CME

Treating cancer patients

Practical monitoring and management of therapy-related complications

Malcolm Brigden, MD, FRCPC Michael McKenzie, MD, FRCPC

abstract

OBJECTIVE To review investigation and management of some common long-term complications associated with cancer chemotherapy and radiation therapy.

QUALITY OF EVIDENCE Databases searched using MeSH key words "cancer chemotherapy," "cancer chemotherapy complications," "radiation therapy," and "radiation therapy complications" included Ovid and CANCERLIT. Overall the literature in this area is not strong; treatment guidelines and consensus conferences generally are lacking. Recommendations in this paper are mainly based on the results of individual studies and case reports, as few randomized controlled trials have been performed. Where appropriate, recommendations incorporate results of published treatment guidelines and consensus conferences.

MAIN MESSAGE For most solid tumours, patients should be most frequently monitored during the first 3 years after completing initial treatment for cure. Follow-up monitoring usually incorporates physical examination as well as radiologic and laboratory investigations. Patients should not be lost to follow up once treatment is completed, but monitored regularly, especially while they are at highest risk for disease recurrence. Long-term complications associated with cancer therapy include postsplenectomy sepsis syndrome; central and peripheral nervous system toxicities; ocular complications; thyroid, pituitary, testicular, or ovarian dysfunction; pulmonary toxicity; vascular or lymphatic, gastrointestinal, or osseous complications; genitourinary problems; and possible secondary malignancy.

CONCLUSION Primary care physicians are key to facilitating appropriate follow up of treated cancer patients. To do this, they must be aware of practical aspects of monitoring and management of therapy-related complications.

résumé

OBJECTIF Passer en revue l'investigation et la prise en charge de certaines complications à long terme associées à la chimiothérapie contre le cancer et à la radiothérapie.

QUALITÉ DES DONNÉES Au nombre des bases de données dans lesquelles une recension a été effectuée à l'aide des mots clés MeSH en anglais pour « chimiothérapie contre le cancer », « complications de la chimiothérapie contre le cancer », « radiothérapie » et « complications de la radiothérapie » figuraient Ovid et CANCERLIT. Dans l'ensemble, les ouvrages scientifiques dans ce domaine ne sont pas très concluants; il y manque en général des lignes directrices et des conférences consensuelles. Les recommandations dans le présent article se fondent principalement sur les résultats d'études et d'exposés de cas précis, étant donné la rareté des essais aléatoires contrôlés qui ont été effectués. Le cas échéant, les recommandations comportent la teneur des lignes directrices publiées et des conférences consensuelles.

PRINCIPAL MESSAGE Dans la plupart des cas de tumeurs solides, les patients devraient faire l'objet d'une surveillance plus fréquente durant les trois premières années suivant la fin de la thérapie curative initiale. La surveillance de suivi comporte habituellement l'examen physique et des investigations radiologiques et en laboratoire. Une fois le traitement complété, il ne faudrait pas omettre le suivi des patients, mais plutôt le faire régulièrement, surtout en raison du risque plus élevé de récurrence de l'affection. Au nombre des complications à long terme associées à la thérapie contre le cancer figurent le syndrome de la septicémie postplénectomie; la toxicité du système nerveux central et périphérique; les complications ophtalmologiques; le dysfonctionnement thyroïdien, pituitaire, testiculaire ou ovarien; la toxicité pulmonaire, les complications vasculaires ou lymphatiques, gastro-intestinales ou osseuses; les complications à l'appareil génito-urinaire; et les cancers secondaires possibles.

CONCLUSION Les médecins de première ligne jouent un rôle essentiel pour faciliter un suivi approprié des patients ayant subi une thérapie anticancéreuse. À cette fin, ils doivent être au fait des aspects pratiques de la surveillance et de la prise en charge des complications associées à la thérapie.

This article has been peer reviewed.

Cet article a fait l'objet d'une évaluation externe.

Can Fam Physician 2000;46:2258-2268.

Follow up of cancer patients has a variety of potential end points.[1-3] These include early detection of recurrence with an intention of offering salvage therapy, recognizing and managing treatment-induced complications, providing psychological support associated with continued medical involvement, and gathering academic or epidemiologic data on survival and treatment outcomes (**Table 1**).

Most solid tumours, if they recur, do so within the first 3 to 5 years.[1-3] For this reason, typical follow up might include return visits every 3 months for the first year, every 4 months for the second and third years, every 6 months in the fourth year, and annually thereafter for 5 years.[1-3] Although early detection of recurrence should theoretically offer increased potential for cure via salvage therapy, the effect of such a strategy for most solid tumours remains debatable.[4-7] Primary care physicians are in an ideal position to monitor patients after cancer treatment is completed and ideally should be provided with a follow-up schedule that includes both timing of return visits and investigations appropriate to the individual tumour site suggested by the cancer treatment centre when patients return to the community.

Follow-up monitoring can incorporate results of both history and physical examination as well as selective radiologic and laboratory testing.[3] A detailed description of what might constitute appropriate testing for individual tumour sites is beyond the scope of this article.

