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CHILDHOOD CANCER TREATMENT AND LATE EFFECTS

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Abstract

Many children treated for a cancer will be long term survivors, with the potential to develop specific treatment-related adverse outcomes, compared with the general population. Rates of long term survival after childhood cancer are increasing because of major advances in surgery, chemotherapy and radiotherapy. However, curing childhood cancer can have serious implications about patient's quality of life. In fact, chemotherapy and radiotherapy can harm developing organs, and surgery can lead to loss of normal physical functioning. Usually, survivors of childhood cancer can have physical, mental, or emotional limitations. Risk varies in relation to treatment exposure, age at treatment, type of childhood cancer, duration of follow-up, and genetic factors. In this work, we resume the main long term effects of childhood cancer treatment since the knowledge of possible limitations is important for promoting earlier detection of and intervention for such complications. Furthermore, we provide some useful recommendations for long term follow up.

Keywords: *long term sequelae, childhood cancer, pediatric cancer survivors, follow-up, survival*

Introduction

With recent advances in anticancer treatment including aggressive multi-modality therapies and improved supportive care, there has been a remarkable improvement in overall cure rates. In fact, the past 3 decades has seen many improvements in the survival of children treated for cancer, with the 5-year survival rate approaching 80% (1). This improvement has resulted in a growing population of childhood cancer survivors. In 1997 there were an estimated 270000 survivors of childhood cancer in the United States, more than two thirds were older than 20 years of age (2). One in 640 young adults of age 20-39 years in United States is presently a survivor of childhood cancer (2), and this number is increasing every year. Long term survival rates vary with cancer diagnosis and frequently by demographic characteristics, such as age, gender, and race; and by tumor characteristics, such as location and extent of disease, morphology, and genetic alterations. The mortality rate for 5 years survivors of childhood cancer is greater than tenfold the one of the normal age adjusted population (3).

Pediatric cancers and sequelae

Recent advances in childhood cancer treatment have led to greater cure rates, creating a public health issue of large number of survivors who need continuing health care into adulthood. Numerous studies have shown that cancer and its treatment predispose to late morbidity and increase the risk of mortality in long term childhood cancer survivors (3-7). Surgery, chemotherapy, and radiotherapy are essential to providing a long-term cure in many children with malignant and nonmalignant neoplasms. Surgical procedures can result in structural and functional changes, which can have long term implications in young children who are growing and developing. Chemotherapy and radiotherapy are cytotoxic and thus can have deleterius effects on developing organ systems. Long term survivors of childhood cancer are at risk for many late effects such as neurocognitive dysfunction, cardiopulmonary toxicity, endocrinopathies, early death and secondary malignancies (Table I) (8,9). These complications are related not only to the specific therapy employed but also may be determined by individual characteristics such as treatment exposure, age at treatment, type of childhood cancer, concomitant therapies, duration of follow-up, and genetic factors (9-11). Furthermore, most survivors eventually discontinue follow-up with their pediatric oncologists and receive primary health care from adult physicians, many of whom are unaware of survivors' health risks (12).

Specific issues in follow up

Second malignant neoplasms

Developing a second cancer because of the treatment received in childhood to treat the first malignancy is among the most devastating of the late effects. The cumulative lifetime incidence of second cancers approaches 5% (13). Childhood cancer survivors have a three- to sixfold increased risk of developing a second cancer, when compared with the general population, and this risk continues to increase with patient age (14,15). The incidence and the type of second malignancy differ with the primary dignosis, the type of therapy received, time from initial diagnosis and the presence of genetic conditions. The most commonly reported second primary cancers are breast, bone, and thyroid cancer; therapy-related myelodysplasia; and acute myeloid leukemia.

Younger age at treatment of the primary cancer is associated with an increased risk of second cancers (14).

Female sex is associated with an increased risk, because of the excess number of secondary breast cancers and the increased occurrence of thyroid cancer in female survivors (14).

Ionizing radiation can enhance the risk of cancer. Examples of radiation-associated tumors include breast and lung cancer, thyroid cancer, brain tumors, and osteosarcoma. The large majority of radiation-associated second cancers develop within the radiation field (16). The risk increase with higher doses of radiation and it is higher when exposure occurs at a younger age (14,17-21).

