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The management of cancer in the older adolescent

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Abstract

Cancer in adolescents 15–19 years of age occurs at nearly twice the rate observed in 5- to 14-year-olds, but as of yet they have no explicit organisation for research and care, such as that structured for younger paediatric patients. Adolescents with cancer must be recognised as a subgroup of oncology patients with specific characteristics and needs requiring dedicated interest and management. The need is made most evident as outcome data indicates that adolescents are lagging behind in survival gains made in recent decades by both children and adults with cancer. Improvements in the overall survival, quality of care and quality of survival of adolescents with cancer will only occur by surmounting the challenges, discussed in this review, unique to this group of patients.

Keywords: Cancer; Adolescents; Young adults

1. Introduction

The rate of 5-year survival improvement in children and in adults 45 years of age and older, shown in Fig. 1 for the 1975–1998 era in the United States (U.S.), has averaged a steady and remarkable 1.74% per year for patients of all ages with invasive cancers. However, among adolescents 15–19 years of age, the improvement has been nearly 50% less, at 0.91% per year (Fig. 1) [1]. With the types of cancer that older adolescents develop, their overall survival was better, in the 1970s and 1980s, than in children and younger adolescents. The relative lack of progress has led to worse outcome, such that during the 1990s, the survival of 15- to 19-year-olds fell behind that in younger patients (Fig. 2). In the U.S., Europe, and most socio-economically advantaged countries, cancer develops in more patients between 15 and 20 years of age than between either 5 and 10 or 10 and 15 years of age. Yet, few, if any, countries have nationally organised programmes to address their special problems, including the relative lack of progress in their outcome.

Reasons for this lack of progress are certainly numerous and multifactorial. They include issues specific to this age group: some are inherent in the disease or the patient (differences in biology or intolerance of therapy), some are inherent in the system (treatment by physicians less familiar with the disease, delay in recognition of malignancy, lack of available clinical trials), and others are influenced by the psychosocial milieu of the patient (lack of medical insurance and financial resources, delays in seeking medical attention with symptoms of cancer, poor compliance with treatment, unwillingness to participate in clinical trials). A further consideration is that the physical, emotional and social challenges posed by cancer in adolescence and early adult life are often unique and especially difficult for patients, families and healthcare providers alike; these needs remain largely unstudied and unmet.

This review considers the scope of the problem by reviewing the incidence and mortality burden of cancer in the adolescents, the unique distribution of cancers and the concerning lack of improvement in survival. We then address those issues that make management of this population of oncology patients unique and challenging. The goal is to heighten awareness of a relatively neglected group of patients and improve their recognition, management and outcome. The focus will be on patients in the 15- to 19-year age group, notwithstanding the likelihood that many of the principles are

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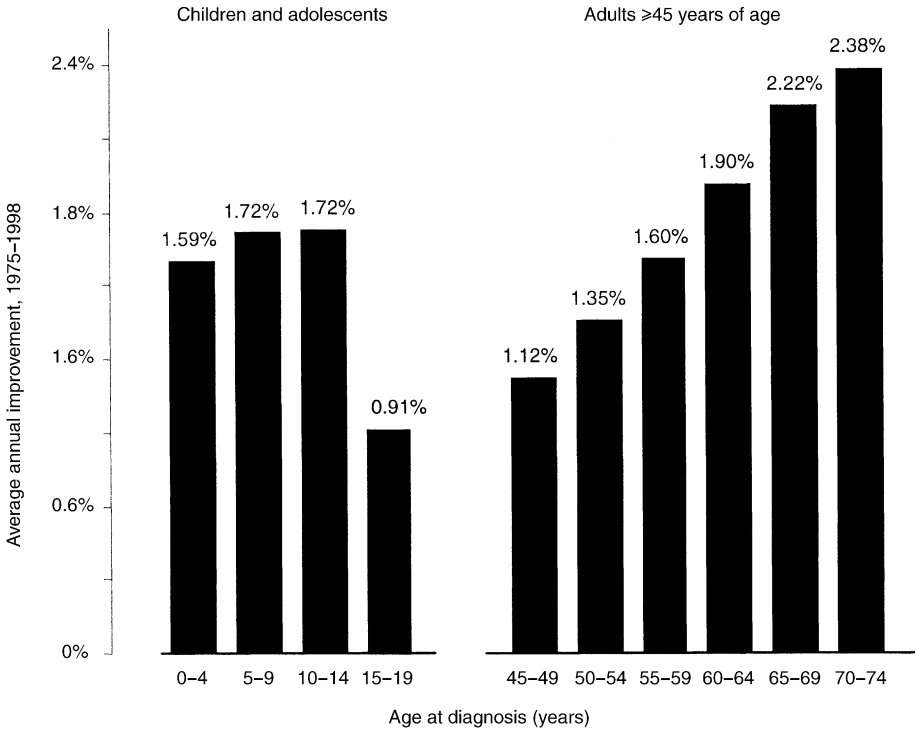

Fig. 1. Average annual percent improvement in the 5-year survival rate among United States (U.S.) cancer patients less than 20 years and 45 years and older at diagnosis. The average annual percent change was derived as a function of patient age from linear regressions of the rates during 1975–1980, 1981–1986, 1987–1992 and 1993–1988 [1]. Data from the U.S. Surveillance, Epidemiology and End Results (SEER) programme [3].

applicable to older patients, especially those 20- to 39-years of age.

2. Scope of the problem

2.1. Incidence

Charles Stiller recently reviewed the epidemiology of cancer in adolescents [2]. In the U.S., data from the National Cancer Institute's (NCI's) Surveillance, Epidemiology and End Results (SEER) programme indicate that the overall incidence of cancer in 15- to 19-year-olds during the 1990s was 203 cases per million per year (Table 1), the highest reported since the U.S. SEER programme began in 1973 (Table 2) [3]. The rate in 15- to 19-year olds is two-thirds more than in those 10- to 14-years of age, nearly twice that in children 5 to 9 years of age, and equivalent to the rate in children under 5 years of age. The Northern Region Young Persons' Malignant Disease Registry (NRYPMDR) in England, calculating rates over the entire interval of 1968–1995, documented a rate of 144.3 cancers per million adolescents per year [4]. A third large study to record incidence in this age group is the Netherlands Cancer Registry which for 1989–1997 found a rate in this age group of 193.3 cases per million per year [5]. This rate is virtually identical to the rate observed in the U.S. during a comparable interval.

Table 1
Average annual age-specific incidence rates per million, all races, U.S. SEER, 1993–1997[a]

Age at diagnosis	Both genders	Females	Males	Female:Male
(Years)	Incidence (per million per year)			Ratio
0–4	206	185	226	0.81
5–9	105	94	115	0.82
10–14	123	119	127	0.94
15–19	203	198	208	0.95
20–24	346	364	328	1.11
25–29	604	645	563	1.15
0–14	145	133	156	0.85
15–29	384	402	366	1.10

[a] Derived from Ries, LAG and colleagues [3]. SEER, Surveillance, Epidemiology and End-Results; U.S., United States.