Quality of evidence

To obtain relevant information for this article, we searched Ovid and MEDLINE using the MeSH words "cancer chemotherapy," "cancer chemotherapy complications," "radiation therapy," and "radiation therapy complications." Recommendations in this paper are mainly based on the results of natural history studies and case reports, as relatively few randomized controlled studies have been performed.

Asplenic or hyposplenic infectious complications

Radiation therapy. If the spleen is irradiated, functional hyposplenism can ensue.[8] When it is impossible to avoid splenic irradiation, management should be similar to that outlined for chemotherapy-induced hyposplenism.[8,9]

Chemotherapy. Chemotherapy can produce functional hyposplenism, as can bone marrow transplantation.[8,9] Patients functionally hyposplenic for any reason are at risk for the overwhelming postsplenectomy sepsis syndrome (**Table 2**), which consists of fulminant septicemia. An encapsulated organism, most commonly *Streptococcus pneumoniae* (pneumococcus) or *Haemophilus influenzae*, usually causes the septicemia. Associated disseminated intravascular coagulation, hypotension, and adrenal failure can appear.

Administration of appropriate vaccines (pneumococcal, *Haemophilus influenzae*, meningococcal) can reduce but not completely eliminate risk of infection.[10] These vaccines should initially be offered to all patients likely to be rendered hyposplenic or asplenic (preferably at least 2 weeks before therapy). Pneumococcal vaccine should be repeated at 3- to 5-yearly intervals.[10]

All postsplenectomy or hyposplenic patients should be aware of their status and cautioned to seek early medical attention at the first onset of systemic symptoms compatible with infection (chills, rigour, high temperature, etc). A Medic-Alert bracelet and wallet card should be provided. Some physicians issue a supply of prophylactic antibiotics on condition that a physician be contacted in the event of infectious symptoms. Patients should be warned about the special hazards of dog bites (the organism of infection is *Capnocytophaga canimorsus*) and of travel in malaria- or babesiosis-endemic areas.[9]

Neurologic complications

Radiation therapy. Partial or whole-brain radiation therapy can be associated with an immediate worsening of pre-existing neurologic symptoms for a short period after treatment because of increased tumour-associated edema.[11-13] Occasionally, such neurologic deterioration is noted weeks or months after treatment.[11,13] Although such "early-delayed" side effects respond to corticosteroids in most cases, on occasion they are difficult to distinguish from tumour progression. Frank radiation necrosis can develop following relatively high-dose radiation therapy to portions of the brain and can also mimic recurrent tumour, both radiologically and clinically with mass effect and edema.[13] Although treatment with corticosteroids is usually sufficient, on occasion surgical decompression is required.

Dr Brigden *is a Regional Medical Oncologist at the Penticton Hospital Cancer Clinic in Penticton, BC.*
Dr McKenzie *is Senior Radiation Oncologist at the British Columbia Cancer Agency in Vancouver Centre.*

Table 1. **Potential complications affecting follow up of treated cancer patients**

	RECOMMENDATIONS	
POTENTIAL COMPLICATION	**INVESTIGATION**	**POSSIBLE THERAPY**
Asplenic or hyposplenic infectious complications	Appropriate microbiologic intervention at first sign of systemic symptoms in asplenic or functionally hyposplenic individuals	Periodic antipneumococccal vaccination. Consider use of hemophilus and meningococcal vaccines. Medic-Alert bracelet, wallet card, and supply of prophylactic antibiotics
Neurologic dysfunction	Depending on presentation, consider nerve conduction studies, computed axial tomographic scan, magnetic resonance imaging, neuropsychologic testing	Appropriate to abnormality. No known therapy for peripheral neuropathy or VIII nerve toxicity. Avoidance of other neurotoxic drugs. Counseling and behavioural therapy for neuropsychologic problems
Ocular complications	Annual ophthalmologic evaluation if prior ocular radiotherapy	Treatment of sicca complex Intraocular lens placement as appropriate
Thyroid dysfunction	Thyroxine, thyrotropin	Thyroid hormone replacement therapy
Gonadal dysfunction	(Males) follicle-stimulating hormone, luteinizing hormone, testosterone, semen analysis (Females) follicle-stimulating hormone, luteinizing hormone, estrogen	Androgen therapy Cyclic hormonal therapy for premature menopause in female patients
Pulmonary dysfunction	Chest x-ray examination, pulmonary function studies including diffusion capacity	Possible steroid therapy Counseling regarding smoking cessation
Cardiovascular dysfunction	Chest x-ray examination, electrocardiography, radionuclide, ventriculography, echocardiography, endomyocardial biopsy, 24-hour ambulatory electrocardiography for suspected arrhythmia Doppler flow study of digital arteries for Raynaud's phenomenon Risk profile for coronary artery disease	Pericardiectomy for constrictive pericarditis Standard measures for congestive heart failure Calcium channel blockers for Raynaud's phenomenon Modification of other risk factors for vascular disease
Lymphatic complications	Monitoring by physical examination if nodes irradiated or dissected	Appropriate use of compression sleeves, bandaging, or pumps
Osseous complications	Careful attention to symptoms following bone irradiation or high-dose steroid therapy	Appropriate to abnormality
Gastrointestinal dysfunction	Liver function studies Consider computed axial tomographic scan, magnetic resonance imaging, hepatitis A, B, and C testing	Appropriate to abnormality Avoidance of alcohol or other hepatotoxic substances
Renal dysfunction	Blood pressure, blood urea nitrogen, creatinine, urinalysis Depending on presentation consider intravenous pyelography, renal ultrasound, cystoscopy, urine cytology	Appropriate to abnormality Avoid aminoglycoside therapy or other nephrotoxic agents
Second malignancy	Appropriate to therapy received: • After alkylating agent or topoisomerase therapy, yearly complete blood counts • After thoracic irradiation, regular breast self-examination and mammography starting at age 35 • After thyroid irradiation, annual thyroid examination, thyrotropin	Appropriate to abnormality Isolated cytopenia or pancytopenia, bone marrow with cytogenetics If secondary leukemia is detected, hematology consultation Supportive care if elderly Consider marrow transplantation if younger

