A Unique Challenge:

Treating Cancer in the Adolescent

by Leonard S. Sender, MD, and Keri B. Zabokrtsky

Over the last five years much work has been done to define a new class of oncology patient—the adolescent and young adult (AYA). This group, while historically good responders to treatment, has a unique set of needs that should be addressed as part of their comprehensive treatment and survivorship plan—whether that care is provided in a university-based cancer center, a community cancer center, or a private oncology practice. Given the defined boundaries of their age category (15 to 39 years), we see AYA patients in both traditional pediatric programs and adult-based programs, regardless of care setting. Our foremost goal is to ensure that this unique and often underserved patient population receives recognition of their unique needs and then receives the appropriate care for their disease.

The spectrum of oncology care has traditionally been split between pediatric oncologists and medical oncologists. This division is tacitly enforced by both physical structures (children's hospitals versus all others) and administrative means (pediatric hematology-oncology board certification versus medical oncology board certification). An unintended consequence of this separation has been the creation of a gap in care through which AYA cancer patients often get lost. To help close this "gap," we propose a new paradigm—five distinct age-categories of cancer patients, each with a unique set of treatment and ancillary needs:

1. The pediatric patient (<15 years of age)
2. The adolescent patient (15 to 19 years)
3. The young adult patient (20 to 39 years)
4. The adult patient (40 to 64 years)
5. The geriatric patient (65+ years).

As you can see, this type of schema presents inherent administrative issues related to the study of AYA patients,

Table 1. Cancer Incidence and Death Rates in Adolescents and Young Adults, 2002-2006

SEER Incidence and U.S. Death Rates, 2002-2006

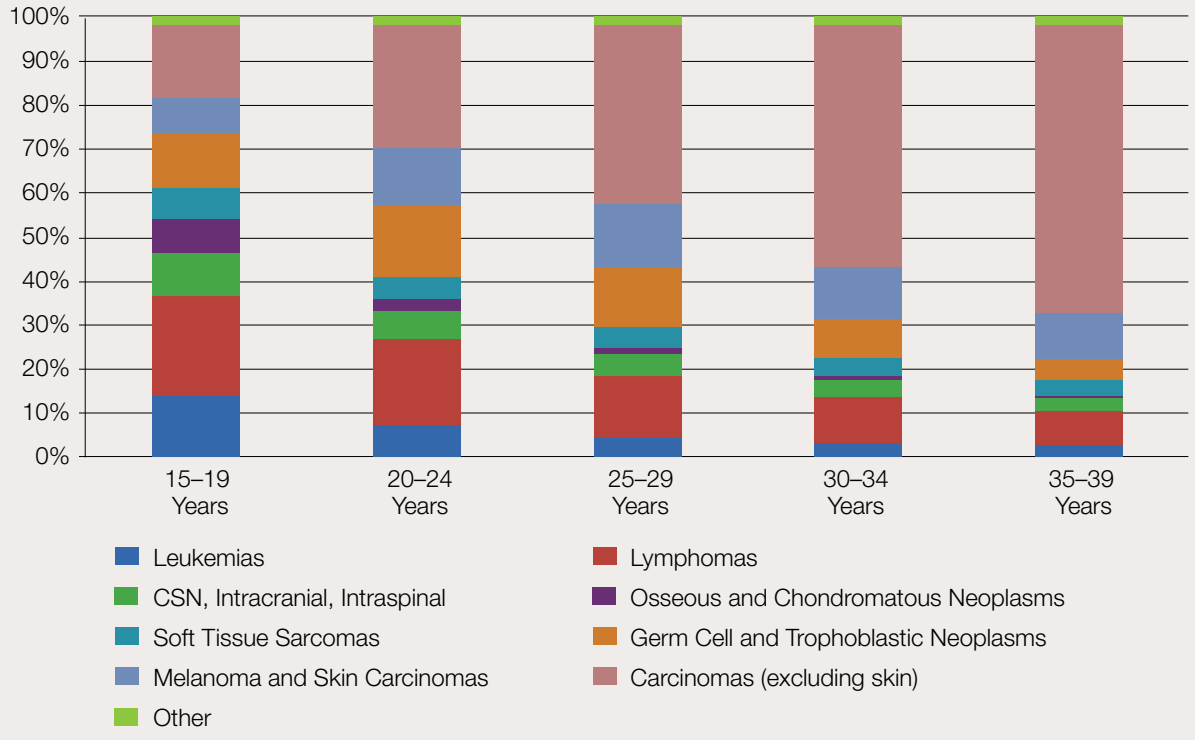
Age (Years)	Incidence per 100,000	Death Rate per 100,000
15–19	21.2	3.4
20–24	34.5	4.7
25–29	53.4	6.7
30–34	81.7	11.7
35–39	125.7	22.0