The overall incidence of invasive cancer in U.S. 15- to 19-year-olds increased an average of 0.9% per year from 1975 to 1997 (Table 2). Similar increases have been noted in England [4] and other Western countries. Non-Hodgkin's lymphoma (NHL) and testicular carcinoma have shown the greatest increases in this age group over this interval, each averaging an increase of more than 2% per year for 24 years (Table 2). These diseases, as well as thyroid cancer, have also been noted to be on the rise in adolescents and young adults in other Western countries [6].

2.2. Types of cancer

The spectrum of cancers in this age group is unique; in order of incidence they include Hodgkin's disease, germ cell cancer, acute leukaemias, CNS tumours, soft-tissue sarcomas, non-Hodgkin's lymphoma, thyroid carcinoma, malignant melanoma and bone sarcomas (Fig. 3, Table 3). Adolescents and young adults rarely develop the cancers that predominate in older adults, such as carcinomas of the aerodigestive and genitourinary tracts [6]. Similarly, most of the common "developmental" malignancies in children younger than 5 years of age are virtually absent in 15- to 19-year-olds, including the embryonal malignancies of Wilms' tumour, neuroblastoma, medulloblastoma, ependymoma, hepatoblastoma and retinoblastoma. The incidence of osteosarcoma, Ewing's sarcoma, gonadal germ cell tumours, and Hodgkin's disease have a peak in incidence during adolescence and young adulthood. The two bone sarcomas peak between 15 and 19 years of age and the gonadal tumours and Hodgkin's disease peak between 20 and 29 years of age (Fig. 3). There are marked differences in the incidence of certain cancers in this age group by gender, ethnicity and country; these are described elsewhere in Refs. [2,7,8].

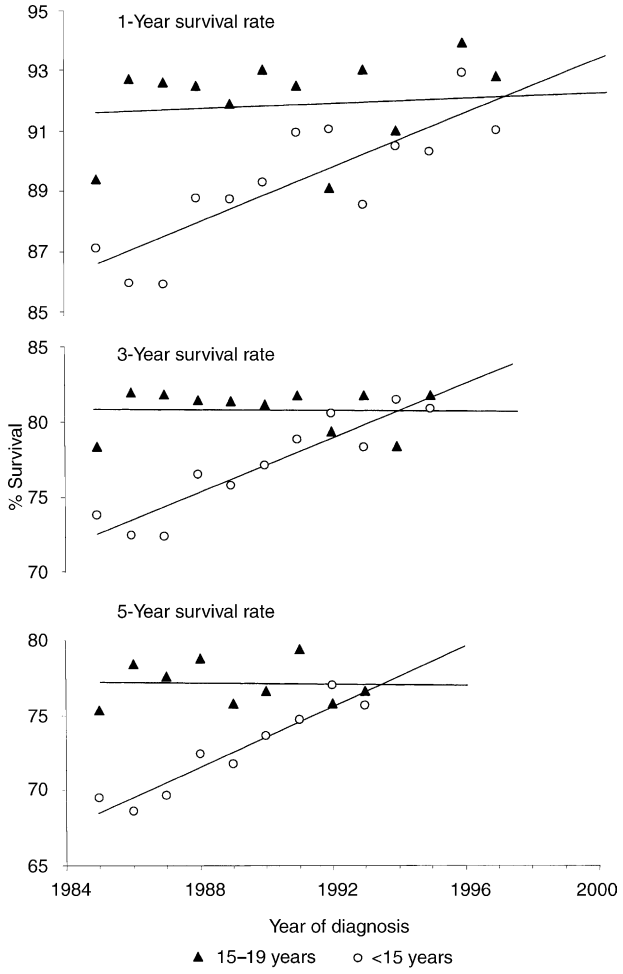

Fig. 2. 1-, 3- and 5-year survival rates and linear regression for 0- to 14-year-old and 15- to 19-year-old U.S. cancer patients since 1985. Data from the U.S. SEER programme [3].

2.3. Mortality

In the U.S., cancer is the leading cause of non-accidental death among adolescents and young adults. In 15- to 19-year olds, cancer is the fourth leading cause of all deaths, following accidental injuries, suicide and homicide [9]. Mortality burden is a function of the survival and incidence rates. In particular, more than 80% of the U.S. national cancer mortality burden among 15- to 19-year-olds is due to four malignancy groups: sarcomas, leukaemia/lymphomas, CNS tumours, and germ cell tumours, with leukaemia being the primary contributor. Although thyroid carcinoma and melanoma are among the more common cancers in this age group, because of their high cure rates, they contribute little to the overall cancer mortality burden.

2.4. Relative lack of improvement in survival

As described in the Introduction and in Figs. 1 and 2, improvements in survival have been considerably

Table 2
Average annual age-specific incidence rates per million adolescents 15- to 19-years old for selected tumours, U.S. SEER, 1975–1995[a]

Tumour type (ICCC[b] category)	Rate			
	1975–1979	1980–1984	1985–1989	1990–1994
All sites	183.0	187.7	199.3	203.8
Acute lymphoblastic leukaemia	10.6	13.2	12.4	13.0
Non-Hodgkin's lymphoma	10.7	14.5	14.4	16.3
Osteosarcoma	6.6	8.9	9.7	9.3
Testicular germ cell tumour	22.1	26.7	24.9	28.4
Ovarian germ cell tumour	7.9	8.3	11.8	13.3
Gonadal carcinoma	2.7	2.4	4.3	5.3

[a] Modified from Smith MA and colleagues [7].
[b] International Classification of Childhood Cancer.

