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Chapter 01 – Introduction

Defining the Elderly
There is no universally accepted age cut-off defining “elderly.” This reflects the fact that chronological age itself is less important than biological events in driving the ageing process within an individual. However, chronological age is a simple and practical way of defining a target population, and 70 years is currently the most commonly used cut-off for defining patients as elderly within the field of geriatric oncology.

Biology of Ageing and Changes in Organ Function
Almost all age-related changes lead to reduced organ function. However, the elderly population is characterised by a marked variability in the rate of functional deterioration, both between individuals and within individuals. Three different trajectories of ageing have been described:

- Ageing with pathology and disability
- Normal ageing with some disability
- Successful ageing with minimal disability

The heterogeneity of the ageing process has practical consequences for the assessment of older cancer patients: patients need individualised assessments to determine their biological age. Biological age is believed to reflect a person’s remaining life expectancy and functional reserves, and will influence treatment decisions and predict treatment tolerance. There is no simple way to assess biological age, and one of the best clinical tools available to date is the comprehensive geriatric assessment (described in chapter 3 of this book).

Traditionally, within gerontology and geriatrics, natural age-dependent changes in structure or function of organs have been distinguished from age-related pathologies. This distinction is perhaps less useful from a practical point of view. Furthermore, normal age-dependent changes are believed to be associated with the prevalence of age-related disease, and organ disease along with the ageing process will exert synergistic effects on each other.

Another important characteristic of organ function and age is the close relation between supply and demand: cardiac output and respiratory function at rest remain largely unchanged with increasing age, but marked age effects appear when the systems need to perform under stress, for example during surgery or chemotherapy treatment.

Within oncology, decreased organ function in older patients may complicate treatment. For example, impairments in renal, hepatic, and bone marrow function increase drug toxicity. However, dose adjustments are usually not straightforward because there is a lack of accurate measurements of function or reserve capacity. Comorbidities and polypharmacy may be associated with an increased risk of side effects and drug
interactions. Again, because of the broad physiological variations seen among the elderly, valid generalisations are difficult to offer.

**Changes in Cognition**

Age is a risk factor for developing cognitive dysfunction. The prevalence of dementia in some studies is about 1% in 65- to 69-year-olds compared with 41% in those aged 90 and over. The presence of dementia or cognitive dysfunction can seriously impact cancer care and treatment. It is important to keep in mind that in some cases formal cognitive testing is the only way to identify cognitive dysfunction, especially in early stages of disease when the patient has preserved language function or if the caregiver does most of the talking.

Pre-treatment counselling often involves complicated decision-making, involving weighing the cost and benefit of different treatment options, and it is paramount for the counselling physician to assess the patient’s decision-making capacity.

For surgical procedures, the risk of post-operative acute confusional state (known as delirium) is markedly increased in the presence of preoperative cognitive dysfunction. Delirium can be prevented, as described below. When a patient is treated with chemotherapy, cognitive dysfunction warrants concern regarding the patient’s understanding of important signs of toxicity, such as fever or bleeding, and arranging more intensive surveillance may be necessary. As both surgery under general anaesthesia and chemotherapy treatment may alter cognitive function, it is important to consider whether the treatment places the patient at risk for being transferred from an independent to a dependent life situation.

**Cancer and Ageing**

Increasing age is one of the strongest risk factors for cancer development. There is a marked increase in epithelial carcinomas from ages 40 to 80 years. Interestingly, the incidence of cancers levels off beyond age 80. The link between cancer and ageing is complex, and most of the fundamental questions remain unanswered. In some instances, such as cellular senescence or telomere shortening, strategies that protect us from cancer may increase our rate of ageing. However, cancer and ageing also seem to share common aetiologies, such as genomic instability and reduced rate of autophagy.

We still do not know whether DNA damage is the ultimate stimulus to both cancer and ageing. Another explanatory model views cancer and ageing as stem cell diseases, where cancer represents the effect of growth promoting mutations within a given stem cell while ageing represents the natural exhaustion and depletion of the stem and progenitor pool.

A common misconception among the general population and some doctors is that all cancers grow slowly in older patients. This is true for some cancers, such as certain types of breast cancer and lung cancer, but the opposite is true for other cancers such as acute
leukaemias, brain tumours, and ovarian cancer, which may be more aggressive in older patients.

**Clinical Aspects**

Since older patients often have reduced reserves in several organ systems, stress such as surgery, chemotherapy, or an acute infection may lead to general symptoms rather than organ-related symptoms. Thus, older patients often have occult or atypical presentations of disease: they may lack fever during an infection and pain in the case of a myocardial infarction. Instead, an older patient may present with general symptoms and signs such as delirium, falls, incontinence (with sudden start or rapid deterioration), or reduced intake of fluids leading to dehydration. It is important that these symptoms are not interpreted as “normal ageing”; ageing does not happen overnight. The physician must search systematically for an underlying cause whenever there is an abrupt change in the functional or cognitive state of an older patient.

