REVIEW

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FROM THE CHILDREN'S ONCOLOGY GROUP

Monitoring pulmonary complications in long-term childhood cancer survivors: Guidelines for the primary care physician

ABSTRACT

Curative therapy for childhood cancers poses the risk of long-term complications, necessitating regular lifelong follow-up for survivors. The Children's Oncology Group (COG) has issued guidelines on this topic (www.survivorshipguidelines.org). This review summarizes the findings of the COG Guideline Task Force on Pulmonary Complications with respect to pulmonary toxicity.

KEY POINTS

Radiation therapy causes pulmonary fibrosis, interstitial pneumonitis, and restrictive or obstructive lung disease. The risk is dose-dependent and increases with concomitant chemotherapy, younger age at treatment, atopic history, and smoking.

Alkylating agents cause pulmonary fibrosis. Bleomycin can cause interstitial pneumonitis, pulmonary fibrosis, or, very rarely, acute respiratory distress syndrome.

Cancer survivors should have a yearly history and physical examination, plus pulmonary function testing and radiography at baseline and repeated as clinically indicated.

All patients who smoke should be encouraged to quit.

CHILDREN who undergo radiotherapy, chemotherapy, or surgery for cancer face a risk of complications later in life, including pulmonary fibrosis and pneumonitis.

These long-term cancer survivors need systematic, lifelong surveillance, in a program that takes into account their individual risk (based on therapeutic exposures, genetic predisposition, lifestyle behaviors, and comorbid health conditions).[1] Optimally, they would receive their care at multidisciplinary follow-up clinics organized by pediatric oncologists at tertiary care centers. However, access to such centers is limited, making this an option for relatively few. Consequently, as childhood cancer survivors age, internists and family practitioners may need to assume an increasing amount of responsibility for their follow-up care.

Because individual primary care providers are unlikely to follow more than a handful of survivors, specialists have developed guidelines for survivors of pediatric cancer. Working with established multidisciplinary clinics may help ensure appropriate follow-up for this population of patients.

This review summarizes the late effects of cancer therapy on the lungs and an approach to

Dr. Morris has disclosed that he has received consulting fees from the Radiosurgery Centers Corporation and that he owns stock in Amgen, Anesiva, and Synarc corporations.

TABLE 1

Monitoring for pulmonary disease after cancer therapy

TREATMENT (EVIDENCE)[a]	POTENTIAL LATE EFFECTS	RISK FACTORS
Radiation (Category 1)	Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease	Greatest risk: Radiation dose ≥ 15 Gy Total body irradiation ≥ 6 Gy in single fraction Total body irradiation ≥ 12 Gy fractionated Other risk factors: Younger age Radiation dose ≥ 10 Gy Chemotherapy with bleomycin, busulfan, carmustine, lomustine, radiomimetic drugs, eg, doxorubicin (Adriamycin), dactinomycin (Cosmegen) Atopic history Smoking
Alkylating agents Busulfan Carmustine (BCNU; BiCNU, Gliadel) Lomustine (CCNU; CeeCNU) (Category 1)	Pulmonary fibrosis	Greatest risk: Carmustine ≥ 600 mg/m^2 Busulfan ≥ 500 mg (transplant doses) Combined with chest radiation, total-body irradiation Other risk factors: Higher cumulative doses Combined with bleomycin Atopic history Smoking
Bleomycin (Blenoxane) (Category 1)[b]	Interstitial pneumonitis Pulmonary fibrosis Acute respiratory distress syndrome (very rare)	Greatest risk: Dose ≥ 400 U/m^2 (injury observed in doses 60–100 U/m^2 in children) Combined with chest radiation, total-body irradiation Other risk factors: Younger age at treatment Higher cumulative dose Combined with busulfan, carmustine, lomustine
Hematopoietic stem cell transplantation with chronic graft-vs-host disease (Category 1)	Bronchiolitis obliterans Chronic bronchitis Bronchiectasis	Greatest risk: Prolonged immunosuppression related to chronic graft-vs-host disease and its treatment Other risk factors: Chest radiation, total-body irradiation Chemotherapy with bleomycin, busulfan, carmustine, lomustine
Surgery Pulmonary lobectomy Pulmonary metastasectomy Pulmonary wedge resection (Category 2A)	Pulmonary dysfunction	Greatest risk: chest radiation, total-body irradiation Other risk factors: Chemotherapy with bleomycin, busulfan, carmustine, lomustine Atopic history Smoking

