Current Clinical Urology
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Cancer and Fertility

Humana Press

Current Clinical Urology

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ISSN 2197-7194 ISSN 2197-7208 (electronic)
Current Clinical Urology
ISBN 978-3-319-27709-7 ISBN 978-3-319-27711-0 (eBook)
DOI 10.1007/978-3-319-27711-0

Library of Congress Control Number: 2016938265

Printed on acid-free paper

This Humana Press imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

To my son, Ned, who is on a path to be an incredible man; my daughter, Emily, who is a bright star for the world; and my beautiful wife, Amy, who has stood by me for over 30 years, I dedicate this book to you. Without your love and support, this would not have been possible.

Preface

We are fortunate to live in a time where, despite a growing incidence of cancer in patients in their reproductive years, medical advances have allowed for long-term survival in the majority of such individuals. While cancer cure must remain our paramount goal, a growing number of patients face quality of life sequela from both the effects of the malignancy and the subsequent treatment. Numerous surveys of pre- and postpubertal cancer survivors reveal disappointment and regret over failure to consider fertility preservation during the period of cancer treatment.

This text is unique in its consideration of reproductive options for both male and female cancer survivors. Drawing on the experience of international experts in the field, this textbook is designed to provide a summary of state-of-the-art developments in fertility and its association with cancer for both new and experienced practitioners. The text provides a comprehensive review of normal female and male reproductive physiology as well as the impact of oncologic treatments on orderly germ cell development. In addition, focus is placed on the management of cancer diagnoses during pregnancy. Finally, future fertility preservation options including stem cell preservation as well as surgical germ cell harvest techniques are reviewed in depth. It is intended to be clear, concise, and readable to allow the reader to obtain rapid answers to this challenging medical issue. Special emphasis is placed on diagnostic and treatment algorithms to aid in standardized evaluations and management of these patients. The text is designed for urologists, gynecologists, medical and surgical oncologists, primary care providers, and allied health providers who have the privilege of assisting with fertility in both men and women.

It is indeed an amazing time to treat cancer patients as we move beyond a sole focus of cancer survival to all components of survivorship. In young patients who dream of a future family, no component of future quality of life is as important as future fertility. It is incumbent upon providers to understand the impact of various medical, surgical, and radiation treatments on a patient's reproductive potential. We hope this book stimulates your interest in this issue as we partner to assist these patients toward a fulfilling post-cancer life.

Cleveland, OH, USA — Edmund S. Sabanegh Jr.

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Demographics of Cancer in the Reproductive Age Male

1

Kiranpreet K. Khurana and Joseph P. Alukal

Fertility preservation for men undergoing treatment for malignancy is a problem of increasing importance for a number of reasons. First, as treatments for varying types of cancers in young men are increasingly successful, more men are given the opportunity to survive their malignancy and pursue family building. Of equal importance are the changing demographics of men pursuing family building; between 1980 and 2008, live birth rates amongst men ages 30–34, 35–39, and 40–44 years increased [1]. Concurrently, live birth rates for men ages 25–29 years decreased. Finally, 13 % of cancer diagnoses worldwide were made in patients under the age of 44 years [2]. As men delay fatherhood, the opportunity for them to have first developed cancer increases; as well the possibility of developing cancers such as prostate or bladder, which are not typically considered cancers of young men but do impact fertility, becomes greater. The changing demographics of men pursuing family building makes understanding the fertility risk of treating malignancy in this population even more important.

We outline in this chapter the demographics of cancer in the reproductive age male. Again, we will focus on those cancers typically thought of as common in this demographic population: leukemia, lymphoma, and testis cancer. We will consider as well the demographics of rare cancers such as central nervous system (CNS) malignancies, and we will also review the incidences of prostate, bladder, and colon cancer in men pursuing fertility. Although the topic is covered in greater detail in the rest of this textbook, we will also review briefly the fertility impact of treatments commonly utilized in this age group for management as well as a broad review of fertility preservation strategies that can be undertaken with these patients. Statistics regarding the prevalence or incidence of these diseases are given for men on an annual basis in the United States; this is in the context of 52 million American men between the ages of 20 and 45 years (the age demographic within which men are most likely to pursue family building), according to the 2010 National Census Bureau Report [3].

Thus, the comprehensive care of males of reproductive age with cancer involves minimizing the effect of treatment on fertility potential, and a focus on improving quality of life. This includes a thorough discussion of impact on fer-

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E.S. Sabanegh, Jr. (ed.), *Cancer and Fertility*, Current Clinical Urology,
DOI 10.1007/978-3-319-27711-0_1

tility and possible consultation with an infertility expert prior to initiating treatment for cancer.