Together with thyroid and bone marrow, breast tissue is known to be one of the most radiosensitive organ of the human body, especially in children. *Breast cancer* continues to be the most common

solid tumor among women who have received radiation to the mantle region, and the risk remains elevated for a long-time (14,22). The risk of breast cancer begins to increase about 8 years after radiation (16,23,24). The 30-year cumulative incidence of breast cancer in female survivors after radiation is 17% (15). The risk of secondary breast cancer occurs after several types of childhood cancers (15), particurarly after Hodgkin disease (22,25,26).

Thyroid cancer is the second most common solid tumor reported among suvivors of Hodgkin disease (14). Secondary thyroid carcinoma occurred with a 1.74 to 36.4 times greater risk than the general pediatric population (14,16). An increased risk of developing thyroid cancer has also been described after radiation therapy for others primary cancers, including acute lymphoblastic leukemia, and brain tumors as well as after total body irradiation for hematopoietic cells transplantation (27-31). Prognosis is currently very good.

Lung cancer has been reported after chest radiation therapy, although it is relatively infrequent. The risk increase among smokers.

Secondary leukemia is one of the most common and well-documented malignant late effects in pediatric and adult literature (23). Acute forms represent more than 95% of cases. Usually secondary leukemia is an acute myeloid leukemia (16). Survivors have a 3.99 to 174.8 times greater risk of developing leukemia compared with the general pediatric population (14,16,2120,24,25). Secondary leukemia is strongly associated with chemotherapy (32). An increased risk of subsequent leukemia is well-documented after exposure to epipodophyllotoxins and alkylating agents (33,34). A dose-dependent relationship is noted with alkylating agents, which typically cause leukemia after latencies of 5-10 years. Increased risk is associated with primary disease recurrence, late disease stage at presentation, and older age (10-16 years old) at presentation. The prognosis of secondary leukemia is generally poor because of the rapidly proliferative nature of pluripotent white blood cells, which are more susceptible and likely to propagate the oncogenic effects of alkylating agents and topoisomerase II inhibitors.

Recommendations: Perform annually physical examination, including a detailed history, breast examination in post-pubertal female patients, inspection of the skin in the radiated area, and complete blood count. Breast self-examination should be taught to all young women who have completed puberty. For female survivors who received abdominal or lung radiation, baseline mammogram at age 25 or 8 years after receiving radiation is recommended (35).

Neurocognitive sequelae

Neurocognitive sequelae frequently occur in children with a history of brain tumors, acute lymphoblastic leukemia, or non-Hodgkin's lymphoma (36). Severe deficits are often noted in children with brain tumors younger than 5 years of age at the time of treatment with radiotherapy (37,38). Three principal risk factors for cognitive sequelae have been clearly identified: age at diagnosis, the volume, the dose of irradiation, and surgical complications (39-44). Patient gender, neurological and perioperative factors, brain tumor location, type of treatment, age at diagnosis and treatment, and interval since treatment are additional variables that may influence the ultimate neurocognitive outcomes of children with cancer (45-47). Neurocognitive deficits usually become evident within 1 o 2 years following radiation and are progressive. Affected children are particularly prone to problems of receptive and expressive language, attention span, memory, engagement, executive functions, processing and fluid abilities, and visual and perceptual motor skills, with irradiation- or chemotherapy-induced destruction in normal white matter partially explaining intellectual and academic achievement deficits (48). The course of white matter injury during cancer treatment and its impact on neurocognitive function is further complicated by significant variance in white matter volume and distribution as a function of age and development. The sensitivity of the developing nervous system to injury increases as the age of the patient decreases. There is a very fine line between destruction of tumour and irreversible damage to surrounding normal neural tissue in infants and young children.

Late effects of cranial radiotherapy are characterized by various neurological deficits and

are largely believed to be responsible for the gradual neurocognitive decline often observed in young children, possibly as a result of an imbalance in the development of gray and white matter (40).

The most common method used to document neurocognitive effects in children treated for brain tumours is the intelligence quotient (IQ) test measuring the intellectual functioning. A decline in IQ is mainly attributed to the effects of radiotherapy. The rate of IQ decline is associated with a several risk factors, including younger age at time of treatment, longer time since treatment, female sex, as well as clinical variables such as hydrocephalus, use of radiotherapy and radiotherapy dose, and the volume of the brain that received treatment.

