

QUALITY OF LIFE ISSUES AND CANCER SURVIVORSHIP

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Prior to the 1970s and the advent and use of multi-modal chemotherapy, children diagnosed with leukemia and other forms of cancer had little hope of long-term survival. Today, advances in treatment and the coordination of pediatric treatment through clinical trials have greatly increased the long-term life chances of these young people. Indeed, recent reports indicate that 75% of children diagnosed with various forms of cancer in the United States are expected to survive their disease and treatment (Greenlee, Murray, Bolden, & Wingo, 2000). Furthermore, young people under the age of 40 with a cancer history comprise 7% of the 7.1 million cancer survivors diagnosed with cancer in the last 20 years, with a large proportion having been diagnosed with cancer as children or adolescents.ⁱ

These statistics indicate increasing lengths of survival for individuals diagnosed with cancer as children and a growing number of childhood cancer survivors. However, these numbers give no indication of the quality of life expected, enjoyed, or endured by these people. In 1998, the American Cancer Society Task Force on Children and Cancer reported that “(T)he progress achieved in attaining 80% survival among children and adolescents and young adults with cancer can be justified only if their physical, emotional, and social quality of life also are protected” (p.822) (Haase, Mauer, & Reaman, 1998). Thus, our successes in pediatric oncology require researchers and health care professionals to attend to the psychosocial consequences of successful treatment and to the quality of life of these survivors.

Cancer Survivorship and Quality of Life

“Cancer survivorship” is a term that has come to represent the state or process of living following a diagnosis of cancer, regardless of how long a person lives. It is a concept used by many health care professionals, researchers, and cancer patients to understand not only the physical but also the social, psychological, and spiritual/existential impact of cancer on one’s life and for the remainder of one’s life. When viewed as a continual, dynamic, and ever-changing process that begins at the moment of diagnosis and continues for the remainder of life, cancer survivorship can be defined as the experience of “living with, through, or beyond cancer.”(Leigh, 1992)

Measuring “quality of life”

There has been substantial debate about both meaning and measurement approaches in psychosocial and quality of life studies of childhood cancer patients and survivors (Eiser & Jenney, 1996; Parsons & Brown, 1998). Even when meaning has been clear, measurement and sample decisions have varied from study to study. Questions about validity and reliability abound. Sample size has varied considerably. Some investigators have used psychometric instruments standardized on “physically normal” populations, while others have normed instruments on the populations directly under inquiry. Some investigators have used approaches that are more responsive to respondent narratives than to investigators’ *a priori* orientations and have included uniquely designed questionnaires, open-ended questions and intensive personal and small group (focus group) interviews.

ⁱ Data Sources: SEER January 1997 Prevalence estimates applied to U.S. January 1997 population estimates from the Census Bureau (January 1997 populations were estimated by averaging July populations from 1997 and 1996).

In an attempt to examine “quality of life” as a specified construct in childhood cancer survivors, some investigators have administered instruments designed specifically to assess multiple and varied aspects, or qualities, of cancer survivors’ lives (Crom, Chathaway, Tolley, Mulhern, & Hudson, 1999; Feeny et al., 1992; Ferrans & Powers, 1992; Van Schaik, Barr, DePauw, Furlong, & Feeny, 1999; Zebrack & Chesler, 2001b). Some of these instruments, such as the European Organization for the Research and Treatment of Cancer (EORTC) – C30 Questionnaire (Aaronson, Ahmedzai, & Bergman, 1993), are widely-used in quality of life research and have well-established norms derived from adult cancer populations. Others, like the Quality of Life – Cancer Survivors (Ferrell, Dow, & Grant, 1995; Ferrell, Hassey Dow, Leigh, Ly, & Gulasekaram, 1995) and the Quality of Life Index – Cancer (Ferrans & Power, 1995) have received less exposure and psychometric analysis. All of these instruments typically assess physical, psychological, social and spiritual/existential domains, and address concerns regarding health status and physical function, sexuality and fertility, emotional distress, future outlook, school and work performance, social and family relationships, and spirituality, as well as other key medical, demographic and psychosocial elements. The validity, reliability and utility of these instruments in childhood cancer *survivor* populations, however, have yet to be established, and no gold standard for assessing “quality of life” in *survivors* of childhood cancer currently exists.ⁱⁱ