Cancers of Young Men: Overview

Pediatric Cancers

Approximately 10,380 children ages 0–14 years will be diagnosed with childhood cancer in 2015 [4]; the incidence of cancer in children has been increasing 0.6 % annually for the last 35 years [5]. A child born in the United States in 2015 has a 0.24 % chance of developing cancer from age 0 to 14 years [6]. Cancers are more common in Caucasian and Hispanic children than children from other races [5]. Due to the advancement in treatment of childhood cancers, over 80 % of children diagnosed with cancer will survive more than 5 years, which is a vast improvement compared to 1970s, when the 5-year survival rate was 58 % [4]. Cancer is the second most common cause of childhood death [4], but the leading cause of death after infancy [5]. About 1250 US children with cancer ages 0–14 years are expected to die in 2015 [4].

The types of cancers in childhood from most common to least common and their respective prevalences are: leukemia (30 %), brain and other CNS cancers (26 %), neuroblastoma (6 %), Non-Hodgkin lymphoma (5 %), Wilms tumor (5 %), soft tissue sarcomas (3 %), bone cancer (3 %), and retinoblastoma (2 %) [4]. Brain and CNS cancers remain the most common cause of cancer deaths in childhood [5].

Acute lymphocytic leukemia (ALL) accounts for 26 % of cancers diagnosed in children ages 0–14 years and 8 % of cancers diagnosed in children ages 15–19. ALL is more common in boys than girls. The 5-year survival in children with ALL has increased from 57 % in mid-1970s to 90 % in mid-2000s [6], and presently, greater than 75 % of pediatric patients with ALL reach adulthood [7]. Brain and CNS tumors are the second most common type of cancers in children below age 20, accounting for about 26 % of all cancers below that age. About one in five childhood cancers are CNS tumors. Three out of four children with CNS tumors will survive at least 5 years [8]. Non-Hodgkin's lymphoma accounts for approximately 5 % of all childhood cancers. In children ages 0–14 years, about 500 cases of Non-Hodgkin's lymphoma are diagnosed each year. In adolescents ages 15–19 years, another 400 cases of Non-Hodgkin's lymphoma are diagnosed [9].

Adolescent Cancers

About 5330 adolescents ages 15–19 years will be diagnosed with childhood cancer in 2015 [6]. An adolescent between ages 15–19 years, who is born in the United States, has a 0.35 % chance of developing cancer [6]. Of these, approximately 610 adolescents are expected to die in 2015 [6]. The types of cancers from most common to least common and their respective prevalence in this age group are: Hodgkin lymphoma (15 %), thyroid (11 %), brain and other CNS (10 %), and testicular germ cell cancers (8 %) [6, 10].

Data up to January 1, 2010 suggests that there are about 380,000 survivors of childhood cancers ages 0–19 years living in the United States [6]. One in 530 young adults between the ages of 20 and 39 years is a childhood cancer survivor [6]. The adolescent cancer incidence has been steadily increasing along with survival from cancer, resulting in greater number of population with history of cancer and cancer-related treatment in the reproductive aged cohort. The most common cancer diagnoses amongst the survivors are acute lymphoblastic leukemia, brain and CNS tumors, and Hodgkin lymphoma [6].

Treatment of Adolescent and Childhood Cancers in Males and Impact on Fertility

Treatment for ALL consists of 4–6 weeks of induction chemotherapy followed by consolidation chemotherapy for several months and 2–3 years of maintenance chemotherapy. There is also a role for allogeneic bone marrow transplant in children with high-risk features at time of diagnosis, recurrence after remission, and the

inability to go into remission after induction chemotherapy. Children with high risk of CNS recurrence may be treated with cranial irradiation, which has largely been replaced with intrathecal chemotherapy in recent treatment protocols. Acute myeloid leukemia has a lower incidence (5 %) in children ages 0–14 as compared to ALL and accounts for 4 % of cancers in adolescents ages 15–19 [6].

A common regimen used in leukemia, namely cyclophosphamide or melphalan in addition to total body irradiation, resulted in permanent sterility in approximately 83 % of patients [11]. Cyclophosphamide has a dose-dependent negative effect on gonadal function, and greater than 10 g/m^2 cumulative dose has a high risk of permanent damage to gonadal function [12]. This detrimental effect exists even in prepubertal testes showing that there is some germ cell proliferative activity in infancy [13].