Table 2. **Features of overwhelming postsplenectomy sepsis syndrome**

Occurs in asplenic or functionally hyposplenic patients
Cryptic infection (no obvious focus)
Can be short, nonspecific prodrome
Massive bacteremia: bacteria might be noted on peripheral blood film
Most commonly encapsulated organism (*Pneumococcus, Haemophilus*)
Less commonly, Gram-negative organism
Can be septic shock with disseminated intravascular coagulation
Virulence can be marked: 50% to 70% reported mortality
Death could ensue in 24 to 48 hours
Appropriate vaccination policy offers partial protection

Although uncommon, Lhermitte's sign (an electric shock–like sensation accompanying flexion of the neck) can appear as a transient form of radiation myelopathy in the first few months following radiotherapy to the cervical spinal cord.[11] There is no specific treatment, and this symptom usually completely resolves within a few months.

Although peripheral and cranial nerves are relatively resistant to late radiation damage, complications can arise, for which no known effective treatment exists. Transient radiation cranial neuropathy and peripheral neuropathy have both been reported after intracranial stereotactic radiosurgery and after intraoperative radiation therapy. Radiation-induced brachial plexopathy is an uncommon side effect of radiotherapy to the axilla and supraclavicular fossa and is most commonly noted in cases of breast cancer.[13] The condition can be differentiated from recurrent disease by detailed neurologic examination; plexopathy secondary to recurrence tends to present as an isolated upper or lower trunk lesion, whereas radiation-induced brachial plexopathy is associated with a diffuse lesion. In difficult cases, magnetic resonance imaging of the brachial plexus can be helpful.

Chemotherapy. Long-term neurotoxicity is fortunately uncommon with chemotherapy, but both vinca alkaloid and cisplatin therapy can induce a persistent peripheral neuropathy in 30% to 70% of treated patients.[14,15] Paclitaxel is a tubulin polymerization enhancer increasingly used with platinum-based chemotherapy for ovary, breast, head, and neck cancer as well as lung tumours.

Unfortunately, paclitaxel therapy can produce severe cumulative sensory-motor peripheral neurotoxicity.[14] Persistent high-frequency hearing loss is an unfortunate long-term complication of platinum-based chemotherapy.[16,17] While attention has focused on cisplatin, carboplatin can also produce significant ototoxicity, especially if coupled with aminoglycoside therapy. While audiologic evaluation is indicated for symptomatic patients, the frequencies most commonly affected are fortunately outside the range of conversational speech.

As in the case of radiation therapy, late-onset neurocognitive defects associated with later life problems involving marriage, employment, or subsequent insurability have been detected in a substantial number of patients who have received intensive chemotherapy directed at the central nervous system.[16] Neurologic follow up should always be appropriate to the abnormality detected. For example, detection of peripheral neuropathy would be followed by nerve conduction studies while central nervous system abnormalities would be investigated by computed axial tomographic scan or magnetic resonance imaging. Early counseling and behavioural therapy is indicated for neurocognitive defects.

Ocular complications

Radiation therapy. Radiation therapy involving the eye can produce xerophthalmia due to radiation effect on the lacrimal and other ocular adnexal glands that contribute to tear production.[12] This in turn can lead to "dry eye syndrome" or keratoconjunctivitis sicca, with pain, sensation of a foreign body in the eye, or even corneal ulceration. While lubricants could be all that is required, prompt referral for ophthalmologic consultation is advisable. Although dry eye syndrome is usually secondary to keratoconjunctivitis sicca, in rare cases it is caused by radiation-related obstruction of the nasolacrimal duct, which will respond to dilation and stenting.

Radiation retinopathy associated with hemorrhage has been noted after relatively high-dose radiation therapy and can be treated with laser photocoagulation. Cataract formation is a well-known complication

of exposing the lens to even modest radiation; latency period shortens with increase in dose.[12] Lens extraction with intraocular lens placement should be undertaken as required. Any patient who has received extensive irradiation to any portion of the eye should be followed at least annually by an experienced ophthalmologist to detect problems early.