Symptoms of cancer may be more difficult to interpret in older patients due to comorbidity, and sometimes this leads to delayed diagnosis. Bone pain caused by a tumour may be interpreted as exacerbation of osteoarthritis, a brain tumour may be interpreted as dementia, and changes in bowel function are interpreted as constipation. Diagnosing cancer is even more difficult in a patient with dementia who is not able to express pain or other problems distinctly.

When cancer is diagnosed, treatment decisions will often be more complicated in the older patient because of several factors, such as reduced remaining life expectancy, the competing risks from comorbidities, reduced treatment tolerance, and potential drug interactions in the presence of polypharmacy. The impact of treatment on the patient’s functional status along with transportation and caregiver issues need to be addressed. In addition, the heterogeneity of this population complicates the development of “one size fits all” evidence-based guidelines.

**Delirium**

Delirium is an acute (hours to days) decline in attention and cognition and is reported to occur in 20% to 80% of cancer patients. Delirium is an underdiagnosed condition associated with functional decline, increased morbidity and mortality, as well as increased health care costs. Two core features separate delirium from dementia:

- First, in delirium the cognitive failure develops rapidly, whereas in dementia it develops gradually.
- Second, delirium, but not dementia, is associated with impaired or fluctuating alertness/attention.
- Moreover, delirium is associated with an altered psychomotor activity.
o When the psychomotor activity is increased (hyperactive delirium), the patient is agitated, sometimes with hallucinations, with a marked motor hyperactivity, and may be difficult to manage.

o In the case of decreased psychomotor activity (hypoactive delirium), the patient is usually lying silently in his bed, but an attempt to communicate with him/her will reveal severe confusion.

Most delirious patients fluctuate between hyperactive and hypoactive periods during the day. A general characteristic of delirium is its fluctuating course, making the condition difficult to diagnose.

The cause of delirium is multifactorial. If the patient is vulnerable because of cognitive impairment or several comorbidities, delirium could be triggered by a small event such as the introduction of a sleeping pill. Conversely, if the patient has few risk factors for delirium, the precipitating factors leading to delirium need to be more extreme such as surgery or major infections. Examples of risk factors for delirium are chronic cognitive dysfunction, high age, serious comorbidity, malnutrition, benzodiazepine withdrawal and sensory impairment.

Common precipitating factors are infections, dehydration, myocardial infarction, pulmonary embolism, urinary retention, electrolyte disturbances, and the introduction of anticholinergic drugs. The introduction of opioid analgesics may also precipitate delirium, but pain and insufficient analgesia seems to be a more common precipitating factor.

It is essential to keep in mind the atypical presentation of diseases in older patients during the search for the underlying cause of delirium. A review of the patient’s medications is mandatory. The most important therapeutic measure is to diagnose and treat the precipitating cause(s) if at all possible.

- Nonpharmacological interventions include the use of orienting influences such as a clock, regular reorienting communication, encouraging normal wake-sleep cycles, and involving family members in care.
- Pharmacological treatment may be necessary if the patient is a danger to himself or others, and haloperidol (orally administered) is usually the agent of choice, at a dose of 0.5 to 1.0 mg twice daily with additional doses every four hours when necessary. An important side effect of haloperidol is extrapyramidal symptoms, and the use of this drug must be reduced to a minimum. Haloperidol is contraindicated in patients with dementia with Lewy bodies or Parkinson’s disease.

In these patients, short-acting sedatives like oxazepam may constitute an alternative.
Dementia
According to the ICD-10 operational criteria, all the following must be fulfilled to make a diagnosis of dementia. There must be impairment in memory and at least one other cognitive function (e.g. language, visuospatial function, or logical reasoning). This impairment must be to a degree that interferes with the person's daily functioning. There must also be impairment of mental functions, such as emotional control, motivation, or social behaviour. Symptoms should last for at least six months, with normal consciousness.

The most common cause of dementia is Alzheimer's disease, followed by vascular dementia. Recent research has documented that the combination of Alzheimer’s and vascular pathology is more common than formerly believed. Other causes of dementia are Lewy body disease, with pronounced motor symptoms in addition to the cognitive failure and a marked intolerance for antipsychotic drugs, and frontotemporal dementia, with dominating loss of emotional and behavioural control.

Most cases of dementia progress over several years from a mild impairment, which does not interfere with the person’s ability to provide an informed consent or to follow up cancer treatment, to severe stages making the person totally helpless in which palliative care should be prioritised.