To date, generalizable knowledge about the impact of cancer on psychosocial and behavioral outcomes and quality of life in childhood cancer survivors has been limited by studies in individualized settings, with relatively small survivor populations, and lacking a control

ⁱⁱ Some “Quality of Life” instruments have been developed specifically for children and adolescents in active treatment (Armstrong et al., 1999)(Goodwin, Boggs, & Graham-Pole, 1994; Varni, Katz, Seid, Quiggins, & Friedman-Bender, 1998), but their administration in off-treatment survivor populations has yet to be reported.

group. Although reports of childhood cancer survivors' "quality of life" are few, long-term physical, psychosocial and behavioral outcomes associated with cancer survivorship have been well reported. Yet, the overall portrait of childhood cancer survivors is as varied as the range of systematic approaches used to portray it.

Psychosocial, behavioral and "quality of life" outcomes

Psychosocial outcomes

Historically, a number of studies have suggested that a sizable proportion of childhood cancer survivors is seriously troubled psychologically, perhaps even exhibiting psychopathologic symptoms (Hobbie et al., 2000; Koocher & O'Malley, 1981; Moore, Glasser, & Ablin, 1987; Mulhern, Wasserman, Friedman, & Fairclough, 1989; Stuber, Christakis, Houskamp, & Kazak, 1996; van Dongen-Melman & Sanders-Woudstra, 1986). In contrast, other studies indicate that childhood cancer survivors score in the normal range on standardized psychometric measures, thereby demonstrating few significant differences in psychosocial adjustment when compared to young people without a history of childhood cancer (Fritz, Williams, & Amylon, 1988; Gray et al., 1992; Greenberg, Kazak, & Meadows, 1989; Wasserman, Thompson, Wilimas, & Fairclough, 1987). Kazak and Meadows (1989) summarize these findings, stating that "most (survivors) score near normal in terms of psychological and social functioning" (p. 187). Kupst et al. (1995) argue that "despite periods of intense stress, most children and families adapt well," although "a significant minority" of survivors have problems (p. 602). Perhaps most provocatively, a few investigators (Eiser & Havermans, 1994; Chesler, 2000) draw attention to anecdotal reports that indicate psychological growth in this population, and several studies have demonstrated the population of childhood cancer survivors to be significantly healthier (in

psychosocial terms) or more appreciative of life than population norms or healthy controls (Arnholt, Fritz, & Keener, 1993; Cella & Tross, 1986; Elkin, Phipps, Mulhern, & Fairclough, 1997; Maggiolini et al., 2000; Weigers, Chesler, Zebrack, & Goldman, 1998).

Many of the above studies agree that whatever the general psychosocial health of this population, survivors who have or report substantial physical late effects, learning problems or relapse also demonstrate less positive self-esteem or adjustment scores and report more problems or worse quality of life (Chen et al., 1998; Fritz et al., 1988; Koocher, O'Malley, Gogan, & Foster, 1980; Kupst & Schulman, 1988; Mulhern et al., 1989; Kazak, Christakis, Alederfer, & Coiro, 1994; van Dongen-Melman & Sanders-Woudstra, 1986; Zebrack & Chesler, In Press; Zeltzer, 1993). In addition, reports indicate that survivors diagnosed at an older age (Kupst et al., 1995) or who are older at the time of inquiry (Barakat et al., 1997; Elkin et al., 1997) show more negative psychosocial outlooks, as do those who are from families of lower socioeconomic status (Kupst & Schulman, 1988; Greenberg et al., 1997) or who have experienced more concurrent stress (Barakat et al., 1997). Others have identified high dose radiation, younger age at diagnosis and female gender as risk factors for mood disturbance in long-term survivors (Zeltzer et al., 1997).

A recent report from the Childhood Cancer Survivor Study indicates that sociodemographic risk factors associated with an increased risk for depression and somatic distress in the general population (i.e. female gender, lower household income, lower educational attainment, not being employed) are the same for leukemia and lymphoma survivors and sibling controls (Zebrack et al., In press). Only exposure to intensive chemotherapy added to childhood cancer survivors' risk for reporting somatic distress. Given these findings from the largest cohort of childhood cancer survivors to date (over 16,000 survivors diagnosed before age 18 and

ranging in age from 14-52 at time of study), the authors suggest that it is not cancer nor its treatment, *per se*, that places a subset of survivors at risk for psychological distress but rather an increased potential for limited educational or employment opportunities that may result from toxic chemotherapy exposures or social disruptions at critical developmental life stages (Zebrack et al., In press). In face-to-face interviews,ⁱⁱⁱ young adult survivors of childhood cancer have connected school problems or difficulties with carrying out job responsibilities or keeping a job with the unpredictability and limitations associated with intermittent treatment-related pain and fatigue.