Chemotherapy. Fortunately chemotherapy tends not to be associated with ophthalmic complications.

Thyroid dysfunction

Radiation therapy. Patients with Hodgkin's disease or other tumours who have received radiation therapy to the neck are at increased risk for subsequent hypothyroidism, as are those who have received total body irradiation for bone marrow transplantation.[18-20] Over a 10-year span, post-therapy symptomatic hypothyroidism could develop in more than 10% of such patients while an elevated level of thyrotropin can be detected in 50%. This risk for thyroid disease persists for up to 25 years after treatment.[18] Because the combination of thyroid irradiation and prolonged thyrotropin stimulation could lead to subsequent thyroid cancer, thyrotropin should be checked annually after therapy ends and the thyroid palpated at each follow-up appointment. Lifelong thyroid replacement therapy is indicated once an elevated thyrotropin level is detected. Rare cases of hyperthyroidism and hyperparathyroidism have also been reported after radiotherapy.[21,22]

Chemotherapy. Fortunately chemotherapy tends not to be associated with thyroid dysfunction.

Panhypopituitarism

Radiation therapy. Radiation therapy for lesions in the neck or central nervous system sometimes includes the hypothalamic-pituitary axis.[18-20] Months to years after such therapy, symptomatic pituitary dysfunction might become apparent.[21] Children with a history of high-dose irradiation to the hypothalamic-pituitary axis should be followed closely for growth hormone or gonadotrophin deficiencies. Both adults and children with a history of such irradiation should undergo annual testing of plasma thyroxine, thyrotropin, random cortisol, and prolactin levels for the rest of their lives.

Chemotherapy. Fortunately chemotherapy has not been associated with pituitary dysfunction.

Testicular dysfunction

Radiation therapy. It is important to be aware that in certain malignancies, such as Hodgkin's disease, endocrine cancer, or testicular cancer, infertility often actually precedes diagnosis of cancer.[23] The germinal epithelium is particularly sensitive to radiation therapy, with modest doses leading to prolonged or permanent oligospermia or azoospermia.[24,25] While Leydig's cells tend to be less susceptible, prolonged androgen suppression can follow somewhat higher doses of irradiation.[25] Although some men with subnormal sperm counts ultimately are able to father children, prospects for future fertility are enhanced by careful treatment planning and pretherapy sperm banking as necessary.

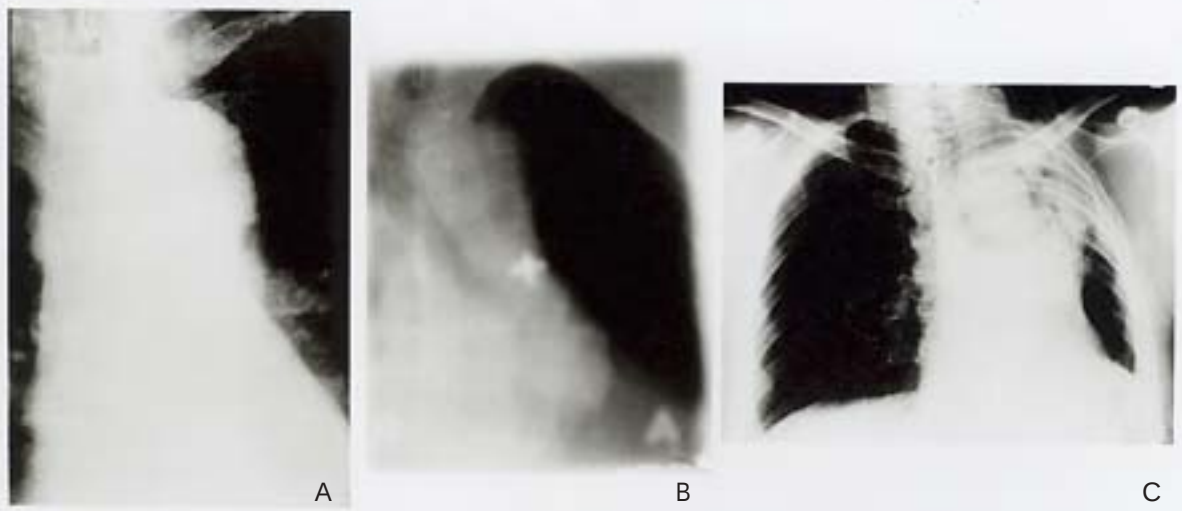
Chemotherapy. Chemotherapy, especially involving use of alkylating agents, frequently results in oligospermic infertility.[25-27] Such patients present with both decreased testicular volume and elevated plasma levels of follicle-stimulating hormone. Recovery of spermatogenesis beyond 5 years after chemotherapy is exceptionally rare. In contrast to germ cells, Leydig's cells appear relatively resistant to most forms of chemotherapy.[27] However, if clinically significant Leydig's cell dysfunction is suggested by changes in libido or a decreased testosterone level associated with an elevated plasma luteinizing hormone level, androgen replacement therapy is indicated.