The most spermatotoxic chemotherapy drugs are nitrogen mustard derivatives, i.e., busulphan and melphalan, and alkylating drugs, i.e., cyclophosphamide and procarbazine [14]. Table 1.1 classifies chemotherapy drugs into high, medium, and low risk of impairment on spermatogenesis. When comparing two regimens used for Hodgkin's disease, namely nitrogen mustard, vincristine (oncovin), procarbazine, and prednisone (MOPP) and adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), MOPP has a higher risk of infertility than ABVD [14]. Males who received >3 courses of MOPP were found to have azoospermia in 85–90 % after >1 year of follow-up. Comparatively, 90 % of patients had normal sperm counts a year after therapy with ABVD. MOPP is also more detrimental to fertility than bleomycin, etoposide, and cisplatin (BEP) for testicular germ cell tumors (TGCT). In one study, TGCT treated with a cisplatin-based therapeutic regimen resulted in normal sperm parameters in 63 % of patients after 1 year, which increased to 80 % at 5 years [14].

The effect of chemotherapy is greater on Sertoli cells than Leydig cells, thereby having a detrimental impact on spermatogenesis. This can result in significant reduction in sperm count to the point of oligospermia or azoospermia. A Norwegian study [15] found the overall prevalence of azoospermia in childhood cancer survivors to be 18 %, with the prevalence being 19 % for leukemias, 53 % for Hodgkin lymphoma, 11 % for non-Hodgkin lymphoma, and 11 % for testicular cancer. Comparatively, the prevalence of azoospermia in normal males is 1 %. In men treated with high cumulative dose alkylating agents or cisplatin, 80 % were azoospermic, whereas this rate was significantly lower at 5.3 % if treated with below-threshold cumulative doses of alkylating agents or cisplatin [15]. See Table 1.2 for threshold cumulative doses of different chemotherapy drugs on spermatoxicity.

Other factors associated with high rates of azoospermia in childhood cancer survivors

Table 1.1 Classification of chemotherapy agents by risk of damaging spermatogenesis

Low risk	Medium risk	High risk
Bleomycin	ABVD (adriamycin, bleomycin, vinblastine, dacarbazine)	Busulfan
Dactinomycine	BEP (bleomycin, etoposide, cisplatin)	Chlorambucil
Mercaptopurine	Carboplatin	Chlormethine
Methotrexate	Cisplatin	Cyclophosphamide
Vinblastine	Doxorubicin	Dacarbazine
Vincristine		Ifosfamide
		Melphalan
		MOPP (nitrogen-mustard, vincristine, procarbazine, prednisone)

Source: Modified from Wallace WH, et al. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncology. 2005; 209–18

Table 1.2 Cumulative threshold doses with high risk of azoospermia for different chemotherapy agents

Chemotherapy agent	Cumulative threshold dose with high risk of azoospermia
Carmustine	1 g/m^2
Lomustine	500 mg/m^2
Chlorambucil	1.4 g/m^2
Cisplatin	500 mg/m^2
Cyclophosphamide	19 g/m^2
Melphalan	140 mg/m^2
Procarbazine	4 g/m^2

Source: Modified from Romerius P, et al. High risk of azoospermia in men treated for childhood cancer. International Journal of Andrology. 2010; 34(1): 69–76

included use of radiotherapy, lower inhibin B levels (≤50 ng/L), elevated follicle stimulating hormone (FSH) (≥10.9 IU/L), and decreased testicular volume (right + left testicular volume ≤ 24 mL). The prevalence of azoospermia was 66 % in men with lower inhibin B level, 50 % in men with higher FSH level, and 61 % in men with lower testicular volume. It is notable that the prevalence of azoospermia in men with normal FSH and inhibin values was only 1–2 %, implying that azoospermia may be due to alteration of these two hormonal values. This study did not find azoospermia in men treated for brain tumor or Wilms tumor, as well as for brain surgery not involving the pituitary and non-testicular radiation [15].

Leukemia, lymphoma, and CNS tumors may affect the hypothalamus and pituitary with direct cell invasion and irradiation is often the treatment option for these patients. A study of 25 males with ALL who received a median of 25 Gray (Gy) (range 15–30 Gy) radiation dosage to the cranium with a median follow-up of 19 years showed that there was no difference in luteinizing hormone (LH), FSH, inhibin B, and testosterone levels between those who received cranial irradiation and those who did not. This study also evaluated seven patients who received total body irradiation and testicular irradiation and showed high levels of LH, FSH, and low levels of inhibin B indicating testicular damage. Age at the time of diagnosis was not a risk factor for alteration of these hormones [7]. Therefore, this data showed that irradiation to the cranium did not impact the hypothalamus pituitary axis in the long term. However, radiation to the testes and whole-body radiation prior to bone marrow transplantation was shown to be damaging to the testicular components. Furthermore, germ cells are more sensitive to radiation than Leydig cells, with a dose more than 4 Gy capable of causing permanent damage, whereas a dose greater than 20 Gy is needed to cause damage to Leydig cells and produce hypogonadism [11].