Falls
An estimated one-third of people over the age of 65 fall each year, and about half of these people experience recurrent falls. Approximately 1 in 10 falls leads to a serious injury such as hip fracture or head injury. As seen in other geriatric syndromes, the risk of falls is multifactorial, and some of the most common risk factors include muscle weakness, history of falls, gait deficits, and balance deficits. Medications that may increase the fall risk include benzodiazepines, opioid analgesics, sleep medication, and antidepressants. A history of falls in the last six months has been shown to predict both chemotherapy toxicity and post-operative morbidity after surgery.

Anticancer therapy often leads to an increased fall risk, examples being surgical treatment involving prolonged bed rest (which leads to muscle loss and orthostatic hypotension), neurological side effects of chemotherapy, and pain treatment with opioid analgesics.

Two relevant clinical points are that patients often forget that they have fallen, and that they rarely volunteer the information about a fall even if they do remember it. Therefore, it is important to ask the patient and caregiver about falls and to assess balance and gait speed.

Polypharmacy
Polypharmacy is most commonly defined as the regular use of five or more drugs but may also be defined as using medications that are not clinically indicated. Among home-dwelling persons over the age of 65, 39% use five or more drugs. Polypharmacy is not a
bad thing per se. It has been documented that older patients are undertreated for many conditions, examples being atrial fibrillation and hypertension. On the other hand, a higher number of drugs increases the risk of interactions and adverse drug reactions.

A diagnosis of cancer will often necessitate a critical revision of the patient’s drug list. For example, cancer may bring about changes in life expectancy that will deem some preventive drugs unnecessary, and the use of chemo-toxic agents or other anticancer drugs increases the risk of drug-drug interactions.

Further Reading

Chapter 02 - Cancer Epidemiology

Introduction
Demography will change dramatically over the next 20 years and will influence the need for health care. An increasing proportion of people will be living longer, and there will be an increase in cancer prevalence. These changes will coincide with increasing dependency ratios and decreasing fertility rates in both developed and developing countries. This will influence the cancer care and treatment of the cancer patient who will be more isolated, frailer, and of an older age category.

Population Demographics
The global population was around 6.7 billion in 2014 and is expected to increase to 9.2 billion by the year 2050. This increase will mostly be seen in less developed countries, where the population will increase from 5.4 billion in 2007 to 7.9 billion in 2050, while the population in developed countries is expected to stay constant at around 1.2 billion.

At the same time, the life expectancy at 60 years of age will increase from 20 years to 22 years in the period between 2010-2015 and 2045-2050, and is again higher in more developed countries. There will also be an increase in the life expectancy at age 80 from 9 years to 11 years in developed countries.

The proportion of the world’s population aged 60 years or over will increase from 12% in 2013 to 21% in 2050 (Figure 1).

Figure 1. World population and percentage of 60+ (United Nations Population Division, 2011)
This means that the global proportion of older people (> 60 years) will increase from 11.7% in 2013 to 21.1% by 2050. In Europe, the proportion of elderly people (≥ 65 years) will reach 28% by 2050.

The proportion of older people requiring support from adults of working age will increase from 12.3% in 1995 to 17.2% in 2025. The proportion of young people under 20 years will at the same time fall from 40% to 32% of the total population by 2025. While the number of people aged over 65 will rise from 390 million to 800 million by 2025, reaching 10% of the total population by 2025. This means increases up to 300% of the older population are expected in many developing countries, especially in Latin America and Asia.

**Cancer Demographics**
Cancer is primarily a disease of old age. According to the National Cancer Institute (NCI), 60% of newly diagnosed malignancies are found in people over the age of 65 years. The same age group accounts for 70% of cancer deaths. Overall, the elderly are 10 times more likely to get cancer and 15 times more likely to die from cancer than people under the age of 65 years.

If all other factors remain the same, the demographic changes (population growth and an increasingly higher percentage of older individuals in the world population) will lead to a global increase of cancer incidence.
Projections state that because of the increase in cancer incidence from 13.3 million in 2010 to 21.5 million in 2030, cancer mortality will rise from 14 million in 2012 to 22 million within the next two decades.

Since cancer treatment has become more effective, the number of cancer survivors and the prevalence of cancer in the population will also increase.

**Society-Related Problems**

Since there will be an increase in the number of cancer patients, the number of health care professionals to take care of these cancer patients will have to increase.

Projections by the NCI show that between 2005 and 2020, in the United States, there will be a 55.8% increase in the demand for oncologists. But in reality there will only be a 14.5% increase in oncologists, leaving a gap of approximately 4,000 oncologists for the United States alone.

The number of human resources working in the health sector in 2005 was estimated to be 23.8 million in Europe. An increase of 23% is needed to maintain the current ratio of health care worker to health care user between 2005 and 2050.