PERIODIC EVALUATION

History and physical examination (yearly; ask about cough, shortness of breath, dyspnea on exertion, wheezing)

Chest radiography and pulmonary function testing (at entry into long-term follow-up; repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction)

[a]Category 1—uniform consensus (near-unanimous agreement of the panel with some possible neutral positions) of the panel that there is high-level evidence (ie, derived from high-quality case-control or cohort studies) linking the late effect with the therapeutic exposure and that the screening recommendation is appropriate based on the collective clinical experience of panel members
Category 2A—uniform consensus; lower-level evidence
Category 2B—nonuniform consensus; lower-level evidence
Category 3—major disagreement that the recommendation is appropriate
[b]Category 2B evidence for acute respiratory distress syndrome

ADAPTED FROM THE CHILDREN'S ONCOLOGY GROUP, WWW.SURVIVORSHIPGUIDELINES.ORG.

surveillance for the generalist or pulmonologist. We also review the quality of the evidence upon which these recommendations are based.

NUMBERS ON THE RISE

An estimated 1 of every 330 children develops cancer before age 19. With cure rates exceeding 75% for many pediatric malignancies, the number of survivors of childhood cancer, currently in excess of 270,000, will continue to increase.[2]

THE CHILDREN'S ONCOLOGY GROUP GUIDELINES

The Children's Oncology Group (COG)[3] released its first set of guidelines in 2003 for the follow-up care of patients treated for pediatric malignancies; the current version is available at **www.survivorshipguidelines.org.** The guidelines contain comprehensive screening recommendations, including those related to pulmonary toxicity, which can be used to standardize care.

The COG guidelines are based both on evidence and on consensus. Examples of specific screening strategies from the COG guidelines as they relate to pulmonary health are summarized in TABLE 1.

Patient education materials accompany the guidelines, offering detailed information on guideline-specific topics in order to promote health maintenance.

HOW WE SEARCHED THE LITERATURE

We performed an extensive review of the literature via MEDLINE for the years 1975–2005. Key search terms were "childhood cancer," "late effects," and "pulmonary toxicity," combined with keywords for each therapeutic exposure. References from selected articles were used to broaden the search. From several hundred citations, fewer than 30 were selected as best illustrating the relevant associations.

RISK IS THREE TIMES HIGHER IN CANCER SURVIVORS

The Childhood Cancer Survivor Study[4] is the largest database of late effects, with more than 12,000 survivors of childhood cancer diagnosed between 1970 and 1986. Its data suggest that the risk of pulmonary conditions is more than three times higher in cancer survivors than in their siblings, as manifested by pulmonary signs (abnormal chest wall growth), symptoms (chronic cough, use of supplemental oxygen, exercise-induced shortness of breath), or specific diagnoses (lung fibrosis, recurrent pneumonia, pleurisy, bronchitis, recurrent sinus infection, or tonsillitis). Limitations: these data are retrospective, and the outcomes were detected by self-report and were not validated by review of medical records. Thus, the figures highlight the fact that pulmonary late effects are an important problem but do not give us a way to calculate risk exactly.

Other limitations of the literature: Treatments are constantly evolving, often in attempts to minimize late effects, and newer agents will need to be monitored for pul-