The major goal of chemotherapy in young children is to delay or to avoid the use of cranial radiotherapy and recently there are efforts to avoid chemotherapy in children with specific tumors (49,50). The rationale for avoiding or delaying radiation therapy is based on the evidence that brain "growth spurt" period extends up to the 3th or 4th postnatal year.

The neurocognitive sequelae of treatment for childhood cancer occur also as consequences of high-dose methotrexate and/or cytarabine, or intrathecal methotrexate (51-53).

Sensorineural hearing loss can be a direct physical effect of the tumor or secondary to the use of radiation and/or ototoxic drugs during treatment (e.g. cisplatin, aminoglycosides). Significant risk factors for hearing loss include age of less than 4 years at the time of treatment, diagnosis of central system neoplasm, treatment with platinum-based chemotherapy, especially when given in combination with cranial irradiation, and treatment involving multiple ototoxic agents (54).

Recommendations: Neurocognitive complications in patients who received therapy that may potentially impact neurocognitive function should undergo a baseline neuropsychological evaluation and annual assessment of their vocational or educational progress. Patients who received platinum-based chemotherapy should undergo a baseline audiological evaluation. Screening for children who underwent radiation therapy involving the temporal bone at doses of 30 Gy or higher include yearly audiological evaluations for 5 years after treatment and until the child is at least 10 years of age.

Cardiovascular and pulmonary late effects

Although many antitumor treatments are cardiotoxic, anthracycline therapy and radiotherapy are mostly responsible for long term cardiac damage. While all the structural components of the heart are at risk for developing radiation-associated injury, the myocardium is the principal focus of damage in anthracyclines toxicity.

Anthracyclines release free radicals that damage the cardiac myocytes. The principle mechanism for compensating for myocyte loss is for the surviving myocytes to hypertrophy to maintain normal cardiac output. Anthracycline-associated cardiomyopathy can be divided into three categories: 1) acute changes, which occur within a week of infusion; 2) early-onset, chronic progressive cardiotoxicity, which occurs within 1 year after completing therapy; 3) late onset, chronic progressive cardiotoxicity, which occurs after 1st year. The incidence of cardiomyopathy is dose-dependent and may exceed 30% among patients who received a cumulative anthracyclines dose in excess of 600 mg/sqm. The probability of cardiomyopathy increase above a cumulative dosage of 450-550 mg/sqm. Younger age at treatment and female gender are additional independent risk factors (55,56).

Radiation-induced vasculopathy has a clinical presentation and morphologic features similar to atherosclerotic coronary disease. Although clinically evident heart failure is rare in survivors treated with radiotherapy alone, subclinical changes are common and may be progressive.

A number of chemotherapeutic agents (e.g. bleomycin, carmustine) together with radiation are known to affect pulmonary function, usually with a restrictive disease pattern. Pulmonary fibrosis and pneumonitis can result months to years after pulmonary radiation therapy. Clinically pneumonitis occurs with cough, fever, or dyspnea.

Recommendations: Long-term survivors who have received potentially cardiotoxic therapies should undergo regular, repeated evaluations of cardiac status. Children at risk may benefit from 2-3 yearly

echocardiogram surveillance with early intervention where a decrease in ejection fraction is documented. A detailed cardiology assessment is also appropriate for survivors who have other major cardiac risk factors. Monitoring for pulmonary dysfunction in childhood cancer survivors includes assessment of symptoms such as chronic cough or dyspnoea on yearly follow-up. Pulmonary function tests and chest x-ray studies are recommended as a baseline on entry into long term follow-up for patients at risk and in patients with symptoms. A healthy diet, regular exercise, and non-smoking should always be encouraged to minimise the risk of adult onset cardiopulmonary problems.

Muscoloskeletal late effects

Disabilities involving bone, teeth, and muscle and other soft tissues are in up to a third of survivors of various pediatric cancers. Bone abnormalities include scoliosis, atrophy or hypoplasia, avascular necrosis, and osteoporosis. Scoliosis is a delayed consequence of radiation therapy to segments of the spinal column; the concavity of the deformity is invariably on the side of irradiation. Many children who have received hemiabdominal or flank irradiation will have a noticeable trunk asymmetry. Young adult survivors of childhood cancer may also have reduced bone density (57-59). Osteopenia in survivors of childhood acute lymphoblastic leukemia has been related to cranial irradiation, methotrexate, and corticosteroid use (60). Dental and maxillofacial abnormalities are the result of radiation effects on bone and soft tissue.