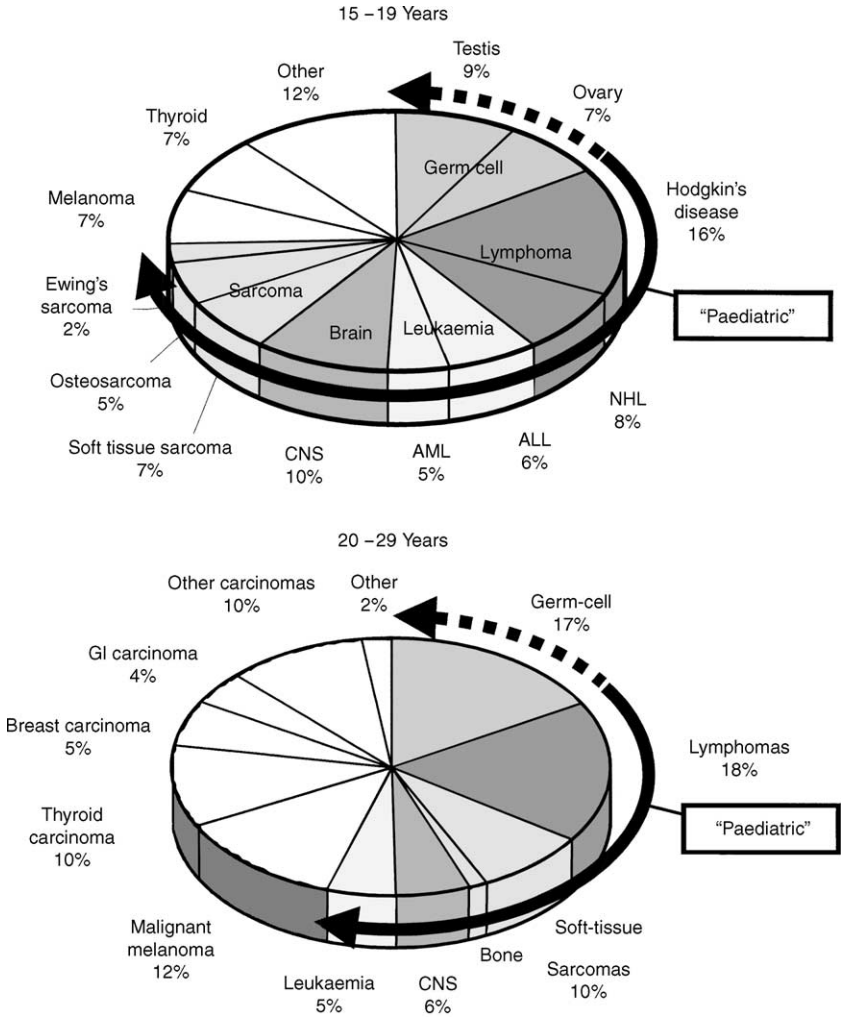

Fig. 3. Common malignancies diagnosed at age 15 to 19 years (upper panel) and 20 to 29 years (lower panel). Data from the U.S. SEER programme [3]. The arrow circumscribes those cancers that are common in children. GI, gastrointestinal; CNS, Central Nervous System; AML, acute myelogenous leukaemia; NHL, Non-Hodgkin's Lymphoma; ALL, acute lymphoblastic leukaemia.

greater in younger patients than in older adolescents. If this trend is projected to 2000, the 5-year survival rate should have been 77% in 15- to 19-year-olds and 84% in younger patients (Fig. 2). This would result in an inversion of superiority from a more than 10% advantage of the older age group in 1975 to a 7% disadvantage compared with the younger patients in 2000 [10].

The worst outcomes among the common cancers in 15- to 19-year-olds are in acute myelogenous leukaemia (AML), acute lymphoblastic leukaemia (ALL), and the sarcomas, particularly rhabdomyosarcoma, Ewing's sarcoma and osteosarcoma. Each of these is associated with a lower 5-year survival rate than that of the same malignancy obtained in younger patients. With the exceptions of thyroid carcinoma, melanoma and germ cell tumours, the remaining common cancers in older adolescents are associated with a worse prognosis than is found with the same cancers in younger age groups (Fig. 4). The reasons for these deficits are considered in the next section, *Challenges*.

3. Challenges

3.1. Different biology

Understanding the aetiology and biology of cancer in the adolescent will impact the management of cancer in this age group, both from a public health standpoint of cancer control, and by adjustment of therapy formulated for a younger or older patient whose tumour may have a different biology.

Very few cancers in this age group have been attributed to single environmental or inherited factors. An exception is clear-cell adenocarcinoma of the vagina or cervix in adolescent females, with most cases caused by diethylstilboestrol taken prenatally by their mothers in an attempt to prevent spontaneous abortion [11]. This association must prompt us to take seriously other hypotheses of carcinogenic exposures with latency periods as long as twenty years old. Radiation-induced cancer may occur in adolescents and young adults after

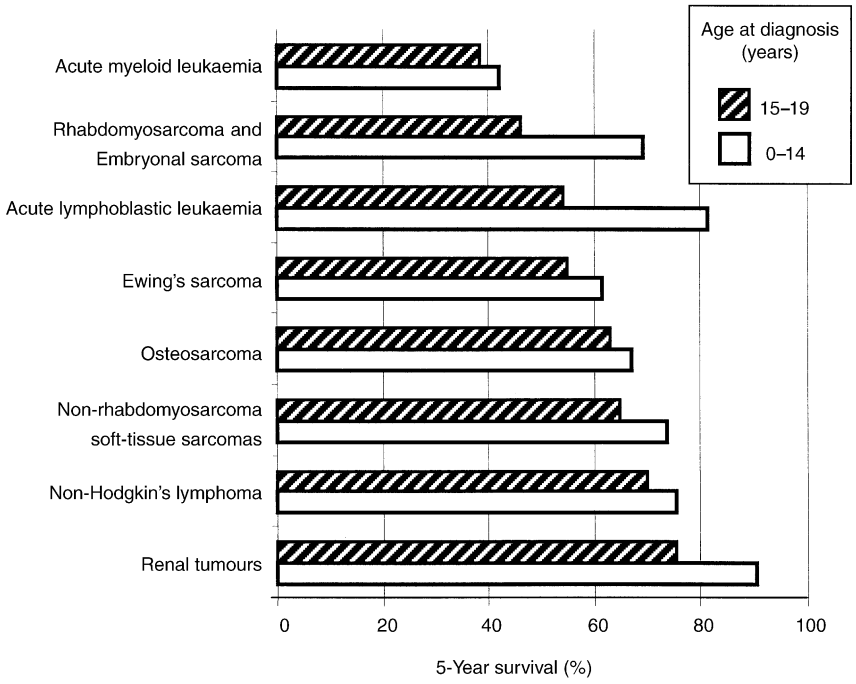

Fig. 4. Gap in survival rates for selected cancers in 15- to 19-year-olds versus <year-olds. Data from the U.S. SEER programme [3].

Table 3
Age-specific cancer incidence rates per million and percentage of total cases by cancer type and age group, U.S. SEER, 1986–1995[a]

	Age (in years) at diagnosis				% of total for 15 to 19-year-old group
Tumour category	<5	5–9	10–14	15–19	
All sites	199.9	110.2	117.3	202.2	100.0%
Acute lymphoblastic leukaemia	58.2	30.3	17.8	12.9	6.4%
Acute myeloid leukaemia	10.1	4.5	5.7	8.5	4.2%
Hodgkin's disease	0.8	3.9	11.7	32.5	16.1%
Non-Hodgkin's lymphoma	5.9	8.9	10.3	15.3	7.6%
CNS tumours	36.0	31.9	24.6	20.2	10.0%
Ependymoma	5.6	1.6	1.3	1.1	0.5%
Astrocytoma	15.0	15.9	15.1	12.3	6.1%
Medulloblastoma/primitive neuroectodermal tumour	9.6	7.3	4.0	2.5	1.2%
Neuroblastoma and ganglioneuroblastoma	27.4	2.6	0.8	0.5	0.2%
Retinoblastoma	12.5	0.5	0.0	0.1	<0.1%
Wilms', rhabdoid, clear cell sarcoma	18.0	5.8	0.6	0.4	0.2%
Hepatic tumours	4.8	0.4	0.4	1.0	0.5%
Hepatoblastoma	4.6	0.2	0.1	0.0	<0.1%
Osteosarcoma	0.3	2.8	8.3	9.4	4.6%
Ewing's sarcoma	0.3	1.9	4.1	4.6	2.3%
Soft-tissue sarcoma	10.9	8.3	10.9	15.9	7.9%
Rhabdomyosarcoma, embryonal sarcoma	6.5	4.4	3.5	3.9	1.9%
Non-rhabdomyosarcoma soft-tissue sarcoma	4.4	4.0	7.4	11.9	5.9%
Germ cell, trophoblastic, other gonadal	6.9	2.4	6.7	30.8	15.2%
Thyroid carcinoma	0.1	1.0	4.1	14.6	7.2%
Malignant melanoma	0.8	0.6	2.8	14.1	7.0%
Other and unspecified carcinomas	0.4	0.8	2.8	10.5	5.2%

CNS, Central Nervous System.
[a] Modified from Smith MA and colleagues [7].

exposure during early childhood. Rates of thyroid cancer in children and adolescents have increased in Eastern European and Slavic countries since the Chernobyl accident in 1986 [12]. Secondary malignancies can occur during adolescence in those children who were treated with chemotherapy and/or radiotherapy for a primary cancer.

