CHAPTER 108

Cancer and ageing

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Introduction

The risk of most types of cancer increases with age and with the growth in the aged segment of the population, the burden of cancer in the elderly will continue to grow. In this chapter, the scope of this problem is reviewed, as is the biology of cancer and ageing. A discussion on cancer prevention and treatment in the elderly follows. Finally, supportive care, survivorship issues and the multidisciplinary care of the senior adult cancer patient are reviewed.

Epidemiology and disparities

Cancer is the leading cause of death in men and women aged 60–79 years and the second leading cause of death in persons aged 80 years and older. By 2030, more than one-fifth of the population in the USA will be over the age of 65 years. The probability of developing cancer is one in three in men and one in four women over the age 70 years. The leading causes of cancer incidence and mortality are detailed in Figure 108.1.

Over the past 60 years, cancer-specific death rates have decreased among younger individuals, while increasing in older individuals. Significant disparities in outcomes between younger and older individuals are likely due to a number of factors, including differences in screening, more advanced stage at presentation in older individuals or less aggressive treatment in older patients. Older individuals are more likely to experience delays in diagnosis, incomplete evaluation and undertreatment. Half of older women receive substandard treatment for breast cancer, with significantly worse survival. Similar trends have also been noted among patients with ovarian and rectal cancer and these persist even when studies control for comorbidities and functional status. Under-enrolment of older individuals in clinical trials further compounds the situation by resulting in a paucity of data on appropriate management of cancer in the elderly.

Ageing and tumour development

Hanahan and Weinberg proposed that there are six attributes that must be attained by a cell to be transformed into a malignant cell: self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of programmed cell death, limitless replicative potential, sustained angiogenesis and tissue invasion/metastasis. Mutations cause cellular changes resulting in these altered characteristics and in malignant transformation.

Theories of biological ageing and carcinogenesis overlap in many ways, potentially explaining the increased incidence of many cancers with age. Over time, DNA damage caused by random events or free radicals can cause either cellular dysfunction/death, resulting in ageing, or may cause mutations in proto-oncogenes or tumour suppressors, yielding carcinogenesis. Further, changes seen in cells with ageing are also observed in early carcinogenesis. The formation of DNA adducts, DNA hypomethylation, chromosomal breakage and translocation are associated with age and increase the susceptibility to late-stage carcinogens.

The immune dysregulation associated with ageing may contribute to the increased incidence of cancer with age. With age, changes in T-cell function result in decreased proliferation, increased proportion of memory cells and a decrease in naive T-cells. B-cell function is intact but dysregulated, with an increase in autoantibody formation and monoclonal protein production. Interleukin-2 levels decrease, whereas interleukin-6 levels rise. A prospective cohort study demonstrated that individuals with better NK cell function had lower rates of cancer 10 years subsequently.

In some ways, however, ageing and cancer biology are at odds: cancer requires limitless replicative potential, while finite replicative potential (replicative senescence) is a hallmark of ageing. Most normal human cell types have the capacity for 60–70 doublings. The cellular ‘abacus’ is the telomere, which consists of several thousand repeats of a...
short base pair sequence at the ends of every chromosome. The telomeres protect the chromosomal DNA. With each successive replication, 50–100 base pairs of telomeric DNA are lost from the ends of the chromosomes. Over time, in normal cells, these protective caps are lost; the chromosomal DNA becomes fused end-to-end with other chromosomes, ultimately leading to death of the affected cell. In contrast, in malignant cells, telomeres are maintained through the expression of telomerase, allowing unlimited replication. Another mechanism of senescence, termed ‘stress-induced premature senescence’ , results from cellular events other than telomere shortening. Mutations in an oncogene or double-stranded DNA breaks induced by chemotherapeutic agents can trigger senescence, resulting in a proportion of clonal cells entering senescence. This permanent growth arrest may be as effective as apoptosis as an anti-cancer mechanism.

In some malignancies, there are age-related differences in tumour biology, making the malignancy either more or less aggressive in older patients compared with their younger counterparts. It is a commonly held, though debatable, dogma that solid tumours, including breast, colon, lung and prostate cancer, are more indolent in older patients; however, epidemiological data do not altogether support this observation. It is clear that in some cancers, there are differences in tumour behaviour over the age spectrum. Breast cancers in older women are more likely to be estrogen receptor positive. Acute myeloid leukaemia is more aggressive in elderly patients and more resistant to conventional chemotherapy due to the increased expression of the MDR1 (multidrug resistance) gene.

Cancer prevention

Cancer prevention is an effective way to reduce cancer morbidity and mortality. Cancer prevention strategies include behavioural/lifestyle modification, such as dietary changes, chemoprevention and screening.

Obesity is associated with post-menopausal breast cancer and weight loss lowers circulating estrogen levels. Large cohort studies demonstrate that weight loss is associated with a decreased risk of post-menopausal breast cancer. Further, a randomized trial of a lower fat dietary intervention, which resulted in weight loss in the intervention group, was associated with an 11% reduction (hazard ratio 0.89, 95% confidence interval 0.80–1.00) in estrogen receptor
positive (ER+) post-menopausal breast cancer diagnoses in the 8 years of follow-up.\textsuperscript{10} Further research is needed into whether it is weight loss per se or dietary modification that results in the reduced risk of cancer. In this same trial, however, there was no change in the incidence of colorectal cancer with the dietary intervention.\textsuperscript{11}

Epidemiological studies suggest a protective effect of increased calcium and vitamin D intake on the risk of colorectal cancer. Randomized trials have demonstrated a modest but significant decrease in risk of recurrent adenomas. In the Women’s Health Initiative randomized trial, supplementation with calcium and vitamin D did not result in a decrease in the risk of colorectal cancer versus placebo.\textsuperscript{12} However, this study was criticized for doses of vitamin D\textsubscript{3} (400 IU daily) that are generally inadequate to achieve sufficient serum levels of 25-hydroxyvitamin D.