Source: National Cancer Institute. *SEER Cancer Statistics Review, 1975-2006*. Horner MJ, Reis LAG, Krapcho M, et al. (eds). NCI, Bethesda, Md. Available online at: *http://seer.cancer.gov/csr/1975_2006/*. Last accessed Sept. 1, 2010.

ILLUSTRATIONS/BIGSTOCKPHOTO

and Young Adult

Figure 1. Age-Specific SEER Incidence by Adapted Classification Scheme for Tumors of Adolescents and Young Adults



Source: Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, Ruhl J, Howlader N, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Cronin K, Chen HS, Feuer EJ, Stinchcomb DG, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD, *http://seer.cancer.gov/csr/1975_2007/*, based on November 2009 SEER data submission, posted to the SEER web site, 2010.

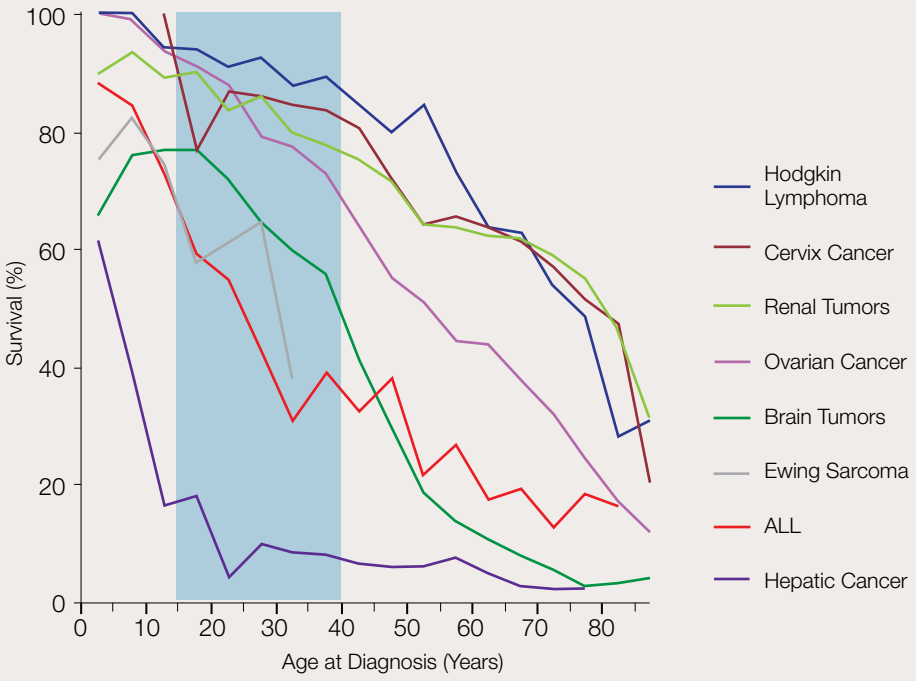
particularly the adolescents. Where do these patients "fit"?

There is no consensus on the definition of "child" or "adolescent." The National Institutes of Health (NIH), for purposes of clinical research, defines anyone under the age of 21 years to be a "child." On the other hand, the Food and Drug Administration (FDA) defines a child to be between infancy and 16 years of age. To further muddy the waters, psychologists often equate "adolescent" with "teenager." One would think that the definition of young adult would be more straightforward and yet, here too, variability exists. The first seminal publication on adolescent and young adult cancer, the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) report, *Cancer Epidemiology in Older Adolescents and Young Adults 15-29 Years of Age, including SEER Incidence and Survival: 1975-2000*, set the upper limit of 29 years for the young adult.[1] Just months later NCI released a second report entitled, *Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer*, that extended the upper age limit to 39 year olds.[2]