Recommendations: Perform scoliosis examination at least annually (every 6 months in patients at high risks during the patient's adolescent growth spurt). Regular dental care should be performed twice yearly and scrupulous oral hygiene is appropriate.

Gastrointestinal function

Fibrosis and enteritis are the most common pathological abnormalities of the gastrointestinal tract in long term survivors of cancer. These can arise as late complications of radiation therapy to any site from the esophagus to the rectum (61,62) and are associated with adhesions or stricture formation, sometimes with obstruction, ulcers, fistulae, and chronic enterocolites or incontinence. Radiation therapy also is a cause of chronic fibrosis of the liver. The degree of damage increased with the volume irradiated. Even in the absence of radiation therapy, chemotherapy may be cause of chronic hepatopathy.

Recommendations: Patients at risk for gastrointestinal complications should be monitored by history or physical examination for hepatomegaly, icterus, and malabsorption. In all patients who have received potentially hepatotoxic therapy (e.g., methotrexate, mercaptopurine, thioguanine, dactinomycin and abdominal/hepatic radiation), a post-treatment baseline screen (transaminase and bilirubin levels) is important. Prothrombin time for the evaluation of liver synthetic function should be obtained in patients with abnormal transaminase or bilirubin levels. Screening for hepatitis A, B, and C should also be considered in patients with abnormal liver function tests.

Renal late effects

A small number of Wilms' tumor survivors develop renal failure. In patients with unilateral disease, Denish-Drash syndrome, progressive tumor in the remaining kidney and radiation nephritis are the most common causes of renal failure. Renal dysfunction is defined as low glomerular filtration rate, hypertension, or increased urinary albumin excretion. Ages of less than 24 months at diagnosis and treatment with chemotherapy and radiation doses exceeding 12 Gy to the remaining kidney are associated with renal dysfunction (63,64).

Drugs who predispose to renal toxicity are: ifosfamide, cyclofosfamide, cisplatin, carboplatin, methotrexate (high dose), nitrosureas (BCNU, CCNU).

Recommendations: Perform annual physical examination with blood pressure measurement, laboratory monitoring of renal function and urinalysis to evaluate for proteinuria and glycosuria. Educate the survivors regarding avoidance of dehydration

and physical activities that may damage the remaining kidney. Avoid prescribing nephrotoxic medications and evaluate renal function before beginning any new medication.

Growth

Growth impairment can result from numerous factors, including: cancer itself, complications of treatment (poor appetite, vomiting, infection, toxicity to growing tissue), and direct/indirect endocrine effects (65).

Cranial irradiation can lead to growth hormone deficiency and less commonly other pituitary hormone (TSH, ACTH, FSH/LH). It can also lead to precocious or delayed puberty, which in turn affects growth potential. The growth hormone axis is known to be the most sensitive to damage by radiotherapy. Severity and speed of onset of growth hormone deficiency is dependent on total radiation dose, number of fractions, fraction size and duration of treatment. Chemotherapy alone occasionally lead to significant effects on growth. Patients at greatest risk for growth impairment include survivors of tumours located in the pituitary-hypophyseal region (e.g. craniopharyngiomas), those who received cranio-spinal irradiation (> 18 Gy) and those who have undergone allogenic bone marrow transplantation (66).

Recommendations: Monitoring long term survivors for growth problems relies on the use of standardized curves; frequent serial measurements should be obtained to establish each child's pattern of growth. Prepuberal children receiving cranial irradiation should be closely monitored for clinical signs of precocious puberty. Children with impaired growth velocity should be referred to a paediatric endocrinologist. If growth hormone deficiency is demonstrated, replacement can be extremely beneficial.

Obesity

Obesity is a well recognised complication of a number of cancers, including leukaemia and cranyofaringioma. It is best documented using the standard body mass index. A recent study shows that the risk for obesity is greatest among females survivors of childhood acute lymphoblastic leukemia diagnosed before 4 years of age and treated with cranial radiation doses ≥ 20 Gy (RR: 3.81 P ≤ 0.001)(65). Furthermore, obesity is not associated with treatment consisting of chemotherapy only or with cranial radiation doses of 10-19 Gy.