The inducible enzyme cyclooxygenase 2 (COX-2) is elevated in the majority of colorectal cancers. Aspirin, a non-specific inhibitor of both COX-1 and COX-2, reduces the risk of colorectal cancer by 24\% in patients who take at least 300 mg of the medication for at least 5 years and after a latency period of 10 years.\textsuperscript{13} However, the benefit of cancer prevention must be weighed against the risk of bleeding complications. The COX-2 inhibitor’s more selective mechanism results in lower risk of bleeding. Indeed, the COX-2 inhibitors rofecoxib and celecoxib effectively prevent the formation of precancerous polyps, but are also associated with an increased risk of cardiovascular events.\textsuperscript{14} Given the increased risk and no data showing a decreased risk of invasive colorectal cancer, COX-2 inhibitors should not yet be used for colorectal cancer prevention.

The selective estrogen receptor modulators (SERMs) compete with estrogen for binding at the estrogen receptor, inhibiting pathways required for cellular growth and proliferation. A randomized, placebo-controlled trial of tamoxifen for the prevention of breast cancer enrolled over 13,000 women. Tamoxifen reduced the risk of invasive breast cancer by more than 40\%. Therapy with tamoxifen was associated with a twofold increased risk of pulmonary embolism and a threefold increased risk of endometrial cancer.\textsuperscript{15} Given the serious potential side effects, tamoxifen is recommended only for women at high risk for cancer using risk prediction models such as the Gail model, weighed against the individual risk factors for adverse events.\textsuperscript{16}

Another SERM, raloxifene, has been studied with regard to its impact on the incidence of post-menopausal breast cancer. Over the 8 years of follow-up, therapy with raloxifene was associated with a 76\% reduction in the incidence of ER+ breast cancers, relative to placebo. Women treated with raloxifene had a twofold increased risk of venous thromboembolic disease.\textsuperscript{17} In a head-to-head comparison, postmenopausal women at increased risk for breast cancer were randomized to either raloxifene or tamoxifen. Raloxifene was as effective as tamoxifen at reducing the risk of invasive breast cancer, with a lower risk of venous thromboembolic events.\textsuperscript{18}

In summary, several cancer prevention strategies hold promise. However, in an individual patient, the risks and benefits must be considered before recommending chemopreventive strategies.

### Cancer screening

Screening as a strategy for prevention is a complicated issue. The goal of screening is to identify a disease during a latent or early symptomatic stage, in order to intervene and alter the natural history of disease. Although there is evidence of benefit of screening for breast, colorectal and cervical cancer in individuals in their 50s and 60s, data for screening older, asymptomatic individuals for these common malignancies is lacking. Complicating the issue are the differences in cancer biology described above, which may result in the detection of more indolent cancers that would not ultimately be life-limiting. The sensitivity and specificity of screening tests may be affected by age-related changes in body composition, such as the change in breast composition with age. The harm due to false-positive screening tests must also be taken into account, including psychological distress and risks of diagnostic procedures. Comorbid medical conditions and functional decline may increase the risk of complications related to screening procedures, such as the sedation required for colonoscopy. Table 108.1 gives a summary of current recommendations regarding screening.

Colorectal cancer screening is effective in selected older patients. In patients aged 70–80 years, randomized trials have shown annual to biennial faecal occult blood testing (FOBT) to be effective at reducing colorectal cancer incidence and mortality, with a lag time of 5 years to mortality benefit. However, the sensitivity and specificity of screening tests are low. Case–control studies of flexible sigmoidoscopy and colonoscopy in older patients suggest a mortality benefit associated with screening; however, sigmoidoscopy has a lower sensitivity in older individuals given the increase in prevalence of right-sided colon cancers, which sigmoidoscopy does not detect. Colonoscopy is more sensitive and specific than FOBT or sigmoidoscopy, but in a cohort of older patients aged 70–75 years, the rate of major complications of colonoscopy, including perforation, myocardial infarction or stroke, was 0.3\%.\textsuperscript{19} Computed tomographic (CT) colonography appears to be as effective as colonoscopy in older patients at detecting advanced neoplasias, with a low false-positive rate,\textsuperscript{20} but must be followed by traditional colonoscopy to confirm abnormal findings.