While seemingly contradictory, the most reasonable conclusion about all the study results described above is that they are all correct in certain regards. Some survivors of childhood cancer have managed to grow in positive ways as a result of their cancer experience. Most probably are relatively normal in psychosocial terms and would score such on most psychological measures. A small but significant minority undoubtedly experiences ongoing psychological and/or social adjustment problems -- how large a proportion and how substantial a set of problems appear unclear. Moreover, all survivors, even those apparently doing quite well, experience at least occasional problems in social adjustment and continue to be concerned about their medical and social futures. As Haase and Rostad (1994) suggest: "The experience of completing cancer treatment has two faces -- one of celebration and hope, one of uncertainty and fear" (p. 1490). In their view, and as affirmed by other researchers, survivors continue to worry, more or less, occasionally or not, about relapses, more treatments, and potential problems with fertility (Gray et al., 1992; Rait et al., 1992; Weigers et al., 1998).

ⁱⁱⁱ Work conducted by the authors as part of a recent project funded by the American Cancer Society, California Division (Special Pilot Research Grant #5-1-00).

Behavioral outcomes

A research topic yet to be fully explored is that of health behavior, which is the extent to which individuals engage in behaviors which are likely to compromise or promote their future health and well-being. It is imperative to promote long-term health in childhood cancer survivors and to develop interventions that support health promotion and disease prevention in this population, especially given a demonstrated excess risk of cancer incidence and mortality later in life (Green, 2000; Green, Hyland, Chung, Zevon, & Hall, 1999; Neglia et al., 1991).

There is some (but certainly not conclusive) evidence that risk-taking behaviors exist at problematic levels among childhood cancer survivors. Compared to national norms, survivors show higher rates of alcoholism (Lansky, List, & Retter-Setter, 1986) and smoking rates equal to those in the general population despite their increased risks for second cancers (Troyer & Holmes, 1988). One study showed survivors were less likely to quit smoking as compared to sibling controls (Haupt et al., 1992); however, another study has shown no significant differences among quit rates across survivors and sibling controls (Tao et al., 1998). One study showed survivors to be significantly less likely to initiate smoking, but once having started, survivors were as likely as controls to become regular smokers (Tao et al., 1998). Furthermore, both survivor and sibling smokers reported substantial habits (greater than 1/2 pack per day). Cigarette smoking and alcohol or drug use are particularly dangerous for this population due to the potential contributions of tobacco or drugs to cancer onset or other deleterious health outcomes either directly (as in the case of smoking) or indirectly (for instance when alcohol or drug use impact upon proper nutrition, sleep, exercise, operating a motor vehicle, etc.). Additionally, certain survivor subgroups are particularly at risk. These include individuals who

received potentially pulmonary-damaging treatments like bleomycin, or cardiotoxic treatments such as anthracyclines.

Work to date suggests that childhood cancer survivors with high rates of anxiety, depression, or self-esteem deficits, limited vocational potential, and physical health or functioning deficits may be especially likely to engage in risk-taking behaviors, particularly if they are male. In contrast, females in the general population are more likely to experience anxiety or depression, low self-esteem and low vocational potential (Nolen-Hoeksema, 1987) which secondarily may increase their risk-taking behaviors. In addition, female leukemia survivors may be more susceptible to neuropsychological damage associated with high doses of cranial radiation treatment given at a young age. Studies have shown that female leukemia survivors, but not males, score significantly below the mean on all subscales of IQ and achievement tests (Waber et al., 1990; Waber et al., 1995). Treatment variables, such as exposure to cranial irradiation and age at diagnosis, have been demonstrated to significantly and negatively affect educational attainment in long-term survivors of childhood leukemia (Haupt et al., 1994), and treatment intensity during childhood may serve as a risk factor for adult survivors' health-compromising behaviors through neuropsychological deficits that arise from cancer treatment (Chen et al., 1998).