Ovarian dysfunction

Radiation therapy. Even modest doses of radiation to the ovaries can lead to infertility and symptomatic ovarian dysfunction, which might be transient or permanent.[28,29] The ultimate incidence of permanent dysfunction varies with patient age, radiation dose, and whether concomitant chemotherapy was administered.[28] In some circumstances, such as in Hodgkin's disease where pelvic radiotherapy is required, oophoropexy can be combined with appropriate shielding to limit radiation scatter to the ovaries. If there is a high likelihood of ovarian failure, most radiation oncologists will recommend that hormone replacement therapy begin when radiation therapy is finished.

Chemotherapy. With chemotherapy, female reproductive status appears to fare better than male fertility.[30] As with radiation therapy, the potential for ovarian damage is strongly age dependent. Standard chemotherapy tends not to cause permanent disruption of ovarian function in those younger than 25 at

Figure 1. **Asymptomatic pulmonary fibrosis in a 57-year-old man after palliative mediastinal radiation therapy for a left hilar recurrence of a bronchioalveolar carcinoma (prior left lower lobectomy)**: *A) Image from pretreatment chest x-ray film, B) Radiation treatment port field, C) Chest x-ray film showing subsequent substantial volume loss involving left upper lobe with associated upward tethering of the main stem bronchus.*



the time of treatment. While transient amenorrhea with a secondary elevation in plasma follicle-stimulating hormone and luteinizing hormone levels might appear, menstruation ultimately returns to normal in up to 70% of women younger than 25. However, the corresponding figure is less than 10% for those 35 or older.[28,30] Once frank ovarian failure has been documented, recovery of normal function is rare. Because women who become prematurely menopausal are at increased risk for osteoporosis, fractures, and coronary artery disease, cyclic hormonal replacement therapy is indicated. Such therapy could also help to combat menopausal vasomotor symptoms and vaginal atrophy. Fortunately children born to cancer survivors of either sex who have not been rendered infertile have consistently shown no increased incidence of either congenital cancer or hereditary defects.[31,32]

Pulmonary complications

Radiation therapy. Radiation pneumonitis occurs in 5% to 15% of patients treated with radiotherapy for lung cancer, breast cancer, or mediastinal lymphoma.[33,34] Precise incidence depends on dose and fractionation, volume of lung irradiated, and whether concomitant chemotherapy (particularly bleomycin or doxorubicin) was also administered.[35,36] Symptoms include fever, non-productive cough, dyspnea, or pleuritic chest pain and usually develop 1 to 3 months after radiotherapy. Such symptoms are often self-limited, resolving within weeks to months and responding to tapering doses of corticosteroids.

Pulmonary function testing will reveal a restrictive pattern with a reduction in diffusion capacity, which could ultimately be permanent. Chest x-ray films might demonstrate a faint infiltrative pattern that conforms to the radiation treatment portal. This could progress to patchy air-space consolidation with an associated volume loss. Such radiologic changes can be noted in the absence of symptoms and will not always evolve to pulmonary fibrosis.[33]

Radiologic findings compatible with radiation-induced pulmonary fibrosis are sometimes noted months to years after therapy. These changes usually stabilize 1 to 2 years after treatment (**Figure 1**). Occasionally, it is difficult to distinguish radiation-induced changes from recurrent disease; in this instance a review by a radiologist experienced in following up radiation-treated patients is helpful.[33] Supportive measures including oxygen and optimizing residual pulmonary function might be helpful.

Chemotherapy. Several chemotherapeutic agents have been associated with acute or chronic pulmonary toxicity.[35-37] These include the nitrosoureas, busulfan, bleomycin, cyclophosphamide, and methotrexate. Late-onset pulmonary fibrosis (up to 10 years after therapy) has been described.[36] While bleomycin toxicity appears to be more severe in children and elderly people, early

accurate detection has proven problematic.[37] Symptoms are nonspecific and can include dyspnea, non-productive cough, or fatigue. Results of physical examination of early cases can also be nonspecific or demonstrate fine Velcro-like basilar rales. The initial chest x-ray film could be normal or nonspecific but ultimately demonstrates extensive pulmonary fibrosis.

Similar to radiation injury, a reduction in diffusion capacity is often a sensitive indicator of early pulmonary damage. Later pulmonary function studies usually demonstrate a restrictive pattern with decreases in both vital capacity and total lung volume. While treatment with steroids should be started early, the ultimate value of such therapy remains unknown. Any patient with a history of bleomycin therapy for whom a general anesthetic is contemplated should have careful preoperative assessment in view of the potential for increased susceptibility to oxygen toxicity. Patients who have received combined therapy or chemotherapy with potential pulmonary toxicity should have careful chest auscultation on each return visit. With the additive potential toxicity of smoking, patients should always be counseled to stop smoking.[3]

Vascular or lymphatic complications

Radiation therapy. The pericardium is most frequently damaged by cardiac or mediastinal irradiation manifesting as acute or chronic pericarditis with possible associated effusion, or as a constrictive pericarditis developing months to years later.[38-40] When necessary, pericardiocentesis, pericardiectomy, and corticosteroid therapy can be helpful. Radiation-induced cardiomyopathy is rare, usually presenting as a constrictive pericarditis that fails to improve following pericardiectomy. Several reports have associated accelerated development of coronary atherosclerosis with mediastinal irradiation, particularly when administered early in life.[40]

In breast cancer patients, post-axillary lymph node dissection, irradiation of the axilla and supraclavicular fossa increases the risk of subsequent troublesome lymphedema of the arm.[41] Lower limb lymphedema could also become a problem after inguinal lymph node dissection with concomitant irradiation. Possible preventive measures include avoidance of extensive dissection as well as lifelong efforts to avoid trauma, injections, blood taking, or blood pressure determinations in the affected limb. Management of established lymphedema can include use of compression sleeves, bandaging, or lymphatic pumps.