Among the randomized trials that established the mortality benefit of mammographic screening for breast
### Table 108.1 Recommendations for cancer screening in older adults

<table>
<thead>
<tr>
<th>Cancer</th>
<th>USPSTF (^{55})</th>
<th>ACS (^{56})</th>
<th>AGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>Age 50–75 years: FOBT, sigmoidoscopy or colonoscopy recommended</td>
<td>Starting at age 50 years and continuing as long as individual is in good health</td>
<td>Age ≥50 years: screening recommended, unless person is too frail to undergo colonoscopy or life expectancy &lt;5 years (^{57})</td>
</tr>
<tr>
<td></td>
<td>Age 76–85 years: recommends against routine screening, although there may be</td>
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<tr>
<td></td>
<td>considerations supporting screening in an individual</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age &gt;85 years: recommends against screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Age 50–74 years: biennial mammography</td>
<td>Beginning at age 40 years and continuing as long as the woman is in good health and would be a candidate for breast cancer treatment</td>
<td>Age &lt;75 years: annual or biennial mammography</td>
</tr>
<tr>
<td></td>
<td>Age ≥75 years: insufficient evidence to assess risks and benefits of screening</td>
<td></td>
<td>Age ≥75 years: mammography at least every 3 years with no upper age limit for women with an estimated life expectancy of ≥4 years (^{56})</td>
</tr>
<tr>
<td>Cervical</td>
<td>Cessation of screening for women &gt;65 years with adequate prior screening who are not otherwise at high risk for cervical cancer</td>
<td>Cessation of screening for women ≥70 years with ≥3 recent, consecutive negative tests and no abnormal tests in previous 10 years</td>
<td>Age ≤70 years: screening every 1–3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age &gt;70 years: little evidence for or against screening women who have been regularly screened in previous years. An older woman of any age should who has never had a pap smear should be screened until two negative pap smears taken 1 year apart (^{59})</td>
</tr>
<tr>
<td>Prostate</td>
<td>Age &lt;75 years: current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening</td>
<td>Healthcare provider should discuss risks and benefits of screening with the men at average risk for prostate cancer and with 10 year life expectancy, beginning at age 50 years</td>
<td>No published recommendations</td>
</tr>
<tr>
<td></td>
<td>Age ≥75 years: recommends against screening for prostate cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{55}\) USPSTF, U.S. Preventative Services Task Force; ACS, American Cancer Society; AGS, American Geriatric Society; FOBT, faecal occult blood testing.

There have been no prospective randomized trials of cervical cancer screening in any age group, although multiple observational studies show that screening with Papanicolaou (Pap) smears decreases the incidence and mortality of cervical cancer. With advancing age, the sensitivity of Pap smears decreases due to the migration of the squamo-columnar junction into the cervical canal and specificity declines due to atrophic changes causing inflammation. Older women who have been regularly screened are at low risk and those who have significant comorbidity are unlikely to benefit from screening.\(^{19}\)

Prostate cancer screening is controversial, even in younger populations. Prospective, randomized trials of prostate-specific antigen (PSA) screening are under way, but do not include men over the age of 75 years. Given the indolent nature of most prostate cancers and high prevalence of clinically irrelevant prostate cancers found among octogenarians at autopsy, screening for prostate cancer...
is generally not recommended in men over the age of 75 years or who have a life expectancy of less than 10 years. In summary, selected older individuals with longer life expectancy may be appropriate for screening for common cancers.

**Cancer treatment**

The basic tenets of cancer treatment involve the determination of whether treatment is being undertaken with curative or palliative intent. Radiation therapy and surgery are the modalities of treatment utilized to control the local extent of cancer. Cytotoxic chemotherapy, hormonal therapy, biological therapy or targeted agents are typically administered orally or intravenously for systemic treatment. Treatment may be administered neoadjuvantly, that is, prior to definitive treatment, to limit the chance of systemic spread and to decrease the extent of local treatment. Adjuvant therapy is administered following definitive treatment, to reduce the risk of recurrence in individuals at high risk. Palliative treatment is administered to improve symptoms or prolong life in patients with an incurable malignancy.

**Decision-making**

Historically, clinical trials of cancer treatment have excluded patients due to advancing age or therapies in older patients. Clinicians have been left to extrapolate from data derived from the treatment of younger individuals. Increasing attention to this problem has yielded both retrospective and prospective studies of the effectiveness of treatment strategies in older adults with cancer, but much work remains to be done. Guidelines for the approach to management of cancer in senior adults have been established (Figure 108.2).

**Surgery**

Surgery is employed in the treatment of cancer to remove the primary tumour with curative intent. Surgery may also be used to palliate symptoms or prevent serious complications in advanced or metastatic disease, such as colonic diversion for an obstructing colon mass. While some studies have been concerned with increased risk of adverse outcomes in older individuals, often these did not account for comorbidities, advanced cancer stage at presentation, functional impairment and other confounding factors. Appropriate preoperative risk stratification must be employed. A tool developed specifically for use in older cancer patients, the Preoperative Assessment of Cancer in the Elderly (PACE), incorporates measures of cognition, functional status, depression, fatigue, ECOG performance status, American Society for Anesthesiology Estimate life expectancy based on function and comorbidity versus risk of morbidity from cancer .

![Figure 108.2](http://www.nccn.org) Guideline for management of senior adult oncology patients. Adapted with permission from the NCCN 1.2010 Senior Adult Oncology Clinical Practice Guidelines in Oncology. ©National Comprehensive Cancer Network, 2010. The most recent and complete version of the guideline is available at http://www.nccn.org.
scale (ASA) and Satariano’s index of comorbidities. In a prospective international study of patient 70 years of age and older undergoing elective cancer surgery for solid tumours under general anaesthesia, 460 patients underwent this oncogeriatric-specific assessment on the day prior to surgery. Any dependencies in instrumental activities of daily living (IADLs), moderate to severe fatigue or abnormal performance status were associated with a 50% increased risk of 30 day morbidity following surgery. Similarly, any dependencies in ADLs or IADLs and abnormal performance status were associated with a longer than expected hospital stay; dependency in ADLs doubled the risk of an extended postoperative hospital stay. Interestingly, in this study, comorbidities did not independently predict postoperative complications. Overall, older adults with cancer should not be excluded from surgery on the basis of age alone, but the decision to proceed should be individualized based on the risks of the procedure, potential benefits, the patient’s functional status and goals of care.