Pulmonary fibrosis in a bone marrow transplant patient

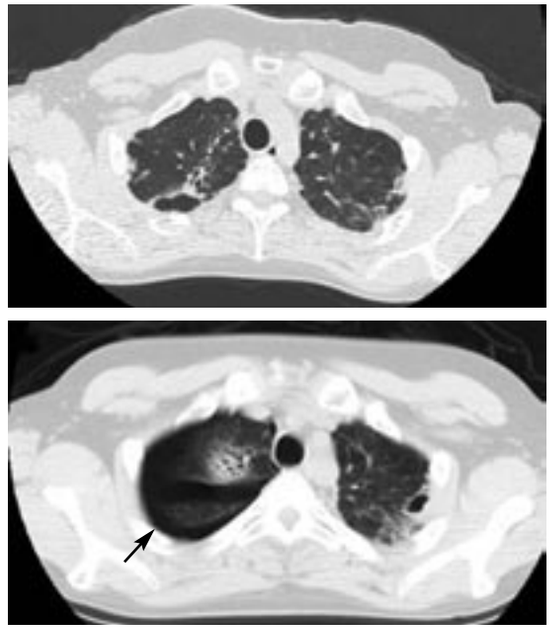

FIGURE 1. Top, a computed tomographic (CT) scan showing bilateral interstitial changes consistent with pulmonary fibrosis in a patient treated with allogeneic bone marrow transplantation for relapsed acute lymphocytic leukemia. **Bottom,** A CT scan of the same patient 9 months later shows spontaneous pneumothorax (arrow). Lung biopsy confirmed pulmonary fibrosis.

The COG guidelines are based both on evidence and on consensus

TABLE 2

Pediatric cancers that commonly involve the thorax

Mediastinum
Germ cell tumors
Hodgkin disease
Neuroblastoma
Non-Hodgkin lymphoma

Lung parenchyma or pleura (metastatic disease)
Carcinoid tumor
Ewing sarcoma
Germ cell tumor
Hepatoblastoma
Hodgkin disease
Osteosarcoma
Soft tissue sarcoma (eg, rhabdomyosarcoma)
Thyroid carcinoma
Wilms tumor

Chest wall
Ewing sarcoma
Osteosarcoma
Soft tissue sarcoma

Lung problems may appear during therapy or years later

monary toxicities. As noted, much of the available information is from studies of survivors of adult cancer; the potential for late effects of similar therapies in children is inferred. Most conclusions—and especially those based upon prospective serial evaluations—derive from small cohorts. For all treatments, the complications in the very long term remain undefined. What we know is summarized below.

CANCER THERAPY CAUSES FIBROSIS, PNEUMONITIS

Pulmonary fibrosis (FIGURE 1) and pneumonitis are the best-described sequelae of cancer treatment during childhood.[5] They are characterized clinically by shortness of breath, exertional dyspnea, or cough with or without fever. In many instances the presentation may be subclinical, apparent only on incidental chest radiographs or pulmonary function tests.

The courses of these diseases are poorly characterized, since few longitudinal studies have been done. However, like most of the late effects of cancer therapy, pulmonary toxicity may first become apparent during the treatment and persist, or it may not appear until years later. Signs and symptoms may be static, progressive, or reversible.

ANGIOGENESIS MAY CONTRIBUTE TO FIBROSIS

On a microscopic level, pulmonary fibrosis is characterized by epithelial injury, fibroproliferation, and excessive extracellular matrix deposition.[6–8]

Evidence is mounting that these findings result in part from angiogenesis. Although this has not been studied in long-term cancer survivors, evidence of neovascularization was seen both in an animal model of lung fibrosis and in patients with idiopathic pulmonary fibrosis.[6–8] High plasma concentrations of angiogenic cytokines (eg, tumor necrosis factor alpha, interleukin 8, and endothelin 1) have been found in these situations. Antiangiogenic agents and other immune modulators such as thalidomide may be beneficial in patients with lung fibrosis.[7]

On a macroscopic level, pulmonary fibrosis results in loss of lung volume in older children and in adults. In contrast, in younger children, interference with growth of both the lung and the chest wall may contribute to pulmonary dysfunction.

CANCER TYPES AND TREATMENTS VARY BY AGE

Cancers that commonly involve the thorax are listed in TABLE 2. Neuroblastoma, hepatoblastoma, extragonadal germ cell tumors, and Wilms tumor typically are diseases of young children; osteosarcoma, Ewing sarcoma, thyroid carcinoma, and Hodgkin disease are most common in older children and adolescents; soft tissue sarcoma and non-Hodgkin lymphoma span all age groups.