Given that the duration of exposure to potential environmental carcinogens is directly proportional to age, it is not surprising that tobacco-, sunlight- or diet-related cancers are more likely in older adolescents and young adults than in younger children. Nonetheless, in most cases, it appears to take considerably longer than one or two decades for these environmentally related cancers to become manifest. An alternate hypothesis is that adolescents who get cancer after a carcinogenic environmental exposure have a predisposing genotype. Most of colorectal carcinoma in young adults, for example, occurs in persons who have the hereditary form (polyposis coli). Skin cancer, lymphoma, sarcoma, thyroid and hepatic cancers may also occur at higher frequency during this period of life in persons with inherited or prenatally-acquired conditions.

For those cancers that have a worse outcome in adolescents than in children, the disease may not the same in the two age groups, and may thereby need different therapeutic approaches. In ALL, several studies have attempted to determine whether it is a different biology or age alone that is responsible for this survival differential. Because adolescents and adults have an increased incidence of T cell immunophenotype, L2 morphology and adverse cytogenetic characteristics, it has been postulated that these adverse prognosticators are associated with inherent drug resistance, and result in lower cure rates [13,14]. Several studies showed that adolescents 10- to 14-years of age fared better than those of age 15 to 19 years [15,16]. Alternatively, the (CCG) 100 series protocols showed that if treatment was risk-stratified on the basis of white blood cell count at diagnosis, the French American British (FAB) classification, and lymphomatous features, that older adolescents did nearly as well as those aged under 15 years [17].

In Ewing's sarcoma, several data sources have consistently shown that survival of patients is inversely proportional to age [7,18,19]. In retrospect, it is unclear if older adolescents and adults presented with more advanced disease (bulky primaries, pelvic primaries, metastases), were treated less aggressively, or both. In a recent analysis of Ewing's patients aged 8 months to 47 years, the age group above 15 years had a significantly higher proportion of pelvic primaries and greater tumour volumes [20]. By including adult patients on paediatric Ewing's trials, the effect of age can be isolated. Verrill's group in England treated Ewing's patients aged 16 to 48 years with an identical intensive regimen and found that the volume of the tumour, and not age, influenced survival [21]. This was corroborated, in part, in the (CESS) 86 study [22], which intensified treatment for patients with large volume tumours and did not find any impact of age on survival.

However, in the most recently published trial, which tested the addition of ifosfamide and etoposide to a standard regimen in non-metastatic Ewing's patients, younger patients again were noted to have a superior outcome (5 year event-free survival of 70% for patients less than 10 years of age, 60% for those 10–17 years and 44% for patients 18 to 30 years) [23]. This was not explained by any difference in dose intensity of the chemotherapy administered, albeit multivariate analysis was not performed to determine if the difference in outcome was due to higher tumour volume, pelvic primary, or male gender, all of which are associated with an inferior survival. Of potential biological significance, the benefit of the addition of ifosfamide and etoposide that was achieved in younger patients (relative risk of adverse event of 1.6) in this study was not observed in patients older than 17 years. This suggests not only that intensification of therapy with ifosfamide/etoposide does not improve outcome in young adults, but also that the tumour has a different biology in the older patients.

3.2. Delay in diagnosis

In a study of the interval between symptom onset and diagnosis in 2,665 children participating in Pediatric Oncology Group therapeutic protocols between 1982 and 1988, Pollock found by multivariate analysis that for all solid tumours except Hodgkin's disease, the lag time increased as age increased [24]. The reasons for delay in seeking medical care and obtaining a diagnosis are multiple.

1. Adolescent and young adults have a strong sense of invincibility and may minimise physical findings. Out of denial or embarrassment, they may delay seeing a physician for symptoms. The authors have had older adolescents with extraordinarily large masses of the breast, testes, abdomen, pelvis and extremity that they had harboured for months because they were too embarrassed to bring the problem to anyone's attention. Even when seen, they may give poor historical information, especially to a physician untrained to "read between the lines" of an adolescent's history.
2. Adolescents and young adults aren't "supposed to" have cancer. Clinical suspicion is low, and symptoms are often attributed to physical exertion, fatigue and stress.
3. Young adults are the most under-insured age group, falling in the gap between parental

coverage and programes designed to provide universal health insurance to children (Medicaid and CHIP) and the coverage supplied by a full-time secure job. Lifetime uninsured rates for those who present for care peak for females between ages 15 and 17 years (19%) and for males between ages 18 and 21 years (24%) [25]. True uninsured rates are likely to be higher, as those who do not present for care may not do so because of a lack of insurance [26,27]. Recent data found that 49.6% of young adults aged 18–24 years were uninsured for at least one month over a 24-month period (2001–2002), with half uninsured for more than 12 months [27].

4. Regardless of health insurance status, adolescents and young adults are more likely than younger children to lack a usual source of care. Young adults and older adolescents have the lowest rate of primary care use of any age group in the U.S. [28]. Without a primary physician who knows the patient's baseline health status, the symptoms of cancer can be missed. Additionally, parents are not visualising or examining the adolescent's body to the extent that they are for the younger child, in the process of daily bathing and dressing, etc.
5. Physicians may be poorly trained or unwilling to care for adolescents [29]. To provide quality health care to teens, providers need to learn to communicate effectively with them, and to ask about sensitive issues such as sexual and substance-use histories. Many practitioners (e.g., paediatricians, internists, nurse practitioners) receive little training in adolescent health issues and are not comfortable with these topics.

How can these barriers be eliminated? Physicians must be educated and trained, and adolescents should be educated in health awareness and self-examination. The Society of Adolescent Medicine is a multidisciplinary organisation of professionals, largely in North America, who are committed to improving the physical and psychosocial health and well-being of all adolescents. Since 1980, the Society has published the *Journal of Adolescent Health*. In Canada, the National Training Initiative in Adolescent Health is a comprehensive multi-disciplinary training programme for professionals working with youth, founded when it was realised that paediatricians were not the primary source of health care for the vast majority of adolescents.