Chemotherapy. Raynaud's phenomenon is a particularly disabling vascular symptom noted in up to one third of long-term testicular cancer survivors previously treated with combinations of bleomycin, platinum, vinblastine, or etoposide.[42] It appears to be more common in patients with pre-existing hypertension and can be confirmed via Doppler flow study of digital arteries. Therapy with calcium channel blockers can provide symptom relief.

For patients receiving anthracycline chemotherapy, factors thought to increase risk for cardiac toxicity include total dose, concomitant radiotherapy, and mediastinal radiation of pre-existing heart disease.[43-45] As cohorts of patients are followed for longer durations, concern has arisen that even conventional doses of anthracycline therapy could ultimately decrease cardiac reserve, producing delayed-onset ventricular dysfunction years after therapy.[44,45] Individual patients have presented with symptoms of congestive heart failure and late-onset ventricular arrhythmia associated with sudden death as late as 10 to 15 years after chemotherapy.[44,45]

Depending on presenting symptoms, patients may be investigated with radionuclide angiography, ultrasound, or endomyocardial biopsy. In patients with suspected cardiac arrhythmia, 24-hour ambulatory electrocardiographic monitoring can be helpful. Congestive failure secondary to anthracycline toxicity might respond to conventional measures, such as diuretic therapy, ACE inhibition, and digoxin, but long-term prognosis is guarded (**Figure 2**).

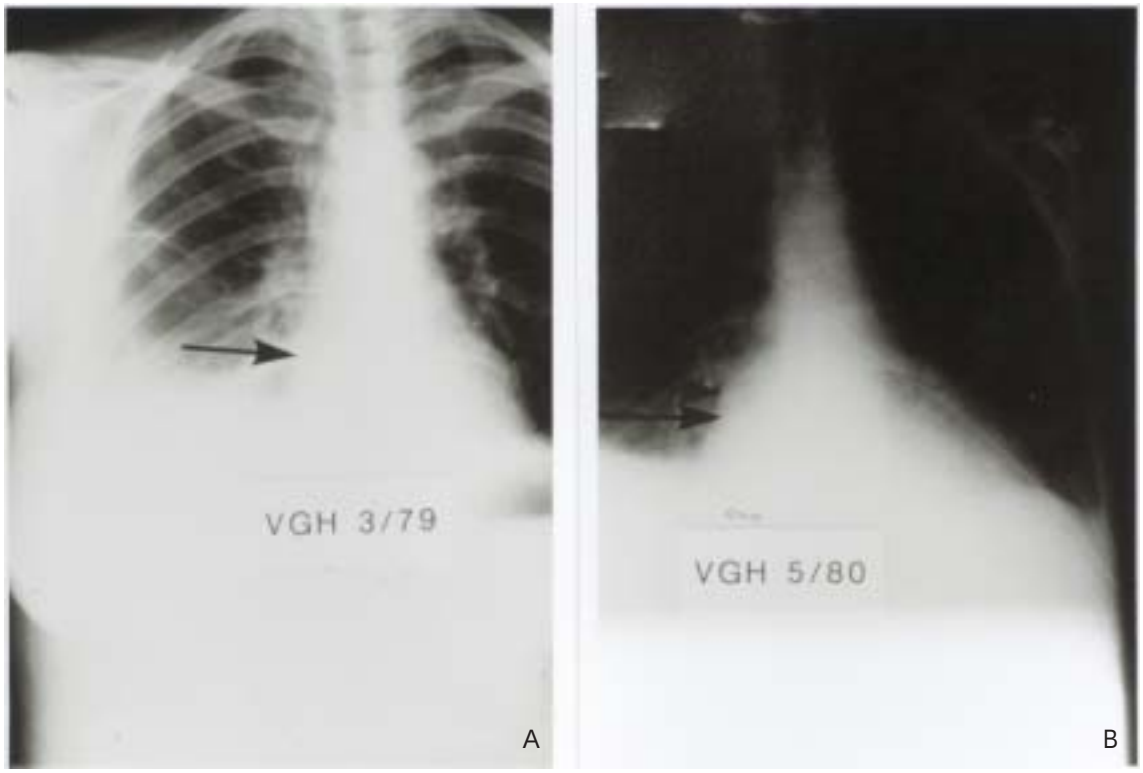
Because of potential long-term additive toxicity, other known risk factors for cardiovascular disease (abnormal lipid levels, smoking, alcohol abuse, hypertension) should be aggressively treated in patients who have received therapy with potential cardiovascular toxicity.[3]