Incidence and Prevalence

Cancer is one of the best-studied medical conditions in the United States; the NCI alone issued over $2 billion to investigators this last fiscal year for research project grants. These monies do not include the millions that are additionally awarded from non-governmental sources such as the American Cancer Society (ACS) or the Susan G. Komen for the Cure Foundation. Despite the outpouring of funds to investigate the causes and cures of cancer,

Figure 2. Cancers with Lower Survival in AYAs than Children, 5-year Relative Survival, SEER, 1993-1997



Source: Bleyer A, Barr R, Hayes-Lattin B, Thomas D, et al. Biology and Clinical Trials Subgroups of the US National Cancer Institute Progress Review Group in Adolescent and Young Adult Oncology. The distinctive biology of cancer in adolescents and young adults. *Nat Rev Cancer*. 2008 Apr;8(4):288-98.

relatively little is known about the biologic, genetic, epidemiologic, therapeutic, psychosocial, and economic factors that affect the incidence, disease outcomes, and quality of life for adolescents and young adults diagnosed with cancer. Approximately 70,000 new cases of cancer are identified in AYA patients each year in the United States; this number represents roughly 5 percent of all new cases annually. While outcomes are typically very good for AYAs (on average, better than 80 percent survival), cancer is the most common *disease* cause of death for adolescents and young adults behind accidents, homicides, and suicides.[3] (See Table 1 on page 18.)

The cases consist, in part, of a mixture of traditional "pediatric" cancers [e.g., brain tumors, acute lymphoblastic leukemia (ALL), and non-Hodgkin lymphoma (NHL)] and common "adult" cancers (e.g., breast cancer, gastrointestinal tumors, and urinary tract carcinomas). Yet certain cancers seem to peak in the AYA cancer patient. In particular, we see an influx of thyroid cancer, melanoma, connective tissue sarcomas, Hodgkin lymphoma, and germ cell-gonadal tumors (see Figure 1 on page 19). Reasons for the development of distinctive cancers in this age group remain a mystery. Efforts to create biobanks of tissues from AYA cancer patients coupled with the interest of developmental biologists around the world may shed some light on this matter in future years.

The Knowledge and Delivery Gap

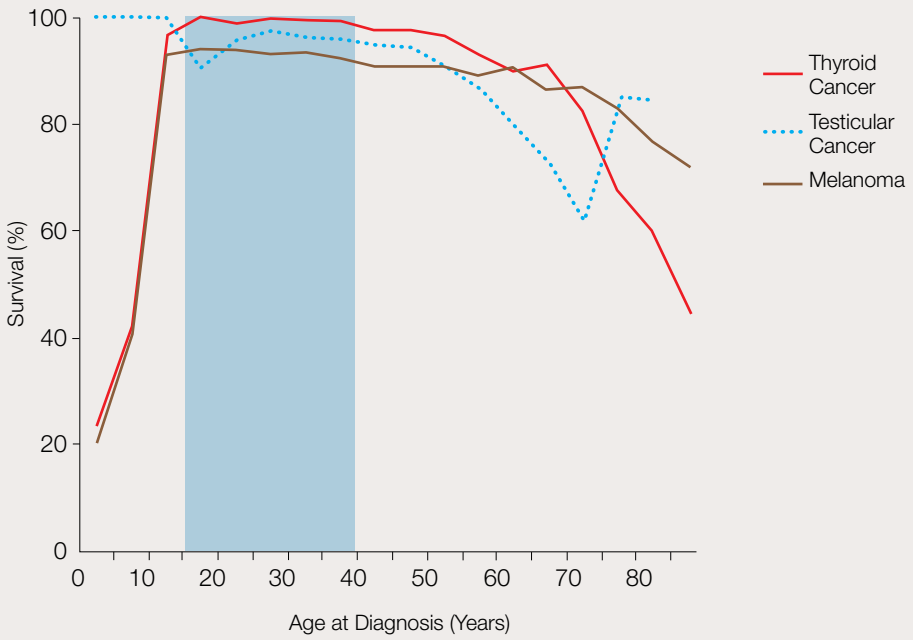
In an ideal world, 100 percent of cancer patients would survive their disease; however, this scenario is simply not the case. Using ALL as an example, we will outline what we see as the "knowledge gap" and the "delivery gap" for AYA cancer patients.