Given the lack of routine care, empowering young adults and older adolescents for self-care and detection is important. The American Cancer Society historically has viewed periodic encounters with clinicians as opportunities for cancer risk counselling and a cancer-related check-up. The American Medical Association and the American Academy of Pediatrics recommend annual visits for adolescents. These encounters may include case-finding examinations of the thyroid, testicles, ovaries, lymph nodes, oral region and skin. Health counselling may include guidance about smoking cessation, diet, physical activity, and the benefits and risks of undergoing various screening tests [30]. In addition, self-examination of the skin, breasts and testicles can be encouraged, as can the importance of an awareness of the symptoms of cancer.

At no other time in life is the sense of invincibility more pervasive that it is in older adolescents. Obviously, then, teaching this age group the importance of prevention and early detection of cancer is most challenging. For the sex organ tumours, testis, breast and gynaecological cancers, the challenge is even greater [31]. Results from a preliminary assessment of teaching testicular self-examinations to high school and college students is reassuring; anxiety was no greater in students who were exposed to presentations on testicular cancer and testicular self-examination than in those who did not receive this training [32]. On the other hand, the evidence that screening results in a decrease in mortality from testicular cancer appears to be insufficient [33]. The same can be said for breast cancer screening in adolescents.

The main problem contributing to delayed treatment of testicular and breast cancer isn't that the tumour goes unnoticed. Rather, the problem is usually that the mass is initially ignored or hidden by the patient. Thus, the issue is one of awareness and not self-examination *per se*. The important message for adolescents is to be aware of gonadal and breast cancer so that they won't ignore tumours or assume that they are harmless.

Additionally, efforts should be made to educate teenagers about the treatment and cure rates of cancer in children and young adults in order to dispel the fatalistic perception that arises from knowing older individuals (grandparents, etc.) who have died from cancer.

3.3. Who Treats? Where Treated?

A central, complex issue is determining the appropriate specialist to manage the treatment of the young adult and adolescent — a paediatric oncologist or an adult oncologist (medical, radiation, surgical or gynaecological oncologist). As noted by Leonard and his colleagues in the United Kingdom, adult oncologists may be "untutored in arranging ancillary medical, psychological, and educational supports that are so important to people who are facing dangerous diseases and taxing treatment at a vulnerable time in their lives" and "unpracticed in managing rare sarcomas," whereas paediatric oncologists may "have little to no experience in epithelial tumours or some of the other tumours common in late adolescence [34]." The (admittedly

biased) American Academy of Pediatrics issued a consensus statement in 1997 in which it indicated that referral to a board-eligible or board-certified paediatric haematologist-oncologist and paediatric subspecialty consultants was the 'standard of care' for all paediatric *and adolescent* cancer patients [35]. A wider consensus panel that included adult oncologists, the American Federation of Clinical Oncologic Societies, also concluded that "payors must provide ready access to paediatric oncologists, recognizing that childhood cancers are biologically distinct" and that the "likelihood of successful outcome in children is enhanced when treatment is provided by paediatric cancer specialists [36]." However, neither of these statements defines an age cut-off point for the recommendation.

Currently, the choice of specialist is made haphazardly and probably depends on the judgment of the referring physician. In contradistinction to children and early adolescents, who are nearly always referred to paediatric oncologists, older adolescents are seen by a breadth of specialists for their presenting symptoms of cancer. These include internists, family physicians, gynaecologists, emergency room physicians, dermatologists, gastroenterologists, neurologists and other specialists, each of whom may have different referral patterns to cancer specialists [37]. The oncology specialist may be a medical, radiation, surgical, gynaecological or other oncology specialist, and more often than not the specialist is not associated with a comprehensive cancer centre such as those with which paediatric oncologists are affiliated.

In the U.S., the switch from predominantly paediatric to adult specialty management occurs not at age 21 years or even at age 18 years as might be expected, but around age 15 years. A cancer registry review in Utah, a state that has only one paediatric oncology treatment facility, showed that only 36% of oncology patients aged 15 to 19 years were ever seen at the paediatric hospital [38]. A study of the National Cancer Data Base found that for nearly 20 000 cases of cancer in adolescents aged 15 to 19 years, only 34% were treated at centres that had NCI paediatric cooperative group affiliation [39]. The only survey of medical oncologists on the subject had a poor response rate (29%) and concluded that medical oncologists believe that they appropriately treated adolescents as adults [40].

The answer to which specialist is most appropriate certainly varies from case to case. Patients at any age who have a "paediatric" tumour, such as rhabdomyosarcoma, Ewing's sarcoma and osteosarcoma, will probably benefit from the expertise of a paediatric oncologist, at least in the form of consultation. Children under the age of 18 years and their parents may benefit from the social and supportive culture of a paediatric hospital, regardless of the diagnosis. Individuals between the ages of 16 and 24 years may have varying levels of maturity and independence, and choice of physician and setting for their care should be individually determined. Paediatric oncologists may be less adept at a non-paternalistic relationship with the patient (and potentially his or her spouse and their children) and less inclined to consider issues such as sexuality, body image, fertility, etc. Adult oncologists are more accustomed to dose delays and adjustments and may be less likely to use aggressive dosing that can be tolerated by the younger patient.

Some comparative outcome data is becoming available. In ALL, the CCG and Cancer and Leukemia Group B (CALGB) compared the results of patients who were 16 to 21 years of age when treated on concurrently conducted trials. The 6-year event-free survival was 64% for those treated on the CCG study and 38% for those treated on the CALGB regimen [41]. This difference was recently corroborated in the same age group by the French who found that those treated on a paediatric protocol (FRALLE-93) had a five-year overall survival of 78% versus 45% for those treated on the adult protocol (LALA-94) [42].

For other tumours, data increasingly shows the same advantage to treating adolescents and young adults on paediatric protocols. At the University of Texas M. D. Anderson Cancer Center, results of treatment for AML in adults improved substantively after treatment derived from paediatric trials was introduced into the institution's trials [43]. An analysis of data from the National Cancer Data Base revealed that adolescents (aged 15–19 years) with non-Hodgkin's lymphoma, leukaemia, liver cancer and bone tumours have a survival advantage if treated at a NCI paediatric group institution [39].

Further analysis is required to determine what differences in treatment are producing these differentials in outcome: e.g., amount of drug scheduled, more intensive timing, better supportive care. It is important to determine the factors and disseminate the data, both to medical oncologists and to the referring primary care physicians, because so few adolescents are being treated on protocol at all (paediatric or adult) (see *Clinical Trials* section below) that gains made in clinical trials are accessible only to a minority of adolescents. In the U.S., the 5-year survival for 15- to 19-year-old patients with ALL patients in the SEER programme was only 56.5% between 1992 and 1998 [7]. Yet as described above, the rates achieved on clinical trials conducted in the same age group were over 64% in the U.S. and over 78% in Europe.

Recommending that adolescents and young adults be treated at paediatric hospitals or by paediatric oncologists has practical constraints. Many paediatric oncologists are uncomfortable caring for older adolescents and young adults. Adult oncologists are often unfamiliar and uncomfortable with the detailed paediatric protocols and older patients cannot be registered on

paediatric cooperative trials. Many of the paediatric protocols are written for young children and not for older adolescents. Paediatric hospitals cannot admit patients over a certain age.