Radiation

Radiation therapy can be employed with either curative or palliative intent. Some tumours, such as stage I lung cancers or localized prostate cancer, can be effectively treated with radiation alone. Radiation may also be used in conjunction with surgery to improve local control of cancer, as in post-lumpectomy breast irradiation for breast cancer or preoperative radiation for rectal cancer. Radiation may also provide palliation of symptoms in patients with advanced malignancies. Techniques for the delivery of radiation therapy, utilizing three-dimensional imaging reconstruction, have evolved dramatically recently, allowing improved tolerability with sparing of normal tissues. These include conformal radiation, intensity-modulated radiation and stereotactic radiation therapy. Brachytherapy involves the placement of a radioactive source directly within the site of tumour cells and is used in prostate, breast, cervical and skin cancer. Radiation may be delivered systematically in a few instances. Bone-targeting radioisotopes such as samarium-153 and strontium-89 localize to areas of osteoblastic lesions and are helpful in treating painful osteoblastic bone metastases. Radioimmunotherapy consists of radioactive isotopes conjugated to monoclonal antibodies. Examples of radioimmunotherapy include ibritumomab and tositumomab, which are used in non-Hodgkin lymphomas, target the B-cell marker CD20 and are safe and effective in older patients. In general, there is no decrement in the benefit of radiation therapy in older compared with younger patients and no increase in toxicity in the elderly. Rectal cancer and malignant gliomas are exceptions to this statement. In older women with high-risk breast cancer, post-lumpectomy radiation improves survival. Elderly prostate cancer patients receiving radiation for localized disease have similar 10 year survival rates and disease-free survival rates compared with younger patients and should not be denied potentially curative therapy based on age alone. Toxicities in the elderly are similar to those in younger patients, although older patients tend to have more functional decline acutely during therapy. In subset analyses of combination chemoradiation for lung cancer, patients over the age of 70 years tended to have more frequent oesophagitis and neutropenia, but still enjoyed a survival benefit without increased long-term complications. Modern radiation techniques can also minimize long-term consequences of therapy, such as sparing the contralateral salivary glands in head and neck radiation to prevent xerostomia.

The toxicity of radiation to the brain in older patients and its effect on cognition warrant specific discussion. Acute reactions occur during treatment, are associated with cerebral oedema and can be controlled with corticosteroids. Early delayed reactions occur weeks to months after completion of radiotherapy and are characterized by somnolence and lethargy. This is associated with demyelination, endothelial damage, small-vessel thrombosis, accelerated atherosclerosis and long-term memory deficits. Late delayed injuries occur months to years after radiation, and are characterized by parenchymal necrosis. Patients may develop papilloedema, visual loss, hemiparesis, speech and language difficulties, seizures or dementia. Despite these potential toxicities, radiation to the brain remains a cornerstone of treatment for central nervous system tumours and may provide the best option for long-term survival. The risk of cognitive changes must be balanced with the potential survival benefits.

In summary, radiation therapy can benefit older patients in both curative and palliative settings and should not be excluded from the management strategy based on the patient’s age alone.

Systemic therapy

Systemic therapies include conventional cytotoxic chemotherapy, hormonal therapy, biological agents and targeted agents.

Conventional chemotherapy

Chemotherapy is generally administered intravenously, although in some cases it can be administered orally, intraperitoneally or intrathecally. Age is often considered a risk factor for toxicities and poor tolerance of chemotherapy. Indeed, the physiological changes of ageing may alter the pharmacokinetics of chemotherapeutic drugs. Mucosal changes, altered gastrointestinal motility and reduced intestinal blood flow may reduce the absorption of orally administered agents, such as capecitabine. The age-associated decrease in total body water, reduced
plasma protein concentration and lower haemoglobin concentration decrease the volume of distribution of a number of chemotherapeutic agents, increasing the risk of toxicity. Declining renal function may lead to increased toxicity of chemotherapeutic agents that are excreted renally. Changes in hepatic metabolism of chemotherapy with age have not been well studied, but ageing may be associated with increased toxicity due to drugs metabolized by the liver. Polypharmacy is an important consideration, as one-third of hospitalized senior adult cancer patients take at least nine medications, increasing the risk for adverse drug–drug reactions.

Pharmacodynamic effects of chemotherapeutic agents also differ in the elderly, resulting in increased risk of certain toxicities. Older patients are at increased risk of myelosuppression from chemotherapy due to decreased haematopoietic stem cell reserve (see the section below on supportive care). The increased risk of mucositis may also be attributable to a reduced ability to respond to mucosal damage. Older patients receiving anthracyclines are at increased risk for developing cardiomyopathy, which may be mitigated by limiting the total dose of anthracyclines, administering the drug by continuous infusion, using dexrazoxane (which prevents the formation of free radicals) or substituting liposomal doxorubicin. Peripheral neuropathy complicates therapy with a number of classes of chemotherapeutic agents, but is potentially reversible if the clinician monitors for its development (heralded by paraesthesias) and discontinues the offending agent before functional impairment develops.