Gastrointestinal complications

Radiation therapy. Radiation of the oropharynx can lead to xerostomia secondary to impairment of salivary gland function promoting dental caries or tooth loss.[46,47] Pretreatment dental assessment and careful follow up after treatment are necessary. Radiation necrosis of the oral soft tissues is rare and responds to oral rinses, topical corticosteroids, and systemic antibiotics. Postradiation osteonecrosis of the mandible usually presents with mandibular pain and intraoral bone exposure. Although oral rinses, systemic antibiotics, and gentle débridement of exposed necrotic bone might be sufficient, additional therapy can ultimately involve hyperbaric oxygen or mandibulectomy.[47]

Late esophageal complications can occur after mediastinal irradiation or treatment for carcinoma of

Figure 2. **X-ray films show doxorubicin cardiomyopathy in a 49-year-old woman:** *A) Film taken before doxorubicin chemotherapy for metastatic breast cancer shows a normal cardiac silhouette (arrow). B) Film reveals cardiomegaly with evidence of congestive heart failure. Total cumulative dose of doxorubicin was 900 mg (450 mg/m^2). Autopsy revealed patchy myocardial degeneration compatible with doxorubicin cardiomyopathy.*



the esophagus.[48] The most common problem is stricture, although chronic ulceration can also occur. In addition to biopsy required to rule out recurrent disease, management most often includes esophageal dilation. Symptoms from chronic radiation gastritis and ulceration are rare and respond to treatments for peptic ulcer disease. Late small intestinal complications sometimes follow abdominal or pelvic radiotherapy, often presenting with intermittent diarrhea, which might respond to a low-residue diet and antidiarrheal agents. Small bowel obstruction is much less frequent and can often be managed conservatively with nasogastric suction and bowel rest. Radiation proctitis associated with altered bowel habit, tenesmus, rectal bleeding, or pain can follow pelvic irradiation.[48]

For mild cases, treatment with bulk laxatives, stool softeners, and corticosteroid-containing topical ointments or suppositories is sufficient. For moderate cases, topical corticosteroid enemas or foams, sulfasalazine, or endorectal laser therapy can be necessary. For the most severe cases, temporary defunctioning colostomy is sometimes required.

Adding concomitant chemotherapy to irradiation of the liver makes both subacute and chronic radiation-induced liver damage more likely.[49] An important example is the veno-occlusive liver disease that can follow allogenic bone marrow transplantation regimens incorporating total body irradiation.

Chemotherapy. With chemotherapy, the most common gastrointestinal abnormality is chronic liver damage associated with use of methotrexate or mercaptopurine therapy.[50-52] Patients who received low-dose daily methotrexate therapy for prolonged periods appear most prone to asymptomatic liver fibrosis.[50] Patients who present with hepatic symptoms after chemotherapy should be investigated with liver function studies, as well as computed tomography or magnetic resonance imaging to rule out cirrhosis.[52] Because any other cause of hepatitis can result in added morbidity, serology for hepatitis A, B,

and C should be obtained if abnormal liver function is detected. Patients with radiation- or chemotherapy-induced hepatic toxicity should be cautioned against excess alcohol consumption or future use of any hepatotoxic agents.[3]

Genitourinary complications

Radiation therapy. Radiation nephropathy might be noted from a few months to many years after kidney irradiation.[53,54] Toxicity noted within the first 6 months after therapy might improve with time, but abnormalities detected later are unlikely to do so.[54] Treatment is similar to that administered for renal toxicity secondary to other causes. Patients with a history of renal irradiation should have blood pressure determinations and urinalysis performed annually, as early remedial therapy can optimize remaining renal function and prevent end organ failure.

Radiation cystitis represents a serious but rare late complication of pelvic irradiation for carcinoma of the prostate, bladder, or female genitourinary tract. The usual presentation involves one or more of the following: clinical cystitis, hematuria, bladder contracture, ulceration, or fistula.[54] Cystoscopy, cystography, and urodynamic studies can be helpful. Hematuria from radiation cystitis can be treated by laser; by other types of fulguration; or by bladder irrigation with alum, formalin, or other agents. Exceptionally severe cases can require urinary diversion.[54] Urethral stricture can follow irradiation for prostate cancer, particularly in cases of prior transurethral resection. Although the condition is usually treated with simple urethral dilation, urethral stenting is required on occasion.