In a subset of adolescent and young adult cancer patients with ALL, age 16 to 29 years, the best outcome practicing oncologists can achieve—using age-appropriate treatment—is 75 percent survival. The difference between the ideal world (100 percent) and best outcomes (75 percent) is defined as the "knowledge gap." Research on current treatment modalities and new treatment options continues to be necessary to bridge the knowledge gap. On the other hand, when an adolescent or young adult cancer patient with ALL is treated on an "adult-based" treatment protocol, the overall survival rate is roughly 40 percent—more than 35 percentage points below best outcomes.[4-7] The "delivery gap," unlike the knowledge gap, is an opportunity for practicing oncologists to acutely correct and immediately improve outcomes for AYA cancer patients with ALL.

In addition to the knowledge gap and the delivery gap, other factors may contribute to the differences noted in survival of AYA cancer patients. Studies of molecular, epidemiological, and therapeutic outcome comparisons indicate that there is, in many cases, a biological underpinning for disparate outcomes.[8] Lower survival in AYA cancer patients, compared with their younger and older peers, is seen in breast cancer, colorectal carcinoma, soft tissue sarcoma, non-Hodgkin lymphoma, and leukemia (see Figure 2 above). But not all is lost for the AYA cancer patient. In some cases, these patients actually have better clinical outcomes than their younger and older peers; in particular, AYAs with thyroid cancer, testicular cancer, and melanoma all fare better, with five-year relative survival rates better than 90 percent (see Figure 3 at right). However, in order to consistently improve outcomes in the AYA age group more research is needed.

While AYA-specific clinical trials are one way to address the "more research" need, it is not the only solution. We must look critically at accrual methods to increase enrollment to clinical trials. Much of the success attained over the last 50 years in pediatric oncology is largely due

Figure 3. Cancer with Higher Survival in AYAs than Children, 5-year Relative Survival, SEER, 1993-1997



Source: Bleyer A, Barr R, Hayes-Lattin B, Thomas D, et al. Biology and Clinical Trials Subgroups of the US National Cancer Institute Progress Review Group in Adolescent and Young Adult Oncology. The distinctive biology of cancer in adolescents and young adults. *Nat Rev Cancer.* 2008 Apr;8(4):288-298.

to the relatively high accrual rate to pediatric clinical trials. We suspect that similar advances could be made in older age groups. More than 5,000 open treatment studies for cancer are currently listed online at: *www.clinicaltrials.gov*, and yet more than 40 percent of these trials will not meet their minimum enrollment goals.[9] (See Figure 4, page 22.) While a full discussion regarding clinical trial management and accrual extends beyond the scope of this article, a number of issues related to sub-optimal clinical trial participation in AYAs has been reported, including:[10]

- Rare diagnoses
- Lack of biological samples
- Limited number of trials
- Poor grant funding.

Treatment Recommendations: ALL Case Study

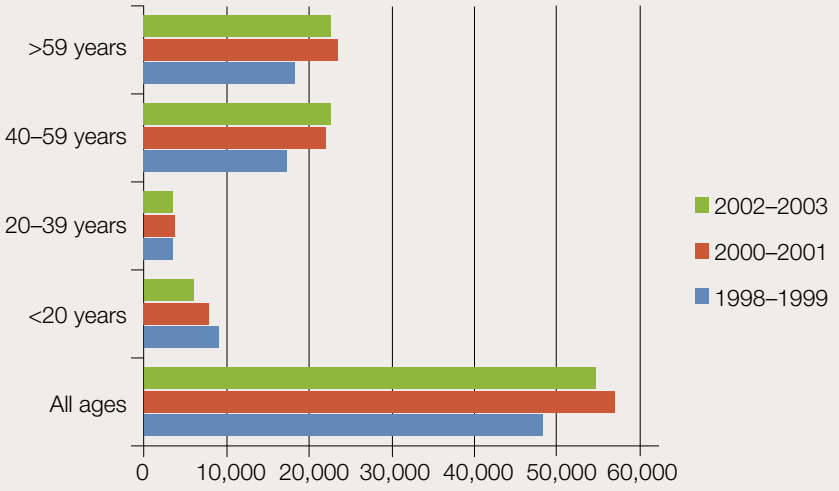
Acute lymphoblastic leukemia (ALL) is one of the best-studied "pediatric" cancers. Over the last 40 years we have seen an estimated five-year survival go from less than 20 percent in 1968-1970 to better than 90 percent in 1996-2001.[11] Large advancements in survival correspond with the introduction of new chemotherapy modalities and/or pharmaceutical agents. These advancements, however, did not translate over to adolescent and young adult ALL patients. Multiple retrospective comparison studies have now been conducted to determine outcomes in this patient population (defined as 15 to 20 years, 15 to 17 years, or 16 to 20 years) depending on whether they were treated on a pediatric-based protocol or an adult-based protocol. Consistently, the AYAs treated on more aggressive pediatric-based protocols had improved event-free survival and overall survival by 15 to 20 percentage points.[4-7]