There is significant interest in utilizing geriatric assessments to predict tolerance of chemotherapy. Preliminary reports suggest that comorbidities, depression, poor performance status and dependence in ADLs predict the development of severe toxicities of chemotherapy. There are currently several ongoing prospective studies utilizing geriatric assessments to predict tolerance of chemotherapy, the development of severe toxicities, hospitalizations and the inability to complete a course of chemotherapy.

**Hormonal therapy**

A number of cancers prevalent in the elderly, including breast cancer and prostate cancer, are hormonally responsive. Medications aimed at blocking these hormonal pathways can result in prevention of recurrence or prolongation of survival.

The selective estrogen receptor modulator (SERM) tamoxifen reduces the risk of recurrence by 40% and the risk of breast cancer mortality by 31% after primary treatment of estrogen receptor positive (ER+) breast cancer. The same risks of SERMs outlined in the discussion of breast cancer prevention apply, although the potential benefit is greater in the adjuvant setting. One-quarter of women are incompletely adherent to their adjuvant hormonal regimen; older age and increasing numbers of comedications are independent risk factors for non-adherence. Also of importance in the efficacy of adjuvant hormonal therapy is hepatic metabolism and polypharmacy. Tamoxifen is transformed by cytochrome P450 2D6 into the more potent anti-estrogen endoxifen. Women who receive the potent 2D6 inhibitor paroxetine concomitantly with tamoxifen are at increased risk for death from breast cancer; the benefit of tamoxifen is reduced or negated by paroxetine, likely due to reduced metabolism of tamoxifen to the more active form. This interaction is not seen with other selective serotonin reuptake inhibitors.

In post-menopausal women, the aromatase inhibitors letrozole, anastrozole and exemestane are the preferred anti-estrogen therapy. Aromatase inhibitors block the conversion of adrenal androgens to estrogens by the enzyme aromatase. Several studies have shown that aromatase inhibitors either in place of or subsequent to tamoxifen are superior to tamoxifen alone as adjuvant therapy. Both tamoxifen and the aromatase inhibitors are used as first-line therapy in women with ER+ metastatic breast cancer. The aromatase inhibitors cause arthralgias and increase the risk of osteoporosis.

Testosterone fuels prostate cancer growth; thus, androgen deprivation therapy is the cornerstone of first-line therapy for metastatic prostate cancer, although over time, prostate cancer will become insensitive to anti-androgen therapy. Surgical castration was historically utilized, though medical castration is now typically preferred. The gonadotropin-releasing hormone (GnRH) agonists leuprolide and goserelin initially cause the release of FSH and LH with an increase in serum testosterone, with subsequent suppression of gonadotropin secretion. This initial testosterone release may cause increased pain in bone metastases, urinary obstruction or spinal cord compression if already impending. This tumour flare can be prevented by the administration of an androgen receptor antagonist for 2 weeks prior to GnRH agonist initiation. The GnRH antagonist degarelix causes rapid suppression of testosterone levels, but its place in the treatment of prostate cancer remains to be determined. Androgen receptor antagonists (bicalutamide, flutamide or nilutamide) are added after failure of first-line androgen deprivation therapy. Common side effects of androgen deprivation therapy are hot flushes, erectile dysfunction, gynaecomastia and anaemia. Androgen deprivation therapy is associated with an increased risk of osteoporosis.

**Biological agents**

Biological agents, including interleukin-2 (IL-2) and interferon, have a limited role in selected cancers such as metastatic renal cell carcinoma and melanoma. Their use in
the elderly is limited owing to their substantial toxicities. IL-2 is associated with a high likelihood of life-threatening toxicities and is generally reserved for younger patients with excellent functional status and limited comorbidities.

**Targeted therapy**

Over the past decade, a plethora of cancer therapeutics referred to as ‘targeted therapies’ have moved rapidly from preclinical development to clinical trial to clinical practice. These drugs, including monoclonal antibodies and small molecule inhibitors of tyrosine kinases, have capitalized on our growing understanding of the molecular mechanisms involved in specific malignancies. Targeting malignant cells holds the promise of less toxic treatments, which is particularly appealing in treating older patients with cancer.

Humanized monoclonal antibodies bind to cell surface receptors on the surface of the malignant cells and induce tumour cell death either by apoptosis, via antibody-dependent cytotoxicity, or through complement-mediated cytotoxicity. Infusion reactions are not uncommon with these agents and require appropriate premedication and observation.

*Rituximab* is a monoclonal antibody directed against the B-cell antigen CD20. A seminal trial of elderly patients (aged 60–80 years) with diffuse large B cell lymphoma randomized patients to standard combination therapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) with or without rituximab. The addition of rituximab improved the complete response rate, event-free survival and overall survival with minimal additional toxicity. Rituximab is now widely used in a number of B-cell malignancies, either as monotherapy in some low-grade lymphomas or in combination with chemotherapy.