The British have pioneered the solution of treating young adult and adolescent patients at a unique "adolescent oncology unit" [44]. This provides the adolescent with age-specific nursing care, recreation therapy, and peer companionship. Perhaps it is appropriate to have as a goal centres and oncologists devoted solely to the care of this group of patients. In the meantime, increased cooperation and communication between paediatric and adult oncologists will facilitate the care of this group of patients.

In the end, the decision should be based in large part on which setting will provide the patient with the best outcome, not only in ultimate survival, but also in the quality of survival, and in the minimisation of trauma during and after therapy. Psychosocial care, consideration of fertility and late effects are especially important for older adolescents and young adults.

3.4. Clinical trials

In the U.S., more than 90% of children with cancer who are less than 15 years of age are managed at institutions that participate in NCI-sponsored clinical trials, and 55–65% of these young patients are entered into clinical trials. In contrast, only 20–35% of 15- to 19-year-olds with cancer are seen at such institutions, and only about 10% are entered into a clinical trial (Fig. 5) [45,46]. Among 20- to 29-year-olds, the participation rate is even lower, with fewer that 10% being seen at member institutions of the cooperative groups, either paediatric or adult, and only about 1% of 20- to 29-year-olds entering clinical trials. Among older patients, the trial participation rate is higher, putatively between 3% and 5%, but still much lower than in children. The high proportion of older adolescent and young adult patients who are not entered into clinical trials is referred to as the "adolescent and young adult gap." This gap has been observed throughout the U.S. and spares no geographic region or ethnic group [35].

The reasons for the gap are to a large extent unknown and are undoubtedly multifactorial. The reasons that were identified at a recent NCI-sponsored workshop on the topic are summarised in Table 4. A factor that does not explain the discrepancy is the participation of minority adolescent patients in clinical trials. Although minority patients are known to be under-represented in visits to physician offices [27], they have equal or higher rates of entry into clinical trials. The participation rate of older adolescent patients is lower than rates of younger patients of corresponding ethnicity and socioeconomic status.

The dramatically lower clinical trial participation rate by young adults helps explain the lower-than-expected improvement in their outcome, relative to younger and older patients. Studies of younger children have certainly shown a survival advantage for children enrolled in clinical trials for ALL [47], NHL [48], Wilms' tumour [49] and medulloblastoma [50]. Similar analyses of data for adolescents are sparse. In the U.S. and Canada, a comparison of 16- to 21-year-olds with ALL or AML showed that the outcome was superior in patients with either cancer treated on CCG trials than in those not entered (17). On the other hand, a population-based study of 15- to 29-year-olds with acute leukaemia in

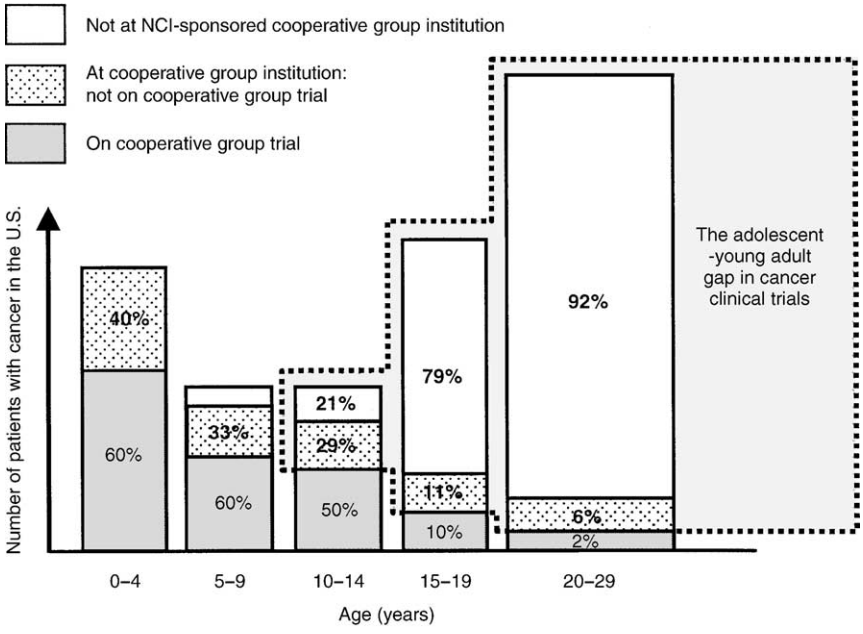

Fig. 5. The "adolescent and young adult gap" in cancer clinical trials [45,46].

Table 4
Barriers to Participation in Clinical Trials

Possible explanations for young adults and older adolescents low rates of participation in cancer clinical trials, as compiled at the National Cancer Institutes (NCI) Workshop on Enhancing Accrual of Adolescent and Young Adult Cancer Patients on Clinical Trials, Bleyer A, Smith M, Coordinators, Bethesda, Maryland, June 17, 1999. The contribution and magnitude of each factor is unknown and many other factors are undoubtedly missing.

Economic, Insurance-Based Factors

- Treating physicians may be reluctant to utilise clinical trials because of the time, cost and effort involved, not only on their part (and that of their team), but also on the part of the patient and family.
- Health insurance organisations may deter referral of adolescents and young adults to centre or cooperative group or entry into clinical trials. Attendees had little direct evidence for this factor.

Provider Bias

- Coping with an older adolescent or young adult is difficult. Adding the additional burden of clinical trial participation is more difficult to achieve for the adolescent than for younger or older patients.
- Treating physicians may be reluctant to utilise clinical trials because they perceive the patient as likely to be non-compliant; the patient is perceived to have enough difficulty in complying with the treatment plan and keeping up their lives, without the additional burden of protocol obligations.

Oncologists (surgeons, radiotherapists, medical oncologists, gynaecologists) in private practice may retain these patients rather than refer them to a tertiary-care facility or cooperative group institution.

- Providers may be biased against clinical trials in adolescents. Reasons may include the historically better results in comparison to older and younger patients, and the need to explain and obtain consent for study entry from both the patient and family.
- Family practitioners, gynaecologists, and internists may not regard multimodal therapy as important in young adults or older adolescents as in younger or older patients. Reasons may include the better results obtained in this age group in comparison to older patients and a higher rate of single-modality therapy normally applied to patients in this age range.
- Providers may be unaware of opportunities for clinical trials participation for adolescents and young adults with cancer.

Patient/Family Preferences

- Patients and/or parents are more inclined to refuse referral to a cooperative group member institution or to be entered into a clinical trial.
- Patients and/or parents may be unaware of opportunities for clinical trials participation for adolescents and young adults with cancer.

Provider Age Policies

- The age policies of hospitals may prevent patient access to clinical trials that are underway at the institution. Children's hospitals may have upper age limits that deny the older patient or deny the treating physician who does not have clinical privileges. The reverse may be true for younger patients accessing clinical trials primarily intended for adult patients.

  The clinical trial itself may have age limits that prohibit entry of an otherwise eligible patient.

Cooperative Group Limitations

- Paediatric cooperative group and adult cooperative group clinical trials may not allow adolescent and young adults because of restrictive eligibility criteria.
- A clinical trial may not be available.
- Adult cooperative groups may lack treatment protocols for the youngest patients.
- Paediatric cooperative groups may lack treatment protocols for older patients.
- Clinical trials for the types of cancer that predominate among adolescents and young adults may not be a priority of the cooperative group enterprise.