The major differences seen between pediatric- and adult-based treatment protocols for acute lymphoblastic leukemia are increased numbers of cycles of therapy, a longer maintenance period, and each administered cycle of chemotherapy is intensified.[12] These differences have resulted in improved survival rates in pediatric patients.[13] This style of intense protocol, however, has not historically been perceived to be well tolerated by the older patient due to its toxic profile. As a result, the oncology community has historically turned to the use of the hyper-CVAD protocol for the treatment of older adolescents and young adults. New research has shown, however, that AYAs can not only tolerate the toxic effects of the pediatric-based treatment protocol but also demonstrate superior outcomes.[14]

Admittedly, the use of a more aggressive "pediatric" treatment protocol in an adolescent and young adult ALL cancer patient presents a myriad of logistical issues. Unlike the relatively straight-forward hyper-CVAD treatment that is most commonly used for the treatment of ALL in "adult" patients outside of academic institutions, the current Children's Oncology Group (COG)-based protocol includes cycles that alternate between those given inpatient and outpatient, each cycle has a different chemotherapy "cocktail" where some drugs may only be administered once or twice over a 42-day course, and there are greater toxicities (e.g., extended periods of neutropenia) associated with its use. This is notwithstanding the fact that AYA patients are traditionally non-adherent to any medical treatment, let alone a protocol that lasts two to three years, depending on gender. AYA cancer patients, for the most part, do not have the hovering mother or spouse tracking their every intake and output, and it can be difficult at times to get patients back to the hospital. However, we have found at our institution that the AYA cancer patient, even up to the age of 40 years, can tolerate the rigors of this type of protocol and we can work with our patients to minimize delays in care.

Using ALL as an example, the bottom line is that clinicians do not need to wait for new drugs to be discov-

Figure 4. Accruals to National Cancer Treatment Trials



Source: National Cancer Institute. *Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, including SEER Incidence and Survival: 1975-2000*. NIH Pub. No. 06-5767. Bleyer A, O'Leary M, Barr R, Ries LAG (eds). NCI, Bethesda, Md; 2006. Available online at: *http://seer.cancer.gov/publications/aya/*.

ered to optimally treat AYAs in their oncology practice. Instead, clinicians should follow current (and often more aggressive) recommendations based on current research such as the CALGB 10403/ECOG C10403/SWOG C10403 intergroup trial for the treatment of ALL in adolescents and young adults. Efforts are underway to make key AYA treatment protocols available to a broader array of oncologists by making them available through the Cancer Trials Support Unit (CTSU). In the interim, cooperative groups have created educational modules and established help lines for clinical care providers to address any questions they have in the implementation of these intricate research protocols. We do, as a community, need to collectively develop better resources for the treatment of rare AYA cancers.

Unique Challenges and Needs of AYAs

Cancer does not occur in a vacuum. As such, we need to be as cognizant and attentive to the "host" as we are to the cancer that we have been trained to eradicate. Adolescent and young adult patients with cancer are at an age when crucial developmental stages are occurring—not only are they reaching physical and sexual maturity, but they are also acquiring the skills needed to carry out their "adult" roles. Some of the key changes include gaining increased autonomy from parents and the realignment of social ties with members of both the same and the opposite sex. Key challenges can be grossly categorized into health concerns, psychosocial worries, and socioeconomic issues (see Table 2, at right).

Long-term Follow-up and Survivorship

Survivorship is a natural part of the oncology continuum. Most practitioners now agree that cancer is, in essence, a chronic condition that requires long-term follow-up not unlike care provided to other patients with chronic disease. In 2007 the NCI estimated that there were 11.9 million cancer survivors in the United States. Much discussion has revolved around who is best suited to care for our growing population of cancer survivors. Clearly, it is unrealistic that oncologists can remain the "office of record" for this growing population. On the one hand, general practitioners are best suited to provide long-term follow-up as:

- They typically have existing relationships with the patient
- It is often easier to get the patient scheduled for appointments and referrals
- There are lower costs of care in a family practice
- This type of arrangement enables oncologists to focus on acute care.