It is still unclear which treatment factors (age of diagnosis, type and level of chemotherapy or radiation therapy) and quality of life issues (psychological distress, vocational potential, or physical health and functioning) will best predict high-risk behavior and in what way sociodemographic variables such as gender, ethnicity or socioeconomic status modulate these predictor variables. For example, limited investigations into the role of race and ethnicity in health behavior outcomes for childhood cancer survivors have not demonstrated ethnic

differences in health behavior outcomes (Mulhern et al., 1995); yet, race/ethnicity and socioeconomic status are considered predisposing (as well as confounding) factors for increased vulnerability of young people engaging in risk behaviors (Irwin, 1993). It may be that small sample size in reported survivor studies has limited the power for examining race and ethnicity as risk factors.

Physical symptoms

Existing studies of physical effects in childhood cancer survivors have drawn much attention to an increased risk of death at an early age (Green et al., 1999; Nicholson, Fears, & Byrne, 1994), compromise to vital organ systems, including reproduction (Byrne et al., 1992; Neglia & Nesbit, 1993; Schover, 1999), neuropsychological and educational problems (Challinor, Miaskowski, Moore, Slaughter, & Franck, 2000; Copeland, 1992; Deasy-Spinetta, 1993; Haupt et al., 1994; Mulhern et al., 1998; Peckham, 1991; Raymond-Speden, Tripp, Lawrence, & Holdaway, 2000), and visible physical impairments and disabilities (Crom et al., 1999; Holmes, Holmes, Baker, & Hassanein, 1990; Hudson et al., 2000; Tebbi & Mallon, 1988). There are relatively few studies, however, that examine the long-term sequelae of symptoms such as pain or fatigue in survivors of childhood cancer. Studies that do include pain or fatigue as outcome variables are typically survivor studies involving adult cancer patients, although young adult survivors of Hodgkin's disease diagnosed in late adolescence and adulthood have been shown to experience fatigue as a long-term effect of treatment (Bloom, Hoppe, Fobair, Varghese, & Spiegel, 1988; Kornblith et al., 1992).

The few studies of pediatric survivors that do include pain as an outcome report minimal pain in the cohort as a whole but subgroups who continue to experience significant pain. For

example, a review of 62 osteosarcoma survivors found that most survivors had either no or mild ongoing pain, although a subgroup had continued phantom pain and neuralgia (Greenberg et al., 1994). A meta-analysis of studies on health-related quality of life in childhood cancer survivors in the European community found that pain was a lasting problem in about one-third of patients (Calaminus & Kiebert, 1999). In one study of survivors of childhood autologous bone marrow transplantation almost one fourth of the sample had moderate to severe pain, although “96% judged the quality of their life to be good” (Kanabar et al., 1995). Another study indicated that survivors with osteoporosis may have ongoing musculoskeletal pain (Haddy, Mosher, & Reaman, 2001).

The prevalence and severity of ongoing physical symptoms in survivors of childhood cancer remain unclear, as are the many psychosocial and behavioral implications of on-going sequelae. For example, the relationships between physical symptoms and education and employment, and the potentials for increased behavioral risks (i.e. alcohol and substance use and depression) commonly associated with low educational attainment or employment difficulties are not well understood. Also, given documented infertility in some childhood cancer survivors, we still lack an understanding of how experiencing infertility affects these young people’s quality of life, including their attitudes about having children, their concerns about their children being at risk for cancer given their own cancer history, their knowledge about alternative modes of having children (i.e., adoption, artificial insemination) and their ability to financially or emotionally afford alternative modes of creating a family.

Implications for policy and practice

Survivors of childhood cancer pose a particular challenge to the US health care system. In terms of years of productive life saved, childhood cancer is one of the most remarkable examples of the advance of modern high-technology medicine. Each year, of the estimated 7,500 children younger than 15 years of age diagnosed with a malignancy, more than 4,800 will be long-term survivors (Robison, 1993). Despite these successes in medical treatment, we know that a full range of psychosocial services is not available to all children diagnosed with and surviving cancer. Moreover, we also know that these successes, and the provision of a full range of services, are not being achieved equally in the United States. In an era in which good health is not just the absence of disease but also the presence of psychological and social well-being, we must ask if the advances in pediatric oncology are resulting in what van Eys (1977) called a “truly cured child.”