England and Wales showed no difference between patients treated on national clinical trials and those not entered, or between those managed at teaching hospitals as opposed to non-teaching hospitals [51]. However, this observation appears to be exceptional in that subsequent national AML trials in the United Kingdom have shown some of the best results reported to date [52].

3.5. Psychosocial issues

The greatest difference in the management of adolescents and young adult patients is the supportive care, particularly psychosocial care, that they require. The adolescent patient is multifarious, on the cusp between dependent childhood and independent young adulthood. The older adolescent may be living at home, totally dependent on family and friends, or very independent, living with a spouse and/or children, and gainfully employed. The older adolescent can be surprisingly insightful and compliant or foolishly confident of self invincibility and immortality. The older adolescent may be open and talkative, or shy and unreachable. As such, these patients have special needs that are not only unique to their age group, but also broader in scope and more intense than those at any other time in life.

Young adult and older adolescent patients are on the cusp of autonomy, starting to gain success at independent decision-making, when the diagnosis of cancer

renders them "out of control" and throws them back to a dependent role with their guardians. When the diagnosis of cancer hits, what will happen to the new roles they are just trying to master as high school student, college student, recent graduate, newly-wed, new employee or new parent. How can they succeed when in addition to all of these challenges, cancer intervenes? How can they plan and begin their future when they suddenly realise that they may not have one? What will happen if they can't graduate, keep their friends, finish their education, get a good job, get married, have children, or meet other goals they had?

There are two aspects to the issue: how the adolescent patient's developmental abilities and growth affect his approach to and processing of the cancer experience, and how the cancer experience affects his development. To understand both, the provider must appreciate the developmental tasks of an adolescent [53,54]: (1) Establish new self-image, both in relationship to sexually developed body and autonomous intellect and function; (2) Develop abstract and future-oriented thinking skills; (3) Renegotiate relationships with parents; (4) Form committed complex emotional relationships with individuals. Because of the spectrum of circumstances and developmental starting points for adolescents diagnosed with cancer, the impact of the cancer diagnosis and treatment is complex and unpredictable. The providers must be attuned to the needs, spoken and unspoken, of the adolescent with cancer, and they must be aware of the potential for psychosocial developmental delays.

Honing social and interpersonal skills is an important developmental milestone during adolescence. Cancer treatment for these patients must accommodate this process. A patient may need to be discharged from the intensive care unit to be able to attend the senior prom, and readmitted when the party is over. Yet boundaries must be set, so that treatment effectiveness is not compromised to keep a "social calendar." Certainly, cancer therapy causes practical problems in social arenas. Adolescent and young adult patients, who are developmentally dependent on peer group approval, often feel isolated from peers by their experience; the cancer patient's issues are illness and death, while their peers are consumed by lipstick and homework. Their concerns and schedules intrinsically make them "different," which is *not* what an adolescent wants to be.

In addition, many of the adverse effects of therapy can be overwhelming to an adolescent's self-image, which is often tenuous under the best of circumstances [55]. All adolescents agonise over their personal appearance and hate to be singled out or to appear odd. Weight gain, alopecia, acne, stunted growth and mutilating surgery to the face and extremities are examples of adverse consequences that can be devastating to an adolescent's self-image. In particular, hair loss is cited over and over as a huge blow to the adolescent/young adult (especially the female) with cancer.

Other challenges include the time away from school, work and community that therapy requires. The adolescent task of assuming increasingly mature roles and responsibilities is thwarted by the tiresome "job" of cancer therapy. There may be guilt if not attending to these responsibilities, or stress and fatigue if trying to keep up a semblance of normal activity. A wide range of financial situations is seen in the adolescent and young adult population. Some patients are still happily dependent on their parents. Some are just striking out on their own, but, without a long-standing job or savings, may have to return to dependence on parents or get public assistance, which is disconcerting if the patient is trying to "grow up" and show financial independence. Others are trying to begin a career, but long work absences threaten their job security or advancement. As stated above, this age range is the most uninsured. As a result, many young adult patients incur high medical bills at a time in life when they may least be able to afford them. As part of the health care team, social workers should actively address these issues.

This is a period when sexuality, intimacy and reproduction are central. A young adult is supposed to attract a mate and reproduce. But the young adult with cancer may feel or look unattractive, may be uninterested in or unable to have sex and may be infertile. A feeling of impotence can pervade. Adolescents report discomfort talking about their malignancy with peers; they are unsure of the reaction and concerned they will appear unattractive. Some feel a romantic relationship would be "unrealistic"—some are avoidant or cautious [56]. Rarely will patients freely discuss such issues with their medical provider; the team must be sensitive and consider bringing up the topic themselves.

For those in a partner relationship, the union will be tested by the strain of the cancer diagnosis and its therapy. Patients may wonder whether the partner stays in the relationship out of guilt or sympathy. Not yet able to fully understand a complex, committed relationship, they may push the friend away. Medical staff must be sensitive to the role of the "significant other;" although not formally a family member, they may have as much or more impact on the older adolescent's decisions and life than their parents.

Although the cancer diagnosis may disrupt the developmental tasks of the adolescent, the patient's circumstances and the provider's management will determine whether or not the adolescent successfully adapts. Several studies have surveyed adolescents with cancer and healthy controls and found no difference in self-image (including measures such as social relationships, vocational/educational goals, psychopathology, idealism, impulse control) [57,58]. However, there appear to clearly be transient periods of problematic adjustment

during treatment, and also a distinct excess of adolescents that have long-standing psychological disturbances.

Because of the complex issues of dependence, decision-making during cancer therapy is different for the patient, family and physician of an adolescent/young adult than for either younger patients (which is more paternalistic) or for the older adult (which is more patient-centered). The young adult patient may wish to make his or her own decisions, but his or her understanding of the illness may be incomplete or flawed [59]. The provider must be sensitive to this ambiguity.

3.6. Compliance/adherence

Adherence to therapeutic regimens, particularly oral chemotherapy, is also much more problematic in teenagers and young adults than in younger and older patients [60–63], and an increasing issue as the use of oral agents, subcutaneous injections and home intravenous therapy increases. Adolescents with cancer have many of the factors found to be associated with non-adherence: complex regimens, a need for substantial behavioural change, an inconvenient/inefficient clinic (any appointment before noon is inconvenient to a teenager), inadequate supervision (as parents try to give the teenager the space they request), poor communication with health care providers, patient health belief in favour of non-adherence (denial, invincibility or fatalism) and inadequate social support. Concern over ineffectiveness, and fear of side-effects can produce ambivalent or frankly avoidant feelings about adherence [64]. Similar association of age with non-compliance in found in other chronic diseases, such as HIV [65], JRA, asthma [66].

Serum and urine assays have been used to measure adherence in adolescents. One, measuring compliance to oral prednisone, found that 33% of younger children, but 59% of adolescents with leukaemia or NHL were poorly adherent [67]. Similar rates of non-compliance with oral medications by adolescents with ALL or Hodgkin's were found in another study: 48% were non-adherent with penicillin and 52% with prednisone [60]. The characteristics associated with non-adherence were: a poorer understanding of their illness (including causality and prognosis), a perception of invulnerability, less future-orientation and more denial.