On the other hand, oncologists worry about the potential loss of outcome data and information on late effects when cancer survivors are seen and followed by family practitioners. Additionally, family practitioners may lack the necessary expertise to manage cancer survivors or their practice may place too many other demands on their time to provide optimal long-term cancer follow-up.[15]

Regardless of where and by whom cancer survivorship care is provided, it is critical that AYA cancer survivors are provided with an individualized end-of-treatment summary. As a culture we have become highly mobile and lack the same physical familial roots as prior generations. To avoid being "lost in transition," the Institute of Medicine (IOM) recommends that each survivor be provided with a summary of his or her cancer care, including diagnosis, treatment(s), side-effects of said treatments, and a detailed follow-up care plan.[16] The American Society of Clinical Oncology (ASCO) has freely available on its website (*www.asco.org*) cancer treatment plan and summary resources, including modifiable generic templates and breast cancer- and colon cancer-specific templates for use. Finally, while some might be leery of web-based storage, we are proponents of resources such as Google Health and Microsoft HealthVault. These services are particularly useful for the transitory AYA patient population who, in their first 10 years of post-cancer care, might move for college, relocate for employment, and transition yet again for love or other relationships.

Table 2. Challenges that Face Adolescent and Young Adult Cancer Patients

Health

- Second primary malignancies
- Cardiotoxicity
- Infertility
- Amputation
- Increased risk-taking behavior, including alcohol, tobacco, and illicit drug use and abuse

Psychosocial

- Depression and anxiety
- Post-traumatic stress disorder
- Setbacks in education (due to time and/or poor academic achievement)
- Behavioral adjustment problems
- Poor self-image with regard to body
- Psychological distress
- Less likely to marry

Socioeconomic

- Health insurance
- Employment opportunities

Sources: Soliman H, Agresta SV. Current issues in adolescent and young adult cancer survivorship. *Cancer Control.* 2008 Jan;15(1):55-62. Bleyer A. Young adult oncology: the patients and their survival challenges. *CA Cancer J Clin.* 2007 Jul-Aug;57(4):242-55.

Moving Forward

Historically, adolescent and young adult cancer patients have had good outcomes. While this scenario is generally interpreted as good, it has led to decreased research interest and subsequent funding. It has also been difficult, as a field, to make overall improvements to AYA survivorship, as it is hard to improve on an already good survival rate. Despite the good prognosis, we must remember that these outcomes are not seen in all cancer types occuring in AYA patients. As oncologists who treat adolescent and young adult cancer patients, we must be acutely aware of the long-term management of late effects. The guidelines we currently use are abstracted from pediatric- and adult-based resources, yet AYAs may have unique responses to treatment and subsequently have different lasting damage to their internal organs. Ultimately, more research is needed to determine the minimum dose of chemotherapy and other interventions for maximum effect.

Further, unlike their younger and older peers, AYAs have unique psychosocial concerns. In particular, we need to be cognizant that AYA cancer survivors may have difficulty forming lasting and meaningful relationships or they may demonstrate increased risk-taking behaviors. We also need to consider the interruption, caused by cancer care, in school and/or employment performance. Our young adults may also experience an unexpected change of career path due to subsequent medical limitations, such as decreased cardiac function following treatment with doxorubicin or amputation. Unique financial concerns also exist for this population of patients, although these might be changing as a result of healthcare reform.

We strongly encourage clinicians to remember that adolescents are not just "old children" and that young adults are not the same as "regular" adults. As a group, we have much to learn about the AYA cancer patient and the tumors that they get, the problems they encounter regarding access and delivery of care, and the therapy that they should receive (see Figure 5, page 24). Community cancer centers need to know that resources are readily available. At the UC Irvine Medical Center we have created a patient and professional resource reference page as part of the Young Adult Cancer Program website (*http://www.healthcare.uci.edu/youngadultcancer/*). At this site we attempt to address some of the recurrent concerns expressed by our patients and our professional peers. In particular, we have links to comprehensive care summary and follow-up plan templates; PowerPoint presentations on AYA cancer and survivorship; clinical and practice recommendations by the IOM, the NCI, and others; information pertaining to cooperative group activities and relevant research outcomes; and information about relevant federal and state policy regarding employment discrimination and health care insurance.