Surgery can, in some cases, control the cancer, as with mediastinal neuroblastoma and Ewing sarcoma of the chest wall.

Radiation to the chest remains a major component of treatment for Hodgkin disease, unresected thoracic Ewing sarcoma, soft tissue sarcoma with lung involvement or thyroid carcinoma, and Wilms tumor. Central nervous

system tumors and leukemias, the most common pediatric malignancies, may require radiation to the spinal cord—with resulting radiation exposure of the lungs. Total-body irradiation is a component of many preparative regimens for stem cell transplantation.

Chemotherapy remains a mainstay for all types of tumors, and patients with germ cell tumors, Hodgkin disease, and brain tumors are at particular risk of pulmonary toxicity due to heavy reliance on bleomycin (Blenoxane) (for germ cell tumors, Hodgkin disease) and the nitrosoureas (for brain tumors).

RADIATION-INDUCED LUNG DAMAGE

The lungs are particularly sensitive to radiation, and pulmonary problems occur most often in patients with malignant diseases of the chest that are treated with radiation, ie, those involving the mediastinum, the lung parenchyma, or the chest wall.

Abnormal radiographic findings or restrictive changes on pulmonary function testing have been reported in more than 30% of patients who received radiation directly or indirectly to the lung.[9–12] These changes have been detected months to years after radiation therapy, most often in patients who suffered radiation pneumonitis as an acute toxicity.

The amount of damage depends on the cumulative dose, how many treatments ("fractions") this cumulative dose was divided into (dividing the radiation dose into smaller dose fractions can reduce toxicity), the volume of lung tissue involved, and the patient's age (the younger, the worse) at the time of treatment.

Cumulative dose. Whole-lung irradiation is limited to 12 Gy, although localized areas of cancer can be treated with much higher doses.

Clinically apparent pneumonitis with cough, fever, or dyspnea generally occurs only in survivors who received more than 30 Gy in standard fractions to more than 50% of the lung. However, in 12 survivors of Wilms tumor who received median total doses of approximately 20 Gy to both lungs 7 to 14 years previously, 8 patients had dyspnea on exertion and radiographic evidence of interstitial and pleural thickening.[13] Mean total lung volumes and the diffusing capacity of the lung for carbon monoxide (DLCO) were reduced in all patients to approximately 60% of predicted values.

In a prospective study of adults with Hodgkin disease treated after 1980, 145 patients were examined 3 years after receiving more than 44 Gy limited to the mantle area.[9] None were experiencing symptoms; however, 30% to 40% had a forced vital capacity (FVC) less than 80% of predicted, and 7% had a reduced DLCO. Some of these patients also had received bleomycin (see below), which may have exacerbated pulmonary toxicity. Asymptomatic restrictive and obstructive lung changes have been detected after lower doses of whole-lung radiation (11–14 Gy) were given for other malignant diseases.[11,14]

In a recent study of adults and older adolescents with stage I and IIA Hodgkin disease treated with radiation alone (40–45 Gy to involved fields, including the mediastinum), late pulmonary effects observed were minimal.[10] While FVC, residual volume, forced expiratory volume in 1 second (FEV_1), DLCO, and total lung capacity (TLC) were significantly lower at the end of radiation therapy than before treatment, all except DLCO returned nearly to normal within 1 year. The decrease in DLCO remained stable, but the forced expiratory flow rate between 25% and 75% of FVC (FEF 25%–75%) was significantly lower 3 years after treatment than at baseline.

Radiation oncologists try to target the cancer while sparing normal tissue

The high doses of total lung irradiation cited in several of these reports are rarely used in today's cancer protocols. For example, patients receiving radiation as adjunctive treatment for Hodgkin disease now receive lower doses (< 21 Gy), which are restricted to involved fields, and the pulmonary toxicity is less than in the past.