Having identified compliance as a problem, several strategies should be employed. The physician should upfront "acknowledge the reality of variable adherence [64]" and engage the adolescent in problem-solving, rather than blaming. Tangible devices such as appointment and medication reminders, calendars and pillboxes should be liberally used. Clear discussion with the adolescent and the parents should clarify who is responsible for the medication schedule.

3.7. Fertility

Many adolescent and young adult cancer survivors cite fertility as a primary concern that impacts the quality of their life. Most do not recall an adequate discussion of the risks of infertility or methods to decrease the risks with their physician at the initiation of therapy [68]. Teenagers are especially prone to repression or denial, and the responsibility for conveying information about sexuality and childbearing rests with the medical professional. The provider must consider the estimated risk of infertility, the patient's maturity, and the need to initiate therapy immediately in framing the conversation about infertility and the options of germ cell preservation. Rates of infertility are very hard to predict for an individual and depend on gender, age, radiation dose and schedule, chemotherapeutic agent and dose [69].

For women, even low doses of radiation to the ovaries (200–400 cGy) causes some loss of oocytes [70]; permanent ovarian failure can occur with higher doses (depending on the patient's age and concomitant use of chemotherapy). Uterine irradiation increases the rates of nulliparity, miscarriage, intrauterine growth retardation and premature delivery [71]. Among the chemotherapeutic agents, alkylators and platinum agents cause the most ovarian dysfunction. Because of a decreasing pool of follicles, rates of amenorrhoea and infertility are positively associated with increasing age of the patient at the time of treatment, so that the rates in adolescent patients appear intermediate between those of prepubertal children and older women. Although acute ovarian failure may not occur, there may be more subtle changes, including decreased libido and premature menopause (with resultant increase in risk of osteoporosis, heart disease, etc.) which only prolonged follow-up of many cancer survivors will quantify. Even if ovulation does return after the end of therapy, the patient should be counselled about the risk of premature ovarian failure, as it may narrow the window of fertility [72].

There are no established techniques to preserve fertility for women undergoing chemotherapy, but experimental approaches include embryo cryopreservation, oocyte (unfertilised egg) cryopreservation, ovarian tissue cryopreservation, sphingosine-1-phosphate inhibition of somatic cell apoptosis, and gonadotrophin-releasing hormone (GNRH) analogue suppression of follicle development [73–75]. Many of these techniques require referral to specialised centres and/or a cycle of oocyte stimulation and collection, which can prohibitively delay the start of chemotherapy. Oophoropexy is an option prior to pelvic radiation.

Rates of infertility appear higher in male survivors than female; thankfully, fertility preservation options are more feasible and successful. Spermatogenic cells

are extremely sensitive to alkylating agents and radiation. In one study, cyclophosphamide doses of greater than 7.5 gm/m^2 to adolescent/young adult patients resulted in 90% permanent azoospermia [76]. In addition, cisplatin, procarbazine and vinblastine are particularly gonadotoxic. Spermatogenesis is affected at doses as low as 10 cGy of testicular radiation [77]. After both radiation and chemotherapy, spermatogenesis may return after years of apparent azoospermia and adolescents should be counselled regarding this possibility [78]. Sperm cryopreservation should be discussed with all sexually mature males—usually collected via masturbation but epididymal aspiration and testicular biopsy are also possible options.

Although less sensitive than spermatogenic cells, Leydig cells can suffer damage after 2000 and 3000 cGy of testicular radiation (the prepubertal male suffering effects at lower levels), causing diminished testosterone levels. Chemotherapy rarely causes clinically significant impairment of Leydig cell function [79].

3.8. Quality-of-life after cancer treatment

The quality-of-life issues that arise during and after cancer therapy have been the focus of studies in children and older adults, but have not received the same attention or study in adolescents and young adults, another example of the general inattention to the needs of these patients. A few studies have found certain trends that should be examined further. Even after treatment, adolescents can maintain persistently abnormal perceptions of their body and/or their health- manifested either as counterphobic or reckless behaviour or hypochondria. A higher risk-taking behaviour has been noted among survivors of Hodgkin's disease occurring during childhood and adolescence [68]. Such behaviour may be motivated by a mix of feelings including invincibility, inferiority or a sense of uncertainty regarding the future. However, other studies find that risk-taking is equal to that of other adolescents [80,81]. Healthcare providers must guard against thinking that those whose lives have been "saved" should not be so bold or ungrateful as to take life-threatening risks.

Other topics have conflicting data as well. Some studies report that adolescent cancer survivors show better attendance and performance at school and work [82]. Fritz and William found that adolescents who had survived cancer had good global functioning, and their rates of depression were slightly less than their peers. Many even felt there was positive benefit derived from their cancer experience, making them more "empathetic, confident, nature and/or goal-oriented" [56]. Persistent anxiety over relapse, death or late effects is likely to be higher in adolescents who were cognitively aware of the severity of their illness than in those treated in early childhood (the Damocles syndrome) [83]. However, another small study showed anxiety equal to that seen in other chronically ill patients and healthy controls [84]. One study showed that although cancer and other chronic diseases in younger and older patients increased cohesion among families of affected persons, survivors of cancer during adolescence reported lower levels of family cohesion than healthy adolescents and their families [85].

After treatment, commitment to a relationship in the face of fear of relapse or infertility can be difficult for both patient and partner. Those contemplating having children often worry about passing on a genetic predisposition to cancer. Some say they avoid having children because they do not want to go through what their parents did [56]; however, the current data does not suggest that offspring are at an increased risk of congenital anomaly or childhood cancer [86–88].

Future insurability is certainly a stressful issue for all these patients; an inability to obtain insurance reinforces a feeling of "abnormality" that the patient cannot put the cancer behind them. Approximately 12–24% of former paediatric cancer patients have difficulty obtaining health and life insurance [83,89,90].

4. Summary

The types of cancer, their biology and the extraordinary psychosocial challenges intrinsic to this juncture in life render the management of the adolescent cancer patient unique and complex. Medically, the care may be complicated by a delay in diagnosis, an uncertainty over the specialty, centre and therapy best suited to the patient, a lack of available clinical trials and poor compliance. The care is further complicated by the complex psychological mindset of the adolescent, with issues of dependence, self-image and relationships with peers and parents playing larger roles than for other age groups. The health care team must also be cognisant of the social needs of the patient and address fertility, insurability and work issues.

Having lost ground during the past quarter century, older adolescents and young adults with cancer need to catch up with the progress made in improving the quantity and quality of survival in younger and older patients. This will require an effort on many fronts. To be sure, the age-dependent biological differences of the cancers must be investigated and understood. But paramount also is ongoing education of providers regarding the issues central to the management of adolescent cancer patients, reorganising of systems to optimise their care, and increasing clinical trial activity in this age group. In the end, the patient should be treated in a system and by physicians poised to overcome the challenge of management of the adolescent with cancer.

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