Chemotherapy. While acute renal toxicity is an important side effect of many chemotherapeutic drugs, chronic nephrotoxicity appears to be relatively rare except in cases of pre-existing renal disease.[55-58] Long-term follow up after platinum-based therapy has demonstrated as high as a 30% persistent decrease in glomerular filtration rate but little evidence of long-term renal tubular dysfunction.[55] Hypertension with an associated decrease in creatinine clearance has been described after cisplatin therapy.[58] Chronic renal tubular dysfunction associated with acquired Fanconi's syndrome is a late complication of ifosfamide administration, and both ifosfamide and cyclophosphamide have been associated with late-onset bladder fibrosis or transitional cell carcinoma of the bladder.[56,57]

In patients with renal symptoms, urinalysis, serum creatinine, and blood urea nitrogen should be checked along with blood pressure. Appropriate secondary investigations of the genitourinary system (such as contrast studies, ultrasound, and cystography) should be ordered if screening tests were abnormal.[3]

Osseous complications

Radiation therapy. While adult bone is relatively resistant to irradiation, postradiation osteonecrosis of the mandible is sometimes noted after irradiation of the oropharynx.[46,47] Radiation-induced pathologic fracture of the pelvic bones has been reported after external beam radiotherapy and brachytherapy for gynecologic malignances.[59] In children, irradiation can affect growing bone, leading to a reduction in sitting height, scoliosis, leg length discrepancy, slipped femoral capital epiphysis, or hypoplasia of facial bones. Because surgical correction could ultimately be required, long-term follow up of patients irradiated in childhood is advisable.[3]

Chemotherapy. Fortunately chemotherapy is rarely associated with long-term osseous complications. High-dose steroid therapy given as part of multiagent chemotherapy programs can, however, produce aseptic necrosis of the hip.[3]

Secondary malignancy

Radiation therapy. A rare but unfortunate long-term complication of both chemotherapy and irradiation remains therapy-induced secondary malignancy.[60-63] The highest reported risk of secondary cancers has been for treated adult patients with Hodgkin's disease.[63] In this group the cumulative probability of a secondary malignancy is 17% at 15 years (13% solid tumours, 2% leukemias, 2% lymphomas). Mean duration of onset has been 4.5 years for secondary leukemia, 5 years for non-Hodgkin's lymphoma, and 12 years for solid tumours. While the risk for leukemia plateaus at 10 years, the risk for solid tumours continues increasing with time.

With radiation-induced malignancy, relative risk varies with age at the time of treatment, radiation dose, region, and volume of the body irradiated, as well as with concomitant use of chemotherapy.[60,63] Most radiation-induced solid tumours (lung cancer, thyroid cancer, breast cancer, bone and connective tissue tumours) develop within previous treatment fields, so such areas should always be carefully examined on follow-up visits.[63] Women who have received mantle irradiation before the age of 30 should be taught careful breast self-examination. This group should receive

baseline mammography by age 35 and annual screening mammography after the age of 40.[3]

Chemotherapy. The topoisomerase inhibitors and alkylating agents have been especially implicated in producing chemotherapy-induced leukemia.[61,62]

Unfortunately leukemias that arise after chemotherapy or irradiation therapy are usually cytogenetically complex (abnormalities of chromosome 7 or 8).[3,62] Unlike de novo leukemia, often a preceding myelodysplastic phase lasts several months. For this reason, any isolated cytopenia or pancytopenia in a previously treated cancer patient should be investigated by bone marrow examination with accompanying cytogenetics. Once acute leukemia ensues, the process tends to be refractory to standard antileukemic therapy; typical survival times are only 2 to 8 months. At present allogenic bone marrow transplantation represents the only potentially curative option and should be aggressively considered for those younger than 55.[62]

Conclusion

A variety of long-term complications could follow conventional cancer therapy. Primary care physicians will probably be responsible for most follow up of cured cancer patients and need to be aware of possible long-term therapy-related problems. This is especially true for complications that present years after successful treatment of the original malignancy. Awareness of individual complications that are potentially treatable could help cured cancer patients ultimately achieve productive and healthy lives.

Correspondence to: *Dr Malcolm Brigden, Regional Medical Oncologist, Penticton Hospital Cancer Clinic, 550 Carmi Ave, Penticton, BC V2A 3G6; telephone (250) 492-9032; fax (250) 492-9036; e-mail* mbrigden@oshr.org

Key points

- Evidence for the efficacy of follow up after treatment for cancer is based mostly on natural history studies and case reports, not randomized controlled trials.
- Most solid tumours, if they recur, do so within 3 to 5 years.
- Early detection should theoretically offer better chances for cure by salvage therapy, but results are less convincing.
- Family physicians can help their patients after cancer treatment by monitoring signs and symptoms and by providing ongoing psychological support. Ideally, good communication with the cancer treatment centre should form the basis for collaborative care.

Points de repère

- Les données probantes concernant l'efficacité du suivi après une thérapie anticancéreuse se fondent principalement sur des études de l'évolution naturelle et des exposés de cas, et non pas sur des essais aléatoires contrôlés.
- La majorité des tumeurs solides, si elles sont récurrentes, réapparaissent dans un délai de trois à cinq ans.
- Un dépistage précoce devrait en théorie se traduire par de meilleures chances de guérison par thérapie de rattrapage, mais les résultats à cet égard sont moins convaincants.
- Les médecins de famille peuvent aider leurs patients après une thérapie anticancéreuse en surveillant les signes et les symptômes et en leur offrant un soutien psychologique constant. Idéalement, une bonne communication avec le centre de traitement du cancer devrait servir de base à des soins en collaboration.

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