Understanding how young people manage the impact of cancer and its influence throughout the rest of their lives is critical for health care professionals committed to assisting these childhood cancer survivors in their attempts to live vibrant and productive lives. It is incumbent upon the providers of medical and psychosocial care to conceive of childhood cancer as more than just a disease that begins with diagnosis and ends when the treatment protocol ends (Tao, Zeltzer, & Zeltzer, 1999; Zeltzer, 1993). Instead, cancer initiates a life-long trajectory of survival (regardless of the length of that survival) having both positive and negative long-term implications for quality of life. As a result, interventions aimed at enhancing positive adjustment and well-being and the adoption of health-promoting behaviors are equally as important as those geared toward preventing long-term negative sequelae.

Since childhood cancer impacts families (Chesler & Barbarin, 1987), the health and well-being of the childhood cancer survivor population is inextricably linked to the health and well-being of their own parents, siblings, and eventually spouses and significant others, as well as offspring. For example, siblings of children with cancer were found to have more somatic symptoms and poorer health care than healthy controls (Barbarin et al., 1995; Dolgin et al., 1997; Sahler et al., 1994; Sargent et al., 1995; Zeltzer et al., 1996). The long-term trajectory of siblings of childhood cancer survivors is unknown, and studies using these siblings as control groups may in fact underestimate the problems of the survivor cohort as a whole. Thus, support interventions that focus on families are very important. Today's long-term survivor clinics, cancer survivor day celebrations, oncology camps, family retreats, and community-based parent self-help organizations (like those affiliated with the Candlelighters Childhood Cancer Foundation) have become invaluable sources of support to pediatric oncology families throughout an entire span of survivorship – from diagnosis, through treatment, and beyond.

Interventions should also be designed and then implemented in accordance with needs expressed by survivors at various stages of their lives. Few studies have focused on actual needs but suggest areas for intervention (Roberts et al., 1997; Zebrack & Chesler, 2000). These include the need and desire for information about the disease and treatment, health insurance, and family planning (including genetic counseling to address concerns about risks of “passing” cancer to survivors’ off-spring, in spite of existing data that suggests that offspring of survivors are not at an increased risk of developing cancer^{iv}). Survivors also have expressed a need for educational and vocational counseling, supportive counseling, and the desire to meet other survivors.

^{iv} See Kenney et al., 1996

Attending to the special needs of childhood cancer survivors and their families requires not only management of disease and its potential late effects, but long-term expansion and coordination of services, utilization of medical and allied health care professionals, mobilization of community resources, and assistance in managing the emotional and financial impact of the illness. These tasks must be performed in the context of a changing and unstable health care delivery system in the United States. Unfortunately, anecdotal reports and a growing body of empirical evidence of undue hardships associated with economic pressures on the health care system do not bode well for the provision of medical and psychosocial support services to individuals and their families who rely on the system over extended periods of time (see Zebrack & Chesler, 2000).

Implications for research

Knowledge about the determinants of psychosocial functioning and behavioral outcomes in this population is needed as a basis for the development of appropriate supportive and potentially preventive interventions throughout a continuum of care, from diagnosis through treatment and over the long-term. Investigators and health care providers have yet to test interventions that may promote positive psychosocial adjustment and the adoption of health promoting behaviors, and/or prevent negative outcomes and health risk behaviors at various points throughout the life span. Given studies documenting treatment-related physical effects (e.g., cardiac and pulmonary problems, hormonal problems, etc.) in a childhood cancer survivor population, we do not know how and to what extent these conditions contribute to psychological well-being, psychosocial functioning and health behaviors over the long-term. While physical late effects such as fatigue or limited physical function may assumedly contribute to decreased

self-worth or sadness in some childhood cancer survivors, these same effects may also just as well increase survivors' awareness and practice of important health promoting behaviors such as proper diet and exercise. Similarly, perceived benefits from the cancer experience may enhance self-esteem, self-confidence and mastery but still not prevent worry, self-doubt or the experience of employment or insurance discrimination that may arise as survivors age and face new life challenges such as going to college, entering the work world or starting a family. While empirical research has documented long-term sequelae in survivors of childhood cancer, we still lack knowledge about (1) the relationship between psychosocial functioning and behavioral outcomes for long-term survivors of childhood cancer; and (2) factors that mediate and/or moderate this relationship over time.