*Bevacizumab* is a monoclonal antibody directed against vascular endothelial growth factor (VEGF). It is utilized in combination with chemotherapy in metastatic lung, breast and colorectal cancer. However, there are increasing concerns about toxicity with bevacizumab in older patients with comorbidities. In a randomized trial, patients over the age of 70 years who received bevacizumab in combination with chemotherapy for non-small cell lung cancer had a higher incidence of bleeding, neutropenia and proteinuria compared with both older patients who received chemotherapy alone and patients under the age of 70 years receiving the same therapy, without a significant benefit in response rates or survival. A pooled analysis of randomized trials of patients receiving chemotherapy with or without bevacizumab for metastatic cancer of the breast, lung (non-small cell) or colon/rectum demonstrated a twofold increased risk for arterial thromboembolic events in patients receiving bevacizumab. Risk for arterial thrombotic events was associated with a prior history of cardiovascular events and age over 65 years. Aspirin use was associated with an increased risk of bleeding events. Although age alone should not exclude consideration of therapy with bevacizumab, careful attention to the patient’s comorbid medical conditions and medications is warranted.

*Cetuximab* is a monoclonal antibody directed against the epidermal growth factor receptor, utilized in metastatic colorectal cancer and squamous cell carcinoma of the head and neck. Data specific to the elderly are sparse, but in a case series of patients over the age of 70 years with metastatic colorectal cancer, therapy with cetuximab was well tolerated, with toxicities and response to therapy commensurate with those reported in clinical trials. *Trastuzumab* is a monoclonal antibody against the HER-2 receptor, present in up to 20% of tumours in older women with breast cancer. In clinical trials, treatment with trastuzumab improved survival in women with HER-2+ breast cancers. A retrospective cohort study of women over the age of 70 years with HER-2 over-expressing tumours who received trastuzumab in combination with chemotherapy showed response rates and survival similar to those in clinical trials, without any increased risk of toxicity compared with clinical trial cohorts. It was noted that 9% of women had a 10–20% decrease in ejection fraction on serial echocardiography. Although this decline did not necessitate discontinuation of therapy, it suggests that close monitoring of cardiac status is warranted in older women receiving trastuzumab.

*Imatinib* inhibits the tyrosine kinase encoded by the bcr-abl oncogene, and also the receptor tyrosine kinases encoded by the c-kit and platelet-derived growth factor receptor (PDGFR) oncogenes. Imatinib is used in the treatment of chronic myelogenous leukaemia (CML), Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ALL) and gastrointestinal stromal tumours (GISTs). Older patients receiving imatinib for chronic-phase CML are slightly more likely to experience haematological and dermatological toxicities, but are less likely to develop oedema or neurological side effects, in comparison with their younger counterparts. Efficacy is similar, although the time to response is slightly delayed in older individuals. In elderly patients Ph+ALL, imatinib is as effective at inducing remission as conventional chemotherapy, but is markedly less toxic (see Chapter 33, Management of myelodysplastic syndromes and acute leukaemia).

*Erlotinib* is a small-molecule inhibitor of the epidermal growth factor receptor which is used in patients with non-small cell lung cancer who have progressed after conventional chemotherapy or in whom poor performance status contraindicates chemotherapy. In a phase 3 trial of erlotinib versus placebo, older patients enjoyed a similar benefit to younger patients concerning response and survival. However, this was at the expense of a more
frequent severe toxicity, particularly rash, gastrointestinal side effects and fatigue.\textsuperscript{36}

The tyrosine kinase inhibitor \textit{sunitinib} is used in the treatment of advanced renal cell carcinoma and GIST. In an expanded access trial of sunitinib in advanced renal cell carcinoma, older patients experienced clinical benefit and survival similar to the entire cohort, with similar frequency of grade III–IV toxicities.\textsuperscript{37}

Another multi kinase inhibitor, \textit{sorafenib}, also appears to be safe and effective in older patients. Older patients with advanced renal cell carcinoma had similar response rates and similar rates of toxicities to younger patients and earlier trials.\textsuperscript{38}

Lastly, \textit{lapatinib} is an inhibitor of HER-1 and HER-2 indicated for the treatment of metastatic HER-2+ breast cancer. To date, no data on effectiveness or toxicity specifically in the elderly are available.

\textbf{Supportive care}

Senior adults receiving radiation or chemotherapy must receive aggressive supportive care to minimize the toxicities of therapy and adequately address symptoms directly related to their malignancy. Interventions that can decrease the risk of adverse events due to chemotherapy include haematopoietic growth factors, treatment of anaemia and prevention of mucositis.

Neutropenia frequently causes dose delays and dose reductions in older patients, which potentially reduces the chance of cure. Colony-stimulating factors (CSFs) or myelopoietic growth factors, including filgrastim and pegfilgrastim, decrease the incidence and duration of neutropenia and decrease the risk of neutopenic fever and hospitalization. Current recommendations include the use of CSFs for the primary prevention of febrile neutropenia when the risk of febrile neutropenia is greater than 20%. Patients at increased risk for febrile neutropenia due to age >65 years, poor performance status, poor nutritional status or serious comorbidities should receive primary prophylaxis with CSFs, even if the risk of febrile neutropenia is less than 20%.\textsuperscript{39}

As several chemotherapeutic drugs are bound to haemoglobin in the circulation, anaemia can result in increased free fraction of cytotoxic drugs. Anaemia may also contribute to fatigue and decreased exercise tolerance. Erythropoiesis-stimulating agents (ESAs), including epoetin alfa and darbopoietin alfa, were initially embraced with enthusiasm to increase haemoglobin levels, reduce need for transfusions and improve fatigue in patients receiving chemotherapy. However, more recent data show that these agents may shorten the time to tumour progression, are associated with a 60% increase in relative risk of venous thromboembolism and are linked to a 10% increased risk of mortality [hazard ratio (HR), 1.10; 95% CI, 1.01–1.20].\textsuperscript{40} As such, the US Food and Drug Administration (FDA) has indicated that ESAs should not be used in patients who are undergoing chemotherapy with curative intent. Current guidelines recommend discussion with the individual patient on the risks and benefits of therapy (see www.nccn.org).