In one series, 159 children and adolescents with unfavorable Hodgkin disease treated from 1993 to 2000 received six cycles of chemotherapy followed by response-based, involved-field radiation therapy. Patients who achieved a complete response after the first two cycles of chemotherapy got 15 Gy, and those who achieved a partial response got 25.5 Gy to all sites of bulky lymphadenopathy.[15] All patients underwent pulmonary function testing. Only 24 (30.8%) of them had pul-

The mantle port for radiotherapy

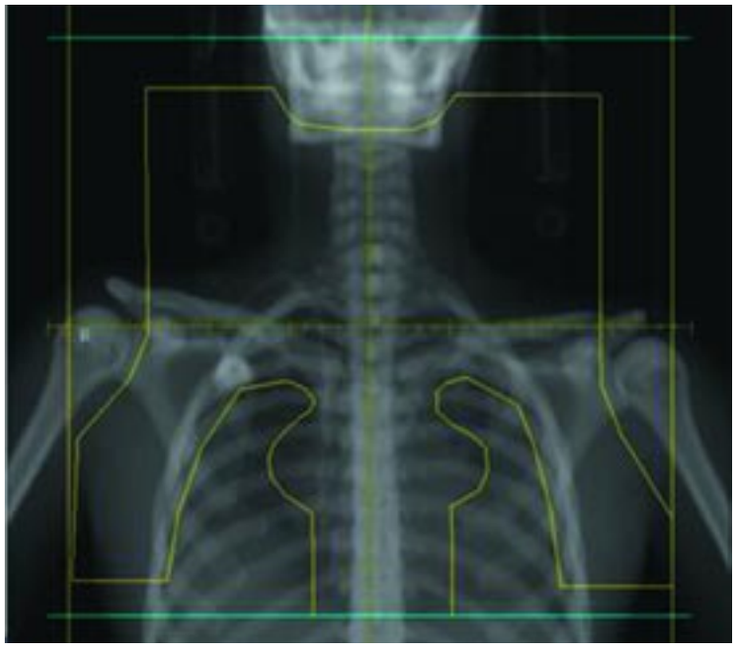

FIGURE 2. The yellow outline depicts the typical mantle port involving the neck, axilla, and mediastinum used in radiotherapy for Hodgkin disease.

monary toxicity, which was limited to asymptomatic deficits of restriction and diffusion.

Bleomycin toxicity is dose-dependent

Volume of lung exposed. Radiation oncologists try to target the cancer while sparing normal tissue. Mantle irradiation, designed to treat the submandibular, submental, cervical, supraclavicular, infraclavicular, axillary, mediastinal, and pulmonary hilar lymph nodes (FIGURE 2), is commonly used in patients with mediastinal Hodgkin disease. The configuration of this and other radiation ports, as well as cumulative doses, is dictated by how much radiation exposure the surrounding normal tissues (eg, lung, heart, bone, breast) can tolerate.

Nevertheless, the lungs receive some radiation even when they are not the target, such as in patients with malignant brain tumors, and this exposure can contribute to the development of lung disease, although these patients are likely to have no symptoms during day-to-day activities. Innovations in targeted radiation delivery (eg, conformal radiation) should further limit damage to normal lung tissue.

Age at the time of treatment also may influence the type and incidence of pulmonary sequelae. In older children and adults, radiation for thoracic malignancy results in pulmonary fibrosis with loss of lung volume. Similar injury can occur in younger children, but pulmonary function may also be compromised by inhibited growth of the supportive structures and the chest wall. One report suggests that children younger than 3 years at the time of therapy experience more chronic toxicity.[11]

In contrast, after bone marrow transplantation, children seem to be at less risk of significant late pulmonary dysfunction than adults are, despite similar preparatory regimens.[16] This may in part reflect a lower incidence of severe graft-vs-host disease involving the lung. Nonetheless, in a recent report of children treated with fractionated total-body irradiation between 1985 and 1993, restrictive pulmonary diseases were found in 30 of 42 patients at a median of 3.1 years after treatment (range 0.5-17 years).[17] Most of these patients had asymptomatic mild restrictive disease, and the one patient with severe changes had previously received thoracic radiation for treatment of neuroblastoma. In about half of the cases, pulmonary function abnormalities were permanent although not progressive.