Similar treatment regimens are employed in young adults diagnosed with these malignancies. Alternate fertility preservation strategies may be employed given the possibility of sperm banking in these patients. Negative impacts on spermatogenesis are generally less in postpubertal males.

Testis Cancer

Males of reproductive age are often affected by TGCT as it is the most common cancer in males ages 15–44 years, accounting for over 60 % of cancer diagnoses in this cohort. An estimated 8400 new cases of testicular cancer will be diagnosed in 2015 [16]. A recent study showed that the rates of TGCT increased significantly during 2007–2011 versus 1992–1997 time period, especially for non-seminoma GCT. However, seminomas remained more common overall. The median age at diagnosis of seminoma was 36 years, while it was 28 years for non-seminomas. About 20 % of seminomas were diagnosed at non-localized stages compared to 40 % for non-seminomas [17].

Survival rates for TGCT have been improving in the last several decades with 10-year survival rates over 95 % [18]. Quality of life, including fertility concerns, are therefore of utmost importance for these patients. Common treatment strategies in TGCT include orchiectomy, and possible radiation or platinum-based chemotherapy. These treatment modalities may be particularly harmful to overall gonadal function, including impaired spermatogenesis, detrimental effect on sperm quality, and hormonal disturbance. A study of 117 patients [19] with TGCT showed that about 30 %

of men who had attempted to conceive prior to TGCT diagnosis were successful in fathering children. Of the rest, 31 % had oligoasthenospermia, and 13 % had azoospermia. Post-treatment sperm concentration decreased in all treatment groups including surgery and surveillance alone, surgery followed by retroperitoneal lymph node dissection, surgery and chemotherapy, surgery followed by radiotherapy, and surgery followed by chemotherapy and radiation. After treatment for TGCT, 48 % of patients who attempted to conceive were successful, of which 22 % conceived naturally and 26 % with artificial reproductive technology (ART). Of the latter group, 58 % were able to undergo in vitro fertilization using fresh sperm, and 42 % using cryopreserved sperm. Of all the men who did not have children prior to diagnosis, only 22 % banked sperm. This was attributed to lack of adequate information or inadequate sperm parameters for cryopreservation.

Another study of 1433 men [20] with testicular cancer showed that 15-year post-treatment paternity rate was 71 % without the use of cryopreserved semen. The rate was 48 % in men treated with high-dose cisplatin-based chemotherapy (>850 mg cisplatin) versus 92 % in men on surveillance. As discussed above, the effect of chemotherapy on spermatogenesis is dependent on type and cumulative dose of chemotherapy. Another study evaluated 45 patients treated with 1–6 cycles of BEP in TGCT patients. They found that the rate of recovery of spermatogenesis at 2 years after 1–2, 3, 4, 5–6 cycles of BEP chemotherapy was 83 %, 80 %, 67 %, and 0 %, respectively [21].

In the aforementioned study by Brydoy et al. [20], ART was used by 22 % of couples attempting to conceive after treatment. The paternity rates of those treated with retroperitoneal lymph node dissection, radiotherapy, and low-dose chemotherapy (≤850 mg cisplatin) were similar [20, 22]. One hundred seventy-eight men with seminoma were treated with dog-leg or L-field radiation, and 63 % of those men were able to conceive successfully. There was no significant difference in paternity rates amongst<31 Gy, 31–36 Gy, and >36 Gy radiation dose groups. Nine out of 16 patients (56 %) who received a combination of cisplatin-based chemotherapy and infradiaphragmatic radiation with a median dose of 40 Gy had successful conception after treatment.

Ejaculatory function may be affected by certain treatments for TGCT, especially retroperitoneal lymph node dissection. The 10-year paternity rate after treatment amongst men with dry ejaculate was only 10 % compared to 83 % in men with normal ejaculation. The 19-year paternity rate was slightly better at 31 % and 91 %, respectively. In this study, dry ejaculate was the strongest negative predictive factor for achieving paternity [20]. Treatment options for fertility for these men include use of α-sympathomimetic drugs, testis sperm extraction, and transrectal electroejaculation.