In older adults, painful inflammation of the gastrointestinal tract mucosa (mucositis) is a potentially serious complication of chemotherapy. Chemotherapy drugs most commonly associated with oral mucositis include melphalan, cisplatin, 5-FU, methotrexate and cyclophosphamide. Oral mucositis impairs oral intake, causing dehydration and malnutrition. There are few effective interventions for the prevention of oral mucositis. Routine oral hygiene and bland mouth rinses, such as 0.9% saline or bicarbonate solutions, are recommended universally for the prevention and treatment of oral mucositis. Oral cryotherapy (holding ice chips in the mouth) is recommended during infusion for patients receiving stomatotoxic drugs in bolus form; it is hypothesized that vasoconstriction in the oral mucosa prevents delivery of the drug to the oral mucosa, decreasing the risk of oral mucositis.\textsuperscript{41} Palifermin, a keratinocyte growth factor, has been approved for prevention of oral mucositis in patients undergoing stem cell transplantation, but it is not used in solid tumours. Amifostine is an organic thiophosphate approved for use in prevention of xerostomia after radiation therapy for head and neck cancer. Whether it prevents oral mucositis is controversial. The infusion can cause hypotension and it is recommended that all anti-hypertensive agents be held for 24 h prior to infusion, which may not be feasible in older adults with comorbidities. The treatment of oral mucositis includes management of xerostomia with saliogues, management of pain with bland rinses, topical anaesthetics, systemic analgesics and prevention/treatment of superimposed infections, such as thrush.

Diarrhoea also puts patients at increased risk for dehydration; patients and their caregivers must be educated on adequate fluid intake and pre-emptive interventions. Since mucosal injury causes temporary lactase deficiency, milk products should be excluded from the diet for the duration of symptoms. Loperamide and diphenoxylate are both approved for chemotherapy-induced diarrhoea. Octreotide, the long-acting synthetic analogue of somatostatin, is reserved for patients whose diarrhoea does not respond to loperamide.

Remarkably, age over 65 years is \textit{protective} against chemotherapy-induced diarrhoea. In addition, new classes of anti-emetics have dramatically reduced the incidence of chemotherapy-induced nausea. Prophylactic anti-emetics are administered with chemotherapeutic regimens having low, moderate or severe emetogenic potential. Routine prophylactic anti-emetics are not required for regimens classified as having minimal emetogenic potential.
The neurokinin (NK1) antagonist aprepitant is used as prophylaxis for highly emetogenic potential; it has no role in the treatment of breakthrough nausea and vomiting. The serotonin-5(HT)3, receptor antagonists, including ondansetron, granisetron, dolasetron and palonosetron, are used in the prevention of acute nausea and vomiting, but have a limited role in the treatment of delayed nausea and vomiting. Drug interactions between these agents and the selective-serotonin reuptake inhibitors have been reported and clinicians should monitor for toxicities. In addition, constipation is a frequent side effect of drugs in this class. Although the mechanism is unknown, corticosteroids play an important role in the prevention of both acute and delayed nausea and vomiting. The dopamine (D)2 receptor antagonists are widely used in both the prevention and treatment of chemotherapy-induced nausea and vomiting. Extrapyramidal side effects are a dose-limiting toxicity of this class and one agent in this class, metoclopramide, has been associated with seizures in older patients with underlying seizure disorder. Benzodiazepines are commonly used for anxiolysis and prevention of anticipatory nausea and vomiting, but should be used with caution in the elderly.

Pain in older patients with cancer is frequently undertreated. Pain may be directly related to the underlying malignancy or may be chronic pain unrelated to the malignancy. Risk factors for failure to receive analgesics for daily pain include age over 75 years, minority race and impaired cognition. Management of pain in cancer patients should follow the World Health Organization Analgesic Ladder. In patients for whom they are indicated, opioids are safe and effective, provided that they are initiated at a low dose and titrated slowly. Opioid-induced constipation should be universally anticipated and treated prophylactically.

The intravenous bisphosphonates pamidronate, zoledronic acid and ibandronate rapidly reduce serum calcium levels when used in treating hypercalcaemia of malignancy. They are also effective at reducing pain and the risk of skeletal-related events in patients with breast cancer metastatic to bone and in multiple myeloma. Caution should be used with the intravenous bisphosphonates when the creatinine clearance is <30 ml min⁻¹ due to increased risk of nephrotoxicity.

**Multidisciplinary care models**

Combining the disease-oriented approach of the medical oncologist and the patient-oriented approach of the geriatrician may improve the care of senior adults with cancer. Many models for the delivery of geriatric oncology care exist. In an international panel of clinicians involved in the care of senior cancer patients, 20% reported access to a geriatrician and 34% reported that geriatric oncology was incorporated into general oncology. Among those who reported the presence of a dedicated geriatric oncology programme, 85% were located in oncology departments and 15% were located in geriatric departments. Comprehensive geriatric assessment was much more likely to be performed in institutions with a dedicated geriatric oncology programme than those without. Inpatient multidisciplinary teams usually included a medical oncologist, an advanced practice nurse, a social worker, physical therapists and, in about half of programmes, a geriatrician, nutritionist and pharmacist. Most outpatient multidisciplinary teams also included a surgical oncologist and radiation oncologist.