CHEMOTHERAPY-RELATED LUNG DAMAGE

A growing list of chemotherapeutic agents appears to cause pulmonary disease in long-term survivors.[5]

Bleomycin

Bleomycin toxicity is the prototype for chemotherapy-related lung injury: bleomycin was the first chemotherapy drug shown to cause lung injury, this effect is suggested by a large database, and the mechanism is typical.[5,18] Preclinical studies have attributed bleomycin's toxicity to its tendency to promote free radicals.

Although interstitial pneumonitis and pulmonary fibrosis have been reported in children, clinically apparent bleomycin pneumonopathy is most frequent in older adults. Usually, the abnormalities began within 3 months of therapy and persisted or progressed. Like the acute toxicity, it is dose-dependent and more common above a threshold cumula-

tive dose of 400 units/m^2. Above this dose, 10% of adult patients without other risk factors develop fibrosis; data are not available for these doses in children. At lower doses, fibrosis occurs sporadically in fewer than 5% of patients, with a 1% to 2% mortality rate. In some series, bleomycin toxicity was anticipated on the basis of DLCO abnormalities.

Bleomycin pulmonary toxicity is variably exacerbated by concurrent or previous radiation therapy.

Increased oxygen concentrations associated with general anesthesia have also been found to exacerbate prior bleomycin-induced pulmonary injury.[19,20] In one instance (reviewed by Zaniboni et al[20]), the patient recovered with corticosteroid treatment.

Alkylating agents

Carmustine (also called BCNU; brand names BiCNU, Gliadel) and **lomustine** (CCNU; CeeNU) are thought to cause dose-related lung injury. When cumulative carmustine doses are greater than 1,500 mg/m^2, more than 50% of patients develop symptoms.[21]

In a careful clinicopathologic review of 31 children with brain tumors, restrictive changes with lung fibrosis were reported up to 17 years after treatment, most often with carmustine 100 mg/m^2 every 6 to 8 weeks for up to 2 years.[22] Four of the 8 patients still alive at the time of study experienced shortness of breath and coughing; 6 showed a characteristic pattern of upper zone fibrosis on chest radiography and computed tomography; all 8 survivors had restrictive findings on pulmonary function testing, with vital capacities of about 50% of normal. Toxicity increases with more intensive dose-scheduling.

Cyclophosphamide (Cytoxan) may cause delayed-onset pulmonary fibrosis with severe restrictive lung disease in association with marked reductions in the anteroposterior diameter of the chest, although the evidence is less convincing than with carmustine and lomustine, coming from case reports and small series.[23]

Melphalan (Alkeran), generally in doses used in stem cell transplant conditioning regimens, is also thought to cause pulmonary fibrosis.[24]

Busulfan most predictably causes toxicity when it is used in transplantation doses (ie, more than 500 mg), and may be associated with a progressive, potentially fatal restrictive lung disease.[25] A current trend is to adjust the dose on the basis of pharmacokinetic analysis, which we hope will reduce toxicity.

Other agents

Methotrexate (MTX; Trexall) also has been associated with chronic pneumonitis and fibrosis.[26] This probably occurs with an incidence well below 1% and may be idiosyncratic and not dose-related. Asymptomatic changes in pulmonary function tests that do not predict clinically significant problems have most frequently been associated with low-dose oral administration during more than 3 years.[27] This is a treatment approach used in patients with psoriasis or rheumatoid arthritis, but is now obsolete for pediatric cancer. Intravenous and, rarely, intrathecal administration also have been associated with pulmonary toxicity.[28] A single report of two patients who developed diffuse interstitial pulmonary infiltrates and chronic pulmonary changes links vinblastine to these sequelae.[29]

LUNG INJURY AFTER BONE MARROW TRANSPLANTATION

Ask about chronic cough, shortness of breath, and dyspnea on exertion

Hematopoietic stem cell transplantation is associated with various late pulmonary complications. The factors that influence these complications are similar to those discussed earlier. However, the intensity of therapy in patients undergoing transplantation and the additive effects of previous therapies magnify the risks.

