breast or colon cancer.[3] If patients are compliant with screening recommendations slightly more than half of breast and colon cancers will be diagnosed at an early treatable stage, with clinical studies documenting improvement in cancer-specific survival.[18, 23]

Breast as SMN site. Breast cancer is the most frequent site for a SMN among female childhood cancer survivors.[1, 16, 39, 46] Although it is not just radiation therapy that increases this risk, the effect of radiation therapy cannot be understated. Indeed, patients at highest risk for invasive breast cancer are those who received ≥10 Gy chest radiation and live to age 50 years when the incidence of invasive breast cancer will reach 30%.[1, 13, 16, 23, 36, 39] The risk for breast cancer is directly related to the age at which the patient was exposed to the radiation therapy and the dosage of Gy received. However, breast cancer is also dependent on the presence of ovarian function, a finding that substantiates the hormonal dependency of this tumor.[1, 13, 46] The risk is substantially enhanced if the patient concurrently is known to have inherited genetic traits that predispose to

breast malignancy.[1, 38]

To detect breast cancer at an earlier and more treatable stage, women who have received ≥10 Gy radiation to the chest are recommended to initiate monthly self-breast and annual clinical examinations beginning at puberty. At age 25 years clinical breast examinations should be performed every 6 months, with yearly breast imaging (mammograms or magnetic resonance imaging) beginning at either age 25 years or 8 years after radiation exposure, whichever occurs last (Appendix 4).[16, 39]

Colon or rectum as SMN site. There is also a marked increase in the risk of colorectal cancer in childhood cancer survivors who live to be 35 years old and were exposed to either abdominal, flank, lumbosacral spinal or pelvic radiotherapy.[13, 16, 23, 32, 39] This likelihood of colorectal cancer development is significantly enhanced if the patient received concurrent alkylating or alkylating-like chemotherapeutic agents (eg cyclophosphamide, ifosfamide and cisplatin).[13, 16, 32, 36] The increased risk ranges from 4.5 to 25 times higher than the control population.[32, 43] The wide variability is based on patient age when radiation therapy was received, length of follow-up, cumulative radiation dose received, and use and dosage of concurrent alkylating and alkylating-like chemotherapeutic agents.[13, 43] As with all SMNs, the risk may be further enhanced if genetic predispositions to colon cancer are present.[13, 38]

For individuals who received ≥30 Gy radiation to the abdominal, flank, lumbar-sacral spinal or pelvic regions the incidence and relative risk for colorectal cancer at age 35 years are comparable to an average aged 50-year-old individual with no known risk factors.[13, 18, 32, 39] Therefore, it is recommended that any childhood cancer survivors who received ≥30 Gy to the aforementioned regions undergo a screening colonoscopy at 5-year intervals beginning at age 35 years (Appendix 4).[16, 23, 36, 39]

SITES OF SECONDARY MALIGNANT NEOPLASMS WITHIN THE GENITOURINARY SYSTEM

Bladder. Individuals who received alkylating agents, especially cyclophosphamide and ifosfamide, pelvic radiation or combined therapy with alkylating agents and pelvic radiation are at risk for bladder cancer.[17, 36, 57, 58] The incidence of malignant tumors in this specific at risk patient population is 2% at 15 years and approximately 10% at 50 years after initial treatment.[17, 36] Annual screening by yearly urinalysis is not a significant benefit and, therefore, not recommended (Appendixes 3 and 4).

Kidney. In general, the risk of renal cancer in childhood cancer survivors is 5.5-fold higher than controls. The elevated risk predominately occurs in patients exposed to alkylating agents, especially cisplatin based chemotherapy and topoisomerase inhibitors.[13, 17, 40, 58-60] The impact of abdominal radiation on the risk of kidney cancer routinely occurs at doses of 5 to 20 Gy to the abdomen. It is noteworthy that this dose is commonly administered for advanced Wilms tumors when the risk of renal cell carcinoma in the contralateral non-involved kidney may be 66-fold higher than normal controls.[13, 17, 57-60] The significant variation in development of this tumor, ranging from fivefold to 66-fold higher risk than in a normal control population, is altered by the age at which the patient received chemotherapy or radiation therapy, and the combination of various chemo-radiation treatments. Specifically, the younger the child at the time of treatment and the combination of an alkylating agent and a topoisomerase agent with radiation therapy place the individual at the highest risk for renal cell cancer.[13, 17, 59, 60] Screening of this at risk patient population with yearly urinalysis and annual renal ultrasound is not of significant benefit and, therefore, is not recommended (Appendixes 3 and 4).[17, 60]