Other Malignancies: Prostate, Bladder, and Colon Cancers

Prostate Cancer

Prostate cancer, bladder cancer, and colon cancer can all have varying degrees of impact on fertility depending upon the nature of the treatment involved. Certainly high-grade cancers requiring extirpative surgery carry the likely risk of anejaculation; adjuvant or neoadjuvant chemotherapy or radiation regimens carry additional risk to spermatogenesis itself. Again, while these cancers are typically not thought of as cancers of young men, more men are potentially susceptible to developing one of these cancers prior to fathering children as trends towards delayed family building strengthen. All three cancers are diagnosed in a fashion where pre-treatment sperm banking can be offered to any male patient desiring future fertility without any dangerous delay of treatment.

Prostate cancer is the most common solid malignancy in men; an estimated 220,000 new cases of prostate cancer will be diagnosed in the United States in 2015 [16]. Trends towards increased incidence of the disease are thought not to be due to increasing prevalence of the disease, but rather increased screening as the driving factor. Changes in screening behaviors in the United States are ongoing, and may influence this trend in the immediate future.

Commonly accepted treatment options for men include radical surgery, radiation therapy, hormonal ablative therapy, nonhormonal chemotherapies, and active surveillance. Increasing research into focally ablative therapies including cryotherapy and high intensity focused ultrasound is ongoing. Amongst these treatments, surgery (open, laparoscopic, and robotic assisted laparoscopic radical prostatectomy), radiation (brachytherapy, external beam radiotherapy, and proton beam radiotherapy), and active surveillance represent the more commonly offered treatments for organ confined prostate cancer. Age, comorbidity, and patient preference generally influence the decision to pursue one or another of these treatments if the patient has localized disease. All of these treatments, with the exception of active surveillance, have at least some impact on fertility with surgical treatments causing de facto anejaculation.

Data regarding the age migration of the population being diagnosed with prostate cancer is well established; Adolfsson et al. [23] outlined the shift in prostate cancer demographics observed in Sweden between the years of 1996–2005 within the Swedish National Prostate Cancer Registry. Age-standardized rates of diagnosis increased steadily in the youngest two groups (patients aged 0–49 and 50–59 years), and median age at time of diagnosis dropped from 75 years in 1996 to 70 years in 2005. This trend was reflected in other countries in the western world and was commonly attributed to a number of factors including, but not limited to, increased utilization of prostate-specific antigen screening.

Bladder Cancer

Bladder cancer is another common genitourinary malignancy with a potential fertility impact; approximately 56,000 bladder cancers will be diagnosed in American men in 2015 with 11,500 deaths [16]. Although bladder cancer is generally a cancer of the elderly (mean age at diagnosis is 73 years), 1 out of 10 patients diagnosed with bladder cancer is under the age of 55 years.

Treatment options include endoscopic management (appropriate in cases where disease is confined to the bladder and not locally advanced), surgical extirpation (partial or radical cystectomy with or without the prostate), chemotherapy, and radiation. In locally advanced disease (approximately 35–40 % of cases), combination treatment with neoadjuvant chemotherapy followed by surgical removal of the bladder and prostate is the appropriate treatment. Commonly utilized chemotherapy regimens include platinum-based agents in combination with other drugs (methotrexate, vincristine, doxorubicin, cisplatinum—MVAC; gemcitabine, cisplatinum—GC). Both have a potential risk of damage to spermatogenesis. Radical surgery carries the risk of erectile dysfunction with risk to the cavernous nerves within the neurovascular bundles adjacent to the prostate as well as the risk of anejaculation.

Colon Cancer

Colon cancer (including both adenocarcinoma of the rectum and colon) represents the third most common malignancy in both men and women; there were more than 132,000 cases estimated for the United States in 2015 [16]. Five percent of Americans will develop colon cancer in their lifetime. Increasing success with early diagnosis due to screening colonoscopy as well as increasingly effective treatment modalities have resulted in decreasing cancer-specific mortality; again this makes it more likely that the male patient with infertility related to colon cancer treatment will survive to attempt family building.

Treatment options include partial versus radical surgery, performed either endoscopically (organ sparing), open, laparoscopically, or robotic assisted laparoscopically. Risks of any of these approaches include (1) erectile dysfunction due to injury to the cavernous nerves within the neurovascular bundles adjacent to both the prostate and rectum or (2) ejaculatory dysfunction due to disruption of the pelvic plexus. Although these risks are possible with each of these approaches, they are least with endoscopic management. However, endoscopic management