Focusing on survivors as a cohort is a relatively new research arena, and we need rigorous designs to overcome the limitations of existing studies (i.e., single institutions, small sample sizes, studies that do not include long-term survivors who have entered their second, third and fourth decades of survivorship). We also need psychometric instruments that demonstrate the potential for being reliable and valid measures of quality of life in the population of off-treatment survivors who have reached adulthood. Testing existing quality of life instruments and assessing their psychometric properties in survivor populations will provide some direction in the area of instrument development (see for example Zebrack & Chesler, 2001a). Furthermore, we must seek to expand the theoretical context for understanding cancer and its impact on life by acknowledging that the experience of cancer in children and adolescents occurs during important phases of psychosocial development and identity formation. The extent to which the cancer experience is or is not incorporated into a survivor's sense of self may affect that individual's quality of life (Zebrack, 2000).

Coping with cancer throughout survivorship requires young survivors to continuously appraise cancer's threat and its potential for change as it appears and re-appears in different forms at various times throughout the remainder of life (e.g., as threat to reproduction, as discrimination when seeking insurance, when certain environmental stimuli remind the survivor of his/her experience, when other friends or family members are diagnosed with cancer, if or when a recurrence or second cancer is diagnosed). Furthermore, quality of life after cancer is a function of social, emotional and behavioral processes involving adaptation to the issues imposed over time by the concrete physical and social realities of the disease. For instance, a survivor's self-esteem or self-image may be influenced by his/her physical capabilities or by whether or not he/she has achieved desired educational or career goals. A young survivor's ability to form meaningful and intimate relationships may be related to the extent to which cancer did or did not disrupt involvement with peers and school during critical periods of adolescence. The ability to achieve desired educational or occupational goals may influence or be influenced by physical health status. Osteoporosis as a result of cancer treatment might be associated with ongoing or recurrent pain that might impact employment, educational achievement, or even sexual satisfaction. Thus, quality of life research must account for the interdependency among the various domains of life that comprise individuals' quality of life. Also, research must occur within the context of examining the life course of these young people. A 17-year old survivors' sense of well-being may be founded on an ability to establish independence in life or perform well in school, whereas achieving expected life goals like getting married or having children may have greater salience/relevance for a 30-year old survivor's well-being.

Prospective longitudinal studies to assess psychological, social, and behavioral outcomes and change over time as these young people pass through different developmental stages appear to be a logical next step. Also, collaborative research among investigators will increase sample sizes. Rigorous research methods that control for salient variables not directly related to cancer (i.e. socioeconomic status), stratify by developmental stage and age at diagnosis, use various respondents (e.g., child, parent, teacher, doctor/nurse), and apply statistical corrections for multiple analyses and multi-directional causal pathways will improve the scientific rigor and potential clinical relevance of future studies (Challinor et al., 2000). Finally, qualitative approaches to research will enhance our ability to capture the subjective experience and meaning that survivors attribute to cancer and its treatment. Survivors' own self-reports are the clearest expressions of their own ways of thinking about and presenting their experience and quality of life. "The role of scholars is to listen to and reflect upon these self-reports, 'test' them for accuracy or unreliability, for defensiveness or obfuscation, and for internal contradiction" (p.6) (Chesler, 2000). Combinations of research approaches, both qualitative and quantitative, can provide us with a sense of the credibility and trustworthiness of our findings.

Conclusion

Expanding our understanding of quality of life and the factors that contribute to it should help subsequent investigations of *who* might benefit from *which* psychosocial support interventions *when*—during early diagnostic and/or treatment stages, at the end of treatment, or in the long-term. While it is important to identify long-term survivors "at-risk" for psychosocial sequelae for the purposes of developing preventive interventions and psychosocial treatment options, identification is not enough. Given the current knowledge that most long-term survivors

of childhood cancer are psychologically well-adjusted, and that some even describe their lives as enriched by the cancer experience, we need a fuller, more comprehensive understanding of what contributes to long-term survivors' positive adaptation. Equipped with this understanding, health care professionals, program planners and policy makers can re-develop and create appropriate services and systems that facilitate and enhance quality of life.

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