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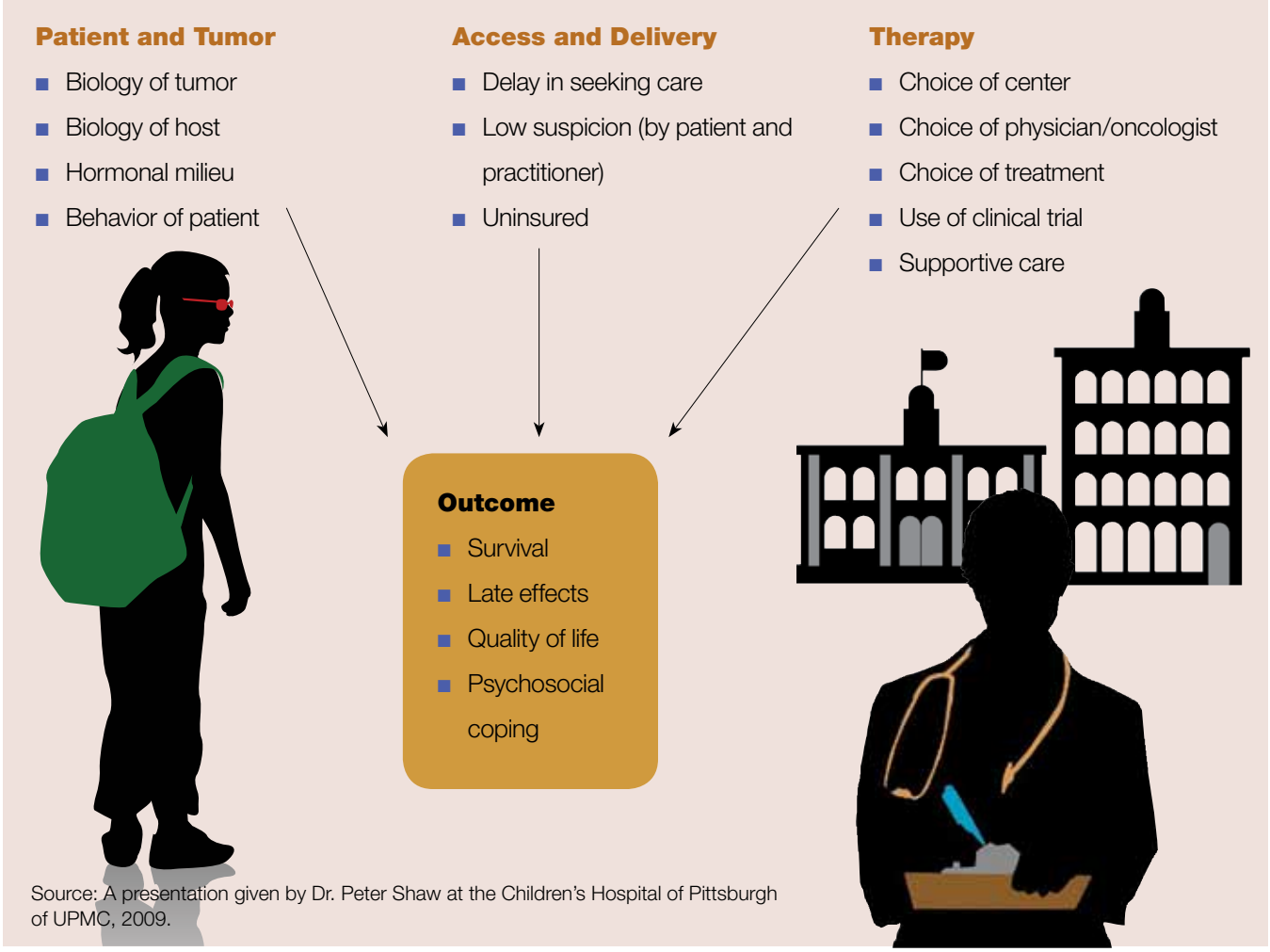
Figure 5. Factors Contributing to Cancer Outcomes in Adolescents and Young Adults



Source: A presentation given by Dr. Peter Shaw at the Children's Hospital of Pittsburgh of UPMC, 2009.

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