Testicle. The incidence of a second primary cancer arising within a testicle is highest in individuals who have a history of contralateral testicular cancer. There is a reported sevenfold to 14-fold increased risk of a testicular malignancy in the previous uninvolved testicle compared to the general population. The degree of this risk appears to be directly related to the use of cisplatin chemotherapy.[61, 62] Specifically, the risk for contralateral testicular cancer is decreased if the patient had exposure to cisplatin as part of the original treatment protocol. Presumably, this reduced risk following exposure to cisplatin is due to its influence on premalignant germ cells that may be present in the contralateral "normal" testes. Cisplatin, in essence, decreases the risk of a metachronous contralateral germ cell malignancy. Routine evaluation of the contralateral testicle by yearly testicular ultrasound and/or the measurement of testicular tumor markers outside of that performed for monitoring the primary testicular tumor may not be beneficial.[63]

CONCLUSIONS AND CAUTIONS

Individuals deemed at high risk for a SMN should be encouraged to participate in lifelong follow-up. **Indeed, the recommended surveillance protocols are of extreme benefit related to SMNs involving the breast and colon. Compliance with these recommendations is associated with almost half of the breast and colon cancers being diagnosed at an early treatable stage, resulting in documented improvement in cancer-specific survival.**[5, 13, 39] The detection of low stage cancers in this population is of extreme importance since options for treatment of more advanced disease may be limited due to past therapeutic endeavors.

The urologist should be aware that it is not uncommon for childhood cancer survivors to present to them as an adult for treatment of the sequelae of chemo-radiation complications (eg infertility, erectile dysfunction, symptomatic hypotestosteronemia and lower urinary tract symptoms) or for follow-up of a urinary diversion performed in childhood, and that approximately 50% of the patients have been lost to long-term follow-up.[5] The urologist's ability to identify the high risk patient and reestablish this patient with physicians who are familiar with the needed long-term surveillance protocols may indeed be a life-saving event. **In the United States information regarding where to refer these patients may be found on the National Children's Cancer Society Long-Term Follow Up Clinics website (www.thenccs.org/long-term-clinics).**

DID YOU KNOW?

- The majority of patients who will have a subsequent (secondary) malignant neoplasm will do so 10 years after treatment of the primary tumor.
- Childhood cancer survivors frequently present to a urologist with complaints of infertility, erectile dysfunction, symptoms of androgen deprivation and lower urinary tract symptoms, or for follow-up of a urinary diversion. Of these individuals 50% will have been lost to follow-up.
- Referral of a patient for follow-up to a pediatric cancer survivor clinic should occur when patient history reveals 1) inherent genetic abnormalities or syndromes that predispose to tumor growth, 2) a persistent non-malignant mass following successful treatment of the primary tumor, 3) a type of primary neoplasm that is known to have a high risk of SMN (eg retinoblastoma, any type of sarcoma or Hodgkin's disease), 4) prior chemotherapy at patient age <2 years and 5) prior radiation therapy as part of their treatment protocol.

Appendix 1. Incidence of increased risk for genitourinary sequela after treatment of childhood cancer[5, 26-30]

Genitourinary Sequela	Incidence or Increased Risk for Survivors
Male infertility	Approximately 45%
Erectile dysfunction	2.5-fold increased risk compared to age matched controls
Symptoms of low testosterone	Approximately 15% of male survivors (age 18-45 years)
Bladder dysfunction	5%-40%, incidence is dependent on percent of patients exposed to ifosfamide, cyclophosphamide, pelvic radiation or surgery, cranial or spinal radiation or surgery
Urinary diversion	15% of children with pelvic tumors had a urinary diversion performed either for initial treatment of cancer or secondary to an end stage bladder developing as a sequela of chemo-radiation therapy

Appendix 2. Classifications of the most common chemotherapeutic agents used for pediatric GU malignancies

Classification of Chemotherapeutic Agent	Treatment for Primary GU Tumors
Alkylating agent:*	
Cisplatin	Germ cell tumors
Cyclophosphamide	Rhabdomyosarcoma, Wilms
Ifosfamide	Germ cell tumors, rhabdomyosarcoma
Temozolomide	Rhabdomyosarcoma
Antitumor antibiotic:	
Bleomycin	Germ cell tumors
Dactinomycin	Rhabdomyosarcoma, Wilms
Plant alkaloid:	
Vincristine	Rhabdomyosarcoma, Wilms
Vinblastine	Germ cell tumors
Topoisomerase inhibitor:*	
Etoposide (VP16)	Germ cell tumors, rhabdomyosarcoma, Wilms
Doxorubicin (anthracycline)	Wilms
Irinotecan	Rhabdomyosarcoma, Wilms

*Risk of secondary malignant neoplasms is directly related to the use of these chemotherapeutic agents.