**Survivorship**

With advances in cancer treatment, there are increasing numbers of older adult cancer survivors. Cancer survivors may experience long-term morbidity due to effects of the cancer itself or long-term sequelae of their therapy. Older adult cancer survivors are more likely to self-report their health as poor; they more likely to report comorbid medical conditions and functional limitations than their peers without a prior history of cancer. In a cohort of older women followed prospectively, the prevalence of functional limitation was highest in women within 2 years of their diagnosis, but improved subsequently. Although the majority of 5-year cancer survivors in this cohort reported no functional limitations, they were more likely to report limitation in activities that required strength and mobility, such as heavy work, walking half a mile or walking up and down stairs, than their peers who had no history of cancer. Studies differ on whether cancer survivors have an increased prevalence of psychological disorders.

Cognitive changes temporally associated with cancer treatment, colloquially known as ‘chemobrain’, are an area of debate. Early reports of selected younger women following adjuvant chemotherapy for breast cancer revealed an association between chemotherapy and impairments on neuropsychological testing, relative to population norms or controls. However, these studies were potentially confounded by a number of factors, including depression and hormonal therapy. Although half of older women reported a subjective decline in their cognitive function 6 months after chemotherapy, prospective longitudinal studies have shown a decline in cognitive testing in only one-quarter of women at 6 months of follow-up. Other studies showed no difference in change in neuropsychological testing between patients and controls over time. A large population-based study of people over the age of 65 years showed no difference in the frequency of self-reported memory problems or positive screens for cognitive impairment between long-term cancer survivors and controls. To date, an association between chemotherapy and functional...
Cognitive sequelae of therapy will be including second malignancies. Potential long-term complications of their prior therapy, for long-term cancer survivor patients must be aware of mediastinal radiation in early adulthood. Physicians caring also an increased risk of coronary artery disease following who underwent mediastinal radiation for Hodgkin lymphoma are at increased risk for breast cancer. There is also an increased risk of coronary artery disease following mediastinal radiation in early adulthood. Physicians caring for long-term cancer survivor patients must be aware of potential long-term complications of their prior therapy, including second malignancies.

**Conclusion**

Cancer in the elderly is a growing problem. Older individuals are likely to be diagnosed at a more advanced stage and to receive substandard treatment for their cancer, although there is a growing body of literature showing that older adults may benefit from cancer treatment to the same degree as younger patients.

Biological changes associated with ageing are associated with increased risk of developing cancer. Strategies for prevention of cancer are promising, but most are not widely utilized due to potential risks of treatments. Decisions about screening for common cancers should be individualized, taking into account a patient’s wishes, functional status, comorbidities and whether they would be eligible for treatment of a cancer detected during screening.

There is little reason why an older patient should be excluded from treatment of their cancer based on age alone. Again, decisions should be individualized based on a comprehensive assessment of the patient’s health status. Geriatric assessments can predict which patients are at increased risk for postoperative morbidity and prolonged hospitalization following cancer surgery. Radiation therapy is well tolerated in elderly patients. Cytotoxic chemotherapy can be tolerated without difficulty in many older patients; results of studies using geriatric assessments to predict which patients are at increased risk for toxicities are eagerly awaited. Targeted therapies are emerging as acceptable, potentially less-toxic options for patients who are not candidates for conventional cytotoxic chemotherapy.

Aggressive supportive care with attention to the toxicities most commonly seen in the elderly, such as myelosuppression, will allow older patients to receive treatments with fewer delays or dose reductions, which could otherwise reduce the effectiveness of treatment.

With improvements in survival, there is a burgeoning population of older adult cancer survivors. Some of these patients will have residual functional limitations or cognitive decline following completion of their treatment. Treatments may leave patients at increased risk for secondary malignancies or the development of secondary comorbidities over time.

Multidisciplinary care with the collaboration of geriatricians, medical oncologists, radiation oncologists, surgical oncologists, pharmacists, social workers, nurses and physical and occupational therapists may optimize the treatment of elderly cancer patients.

**Key points**

- With the growth of the aged segment of the population and the increased incidence of cancer in the elderly, the problem of cancer in the elderly is growing. The historical undertreatment of older adults with cancer must be re-examined, as many older patients with cancer can be safely treated with meaningful prolongation of survival.
- Decisions to pursue cancer screening in the elderly must be individualized based on the patient’s life expectancy, functional status, comorbidities and preferences.
- Advanced age is, in general, not a primary consideration for determining surgical risk. Geriatric assessment predicts which older patients are at increased risk for postoperative morbidity. Radiation is well tolerated in older patients and improved techniques further minimize toxicity by sparing normal tissue.
- The decision to utilize systemic cytotoxic chemotherapy depends on the patient’s preferences, functional status, comorbidities and goals of therapy. Haematopoietic growth factors decrease the risk of complications associated with neutropenia. Targeted therapies may offer less-toxic treatment options. Polypharmacy must be monitored, as comedications may decrease the efficacy of the anti-cancer treatment, as has been shown with paroxetine and tamoxifen.
- Senior cancer survivors may have unique challenges following therapy and be at increased risk for complications ranging from osteoporosis to dementia to treatment-related acute leukaemia.
References

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