Patients undergoing total-body irradiation as part of their preparation for transplantation have a high incidence of late pulmonary complications.[25,30–32] Busulfan, carmustine, bleomycin, and cyclophosphamide, also commonly used conditioning chemotherapies, are known to cause pneumonitis and fibrosis after transplantation.[33]

Some acute pulmonary toxicities can have long-standing effects, including serious pulmonary infections, idiopathic pneumonia syndrome, bronchiolitis obliterans, acute respiratory distress syndrome, or other damage related to graft-vs-host disease.

OTHER RISK FACTORS FOR LUNG DAMAGE

Additional factors contributing to chronic pulmonary toxicity include superimposed infection, underlying pneumonopathy (eg, asthma), cigarette use, respirator toxicity, chronic graft-vs-host disease, and the effects of chronic pulmonary involvement by tumor or reaction to tumor. For example, a subset of patients with Langerhans cell histiocytosis can develop histiocytic pulmonary infiltrates or honeycombing with severe chronic restrictive lung disease unrelated to therapy or the presence of active tumor.

Although not well documented, scuba diving also has been said to exacerbate pulmonary fibrosis through increased underwater pressures and high oxygen levels.[34]

Lung lobectomy during childhood appears to have no significant impact on long-term pulmonary function,[35–37] but the effect of lung surgery for children with cancer is not well defined.

GET THE PATIENT'S TREATMENT SUMMARY

Many agents are now available to help patients stop smoking

Regardless of the setting for follow-up, the first step in any evaluation is to obtain the patient's medical history and especially a treatment summary. The treatment summary should outline the cancer diagnosis, involved sites of disease, age at diagnosis, specific treatments (surgery, chemotherapy, radiation), and other key interventions and events during and after cancer therapy. Sample forms for physicians and patients are available at **www.survivorshipguidelines.org**.

Before the long-term survivor of childhood cancer graduates from the care of a pediatric oncologist, this treatment record and possible long-term problems should be reviewed with the family and, in the case of an adolescent, with the patient. Correspondence between the pediatric oncologist and subsequent caregivers should also include a treatment summary. The treatment summary allows the survivor or his health care provider to interface with the COG guidelines to determine recommended follow-up care. The primary care physician and the patient both should have copies of this document.

We are developing an interactive Web-based version of a standardized summary form, designed to interface with an automated version of the COG guidelines in order to generate individualized follow-up recommendations.

ASK ABOUT LUNG SYMPTOMS

We recommend that health care providers investigate symptoms of pulmonary dysfunction, and specifically ask about chronic cough with or without fever, shortness of breath, and dyspnea on exertion during yearly health care visits.

Baseline pulmonary function testing (including DLCO and spirometry) and chest radiography are recommended 2 or more years after completion of therapy to document persistent deficits and determine the need for continued monitoring. Reevaluation of pulmonary function should be considered in patients with established deficits who require general anesthesia and for those treated with bleomycin.

Scuba diving remains controversial for long-term survivors. Consequently, patients with risk factors for lung disease should be encouraged to consult with a pulmonary specialist to determine if diving poses a health threat to their pulmonary status. If clinical pulmonary dysfunction is identified, referral to colleagues in pulmonology for additional evaluation and treatment is essential. Increasing familiarity of primary care providers with surveillance concepts is a key element in survivorship care.

Smoking cessation can enhance the health of all patients and is particularly important among long-term survivors, especially those who received treatments predisposing to pulmonary injury. Strategies for cessation and patient information can be found at **www.cdc.gov/tobacco/how2quit.htm**.

Clinicians can take advantage of every patient interaction to assess readiness for smoking cessation and assist patients in this goal. Following the principles of patient-centered counseling, physicians can guide patients into considering a change of behavior with advice and encouragement. Whenever possible, physicians should personalize the

risks of smoking as well as the short-term and long-term benefits. As smokers prepare to quit, their physicians can assist in developing a plan that includes a quit date.

Many pharmacologic agents are available to assist patients, ie, nicotine inhalers, sprays, gum, and transdermal patches; the antidepressants bupropion (Wellbutrin) and nortriptiline (Pamelor); the alpha-2 adrenergic agonist clonidine (Catapres); and, most recently, the nicotine receptor partial agonist varenicline (Chantix).[38]

Follow-up to prevent relapse is an important part of this process.

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