Recommendations: The population of cancer survivors identified as being substantially overweight or obese are a prime target for intervention because of their potential increased risk for cardiovascular disease. Advice on healthy eating and regular exercise should be given early and reinforced regurarly.

Thyroid function

The thyroid is radiosensitive; consequently there is an increased risk of thyroid abnormalities following radiation therapy. Children who received craniospinal irradiation for brain tumor, mantle radiation for non Hodgkin's lymphoma, radiotherapy for neuroblastoma and Wilms' tumour are at risk for thyroid abnormalities. The risk is dose-dependent. The most frequent disturbance is hypothyroidism; the greatest risk occurs during the first five years after treatment. There is no evidence to suggest that chemotherapy, either alone or in combination with radiotherapy, increase the incidence of hypothyroidism (29). A less well known complication following irradiation to the thyroid is hyperthyroidism (29). Thyroid nodules, both benign and malignant, are known to occur with increased frequency after neck irradiation; they are more likely with higher doses of radiation (> 25 Gy) and are more likely to occur in females (29). The risk of thyroid cancer is proportional to the dose of radiation; there is also an association with younger age at treatment.

Recommendations: Patients who have received direct radiation to the neck should be examined annually for thyroid abnormalities. In addition, careful examination for thyroid hyperplasia and nodules with ultrasound screening if exam is suspicious should be undertaken. Evaluation and treatment by an endocrinologist are recommended if any abnormalities are detected.

Gonadal function

- Female: Most girls who received chemotherapy alone will retain their fertility. However, they may be at increased risk of a premature menopause and require hormone therapy (66). In contrast, high dose busulfan and total body/pelvic irradiation are likely to result in impairment of ovarian function

(67). Prepubertal ovaries are relatively resistant. Ovarian failure is also associated with chemotherapy, especially the alkylating agents, although chemotherapy-related gonadotoxicity occurs less frequently in females than in males (68,69). As with radiation therapy, chemotherapy results in dose- and age-dependent toxicity. The risk factors associated with an early menopause include exposure to high doses of alkylating agents and abdominopelvic radiation therapy. The ability of the uterus to expand and enlarge with a pregnancy may be adversely affected by radiation therapy, causing difficulties in carrying a pregnancy to a healthy outcome. Uterine fibrosis caused by radiation may also lead to impaired placental adherence, which can cause abruption (70). Female survivors who received abdominal radiation have higher occurrences of pregnancy-associated hypertension, malposition of foetus, low-birthweight infants, and infants born with congenital malformations that female survivors who did not receive radiation (71). There is no significant increase in these complications among female partners of irradiated male survivors.

Recommendations: Assessment of female pubertal development and fertility should include: Tanner staging of secondary sexual development; menstrual history (primary or secondary amenorrhea, menstrual irregularity, and pregnancies or difficulties becoming pregnant); measurement of serum gonadotropin (FSH, LH) and estradiol levels. Women with early menopause should undergo assessment of gonatropin and estradiol levels if there are clinical symptoms of estrogen deficiency (irregular menses, amenorrhea, hot flashes, and vaginal dryness). Survivors with concers of fertility are urged to seek consultation with reproductive endocrinologists.

- Male: All therapeutic modalities (radiation therapy, chemotherapy, surgery) cause both germ cell depletion and abnormalities of gonadal endocrine function among male cancer survivors. Radiation to the testes is known to result in germinal loss, with decreases in testicular volume and sperm production and increase in follicle-stimulating hormone. Effects are dose-dependent and follow to fractionated exposure of 0.1-6 Gy (72). Radiation therapy may also be toxic to Leydig's cells. It is important remember that spontaneous progression through puberty does not equate to normal fertility. Alkylating agents decrease spermatogenesis; this effect is dose-dependent. There is some evidence that pre-pubertal testicular germ cells may be relatively resistant to chronic toxicity, while others have reported that damage to spermatogenesis from alkylating agents in the developing testis may be severe and permanent (73). The effects of surgery on the male gonads include impotence or retrograde ejaculation after bilateral retroperitoneal lymph node dissection or partial or complete pelvic exenteration.