Appendix 3. Therapy for primary GU tumor related to secondary malignancy site

Therapeutic Exposure	Primary GU Tumor Treated	Secondary Malignancy Sites
Early induced SMN:		
Alkylating agents	Wilms tumor, germ cell tumors	Myelodysplastic syndromes and acute myelogenous leukemia
Topoisomerase inhibitors	Rhabdomyosarcoma	
Radiation induced delayed SMN:		
Radiation to chest +/- chemotherapy	Metastatic Wilms tumor	Breast, lung, skin, thyroid
Radiation to abdomen/flank	Advanced Wilms tumor	Breast, bladder, colon/rectum, gastric, kidney, pancreas, prostate, skin, thyroid
Pelvic radiation +/- chemotherapy	Rhabdomyosarcoma	Bladder, colon/rectum, prostate, skin, sarcomas

continued

Appendix 3, *continued*

Chemotherapy induced delayed SMN: Alkylating agents Anthracyclines	Wilms tumor Rhabdomyosarcoma	Breast
Cisplatin	Germ cell tumors	Colon, kidney, thyroid
Cyclophosphamide	Rhabdomyosarcoma, Wilms tumor	Bladder, thyroid, sarcomas
Ifosfamide	Germ cell tumors, rhabdomyosarcoma	Bladder, thyroid, sarcomas

Appendix 4. Site for potential secondary malignancies, carcinogenic inducing agents and suggested screening modalities

Potential Secondary Malignancies	Major Therapeutic Risk Factors of GU Malignancies Resulting in Recommendation for Screening	Screening
Myelodysplastic syndromes, acute myelogenous leukemia	Alkylating agents, topoisomerase inhibitors	History and physical exam for 10 yrs after exposure; annual complete blood count not of proven benefit
Bladder cancer	Cyclophosphamide, ifosfamide, pelvic radiation	Annual urinalysis to assess for hematuria and annual cystoscopy not of proven benefit
Breast cancer	Chest radiation >10 Gy	Annual history and physical exam, biannual breast exam at age 25 yrs, mammogram beginning at age 25 yrs or 8 yrs after radiation whichever is later
Colon cancer	Radiation to abdomen/flank or pelvis	Annual history and physical exam, colonoscopy at age 35 yrs or 10 yrs after radiation whichever is later
Lung cancer	Radiation to chest with or without chemotherapy	Annual history and physical exam; annual chest radiographic studies not of proven benefit
Renal cancer	Cisplatin, radiation to kidney	Annual urinalysis to assess for hematuria and annual renal ultrasound not of proven benefit
Skin cancer	Radiation therapy to any site	Annual history and physical exam are to include dermatologic exam focusing on radiation portal sites
Thyroid cancer	Chest radiation	Annual history and physical exam of thyroid; annual thyroid function tests and ultrasound not of proven benefit

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Study Questions Volume 39 Lesson 10

1. The combination of chemotherapeutic agents with the highest risk of causing acute myelogenous leukemia are
   a. cisplatin and etoposide
   b. cisplatin and bleomycin
   c. vincristine and dactinomycin
   d. vinblastine and cyclophosphamide

2. A 33-year-old women presents with lower urinary tract symptoms, and review of her medical history reveals that she is a Wilms tumor survivor. Consideration for referral to a pediatric cancer survivor clinic should occur if her history includes
   a. etoposide chemotherapy exposure
   b. vincristine chemotherapy exposure
   c. stage IV Wilms tumor treated with chemo-radiation
   d. stage V (bilateral) Wilms tumor treated with chemotherapy and bilateral partial nephrectomies

3. Patients who receive chemotherapy when younger than 2 years old are considered to be at high risk for a SMN. Lifelong follow-up for SMN in such patients should include a history and physical examination as well as
   a. additional tests only if abnormalities are detected on history and physical evaluation
   b. complete blood count and urinalysis
   c. complete blood count, urinalysis and chest x-ray
   d. complete blood count, urinalysis, chest x-ray, and abdominal and pelvic ultrasound

4. The 2 SMNs that result in 50% of the deaths of childhood cancer survivors are
   a. breast and lung
   b. thyroid and breast
   c. colorectal and lung
   d. breast and colorectal

5. Childhood cancer survivors who received cyclophosphamide or ifosfamide along with abdominal or radiation therapy after the age of 35 years should undergo annual history and physical examination as well as
   a. additional tests if abnormalities are detected on history and physical evaluation
   b. urinalysis and urine cytology
   c. urinalysis, urine cytology and cystoscopy
   d. urinalysis, urine cytology, cystoscopy and computerized tomography urography

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