Recommendations: Assessment of male pubertal development and fertility should include: assessment of testicular volume; Tanner staging of secondary sexual development; measurement of serum follicle stimulating hormone (FSH), luteinising hormone (LH), testosterone and semen analysis. Furthermore, annual age-appropriate history with specific attention to problems with libido, impotence, or fertility, as well as an examination for gynecomastia is important. Currently, cryopreservation of semen is offered to all postpubertal male patients whose cancer therapy is known to be highly gonadotoxic. When abnormalities in testicular function are detected, close cooperation with an endocrinologist is essential in planning hormone replacement therapy or in monitoring patients for spontaneous recovery.

Model of long term follow-up

The purpose of long term follow-up is to:

- confirm continued cancer remission;
- monitor for therapy related toxicity;
- optimise mental health, social adjustment and educational/occupational achievements;

- promote healthy lifestyle choices to minimise late effects.

There are three supportive care components that are especially important in long term follow-up programs:

- services to address the psycological implications of cancer for survivors and their families;
- educational support through school transition programs;
- a plan to facilitate the transition of grown childhood cancer survivors into adult systems of care (74).

Providing appropriate health care for survivors of cancer is emerging as one of the major challenges in medicine. Generally, the ongoing follow-up is limited to an annual comprehensive multidisciplinary health evaluation, and survivors are encouraged to establish an ongoing relationship with a primary healthcare provider in their local community for routine healthcare needs. Benefits of this approach are that the patient remains in contact with a team that is knowledgeable and committed to long term follow-up care, contact with the original treatment center is maintained, and multidisciplinary referrals are usually available within the healthcare system.

Pediatricians, pediatric oncologists, adolescent medicine physicians, internists, physician assistants, and nurse practioners require ongoing education regarding the potential long term effects for which survivors of childhood cancer are at risk (75). There are a variety of models that can be proposed for long term follow-up clinical care. The "medical home" (76,77) is the most appropriate approach for providing care for adolescents with special health care needs. The medical home is defined by care that should be accessible, continuous, comprehensive, family-centered, coordinated, compassionate, and culturally effective.

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Table I. Potential treatment-related late effects

Category	Therapeutic exposure	Potential late effects
Neurocognitive	Methotrexate, radiation involving the brain, cytarabine	Neurocognitive deficits
Cardiac	Anthracyclines	Cardiomyopathy
	Chest radiation therapy	Cardiomyopathy, early onset atherosclerotic heart disease, pericardial complications, valvular disease
Pulmonary	Bleomycin, BCNU, lomustine	Pulmonary fibrosis
	Bleomycin	Pulmonary fibrosis, interstitial pneumonitis, acute distress syndrome
	Radiation involving the lungs	Pulmonary fibrosis, restrictive/obstructive lung disease, delayed interstitial pneumonitis
Gastrointestinal and hepatic	Methotrexate, mercaptopurine, thioguanine, dactinomycin	Hepatic dysfunction, veno-occlusive disease of the liver
	Radiation therapy involving the liver	Hepatic fibrosis, cirrhosis
	Radiation therapy involving the thyroid	Hypothyroidism (primary or central)
	Radiation therapy involving the hypothalamic-pituitary axis	Hyperthyroidism, growth hormone deficiency, central adrenal insufficiency, hyperprolactinemia
Urinary and gonadal function	Cyclophosphamide, ifosfamide, radiation therapy involving the bladder	Hemorragic cystitis, bladder fibrosis, dysfunctional voiding, bladder cancer
	Ifosfamide, cisplatin, carboplatin, methotrexate, radiation therapy involving the kidneys	Renal toxicity, renal insufficiency, hypertension
Muscoloskeletal	Corticosteroids, methotrexate, radiation therapy to weight-bearing bones, inactivity, amputation	Osteopenia, osteopororosis, avascular necrosis, muscoloskeletal growth problems
Second malignancies (SMN)	Etoposide, anthracyclines, alkylating chemotherapy	Acute myeloid leukemia, myelodysplasia

	Radiation therapy (any field)	SMN in radiation field
	Radiation therapy involving the thyroid	Thyroid cancer
	Radiation therapy involving the breast	Breast cancer
	Radiation therapy involving the colon	Colorectal cancer