The costs of cancer care and treatment will increase in the future, and this poses a heavy burden on the health care budgets of the different societies. The question remains if we will be able to provide optimal cancer care and treatment within a reasonable cost-benefit model in the future.

**Conclusions**

Because of the demographic changes and the fact that cancer is a disease of senior patients, more elderly cancer patients will need care and treatment. For an elderly cancer patient living with cancer, two issues are of special importance.

- **Independence.** Older people are interested in living long years, but they are even more interested in living independently and being able to do things. This means that efforts are needed within society enabling older persons to remain independent for as long as possible.
- **Fragmentation of care.** With older people, fragmentation of care can become a problem for treatment and care. Several different health care professionals will take care of these patients and integration of a multidisciplinary approach between oncologists, geriatrician, and primary care physicians is of the utmost importance.

**Further Reading**


Introduction
Since age is the main risk factor for cancer, most cancer patients are elderly. Many of these patients have accompanying comorbidities or geriatric problems (Table 1).

Table 1: Prevalence of problems in older cancer patients: outpatient oncology clinic setting

<table>
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<tr>
<td>ECOG PS &gt;= 2</td>
<td>~ 20 %</td>
</tr>
<tr>
<td>ADL dependence</td>
<td>~ 20 %</td>
</tr>
<tr>
<td>IADL dependence</td>
<td>50-60 %</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>&gt;90 %</td>
</tr>
<tr>
<td>Severe comorbidity</td>
<td>30-40 %</td>
</tr>
<tr>
<td>Depression</td>
<td>20-40 %</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>25-35 %</td>
</tr>
<tr>
<td>At risk of malnutrition/malnourished</td>
<td>30-50 %</td>
</tr>
</tbody>
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Abbreviations: ECOG: Eastern Cooperative Oncology Group; PS: performance score; ADL: activities of daily living; IADL: instrumental activities of daily living.

In an oncology setting, not all of these problems might need a comprehensive approach beyond what would normally be applied in the general adult population.

In our experience, half of patients aged 70 and older are functionally “old adults” and can be treated with a standard oncologic approach. However, the other half will need more comprehensive care, including a comprehensive geriatric assessment (CGA). The challenge for the oncologist is to distinguish between these two populations. Recent and ongoing research in geriatric oncology has started identifying effective short screening tools that can be used in a busy setting. Some of these have actually been tested in emergency rooms and then adapted for use in an oncology setting. The general work-up of an older cancer patient is outlined in Figure 1.

Figure 1. General approach to treatment planning in an older cancer patient
One should note the importance of doing an early geriatric screening. This allows using the 2-4 weeks usually needed for an oncology work-up to perform a parallel geriatric work-up, if necessary. We provide resources below to accomplish this two-step approach to the onco-geriatric evaluation of older cancer patients.

**Short Screening Tools**

These are rapid triage tools containing questions which only take a few minutes to answer. They can be used broadly to screen which older patients will need further work-up. For example, all new patients aged 70 and older are routinely screened in our clinic.

The International Society of Geriatric Oncology (SIOG) has recently published an extensive systematic review of the tools available, including a copy of each of those instruments (Appendix D). This chapter gives a short summary of the conclusions regarding the clinical use of these tools. The review identified 44 studies reporting on the use of 17 different screening tools in older cancer patients. The tools most studied in these patients are the G8, the Flemish version of the Triage Risk Screening Tool (fTRST) and the Vulnerable Elders Survey-13 (VES-13).

The validity of most tools was tested against a multidimensional assessment with geriatric instruments, or an assessment by a geriatrician.

Across all studies, the highest sensitivity was observed for: G8, fTRST, Oncogeriatric screen, Study of Osteoporotic Fractures, Eastern Cooperative Oncology Group-Performance Status, Senior Adult Oncology Program (SAOP) 2 screening and Gerhematolim.

In 11 direct comparisons (comparing two or more screening tools) for detecting problems on a full geriatric assessment (GA), the G8 was more or equally sensitive than other
instruments in six comparisons, whereas results were mixed for the VES-13 in seven comparisons.

None of these tools are very specific and, therefore, if positive, they need to be supplemented by a more complete GA. However, they can help to focus geriatric resources towards those patients who need them most.

**Practical Tips**
Review a few of the tested tools and choose the one best adapted to your clinical setting. For example, a short tool filled out by patients, such as the G8, is probably best if you want many clinics to test all older patients for referral to a multidisciplinary clinic. On the other hand, if you have a multidisciplinary clinic where team members can assess the patients at first visit, a slightly more extensive tool, such as the SAOP2, can help you identify more precisely which team members to involve. Most screenings can be patient-answered or included in the initial nursing assessment.

**Comprehensive Geriatric Assessment**
Further assessment is needed if a patient screens positive using the short screening tools described above. The format for further assessment is highly dependent on the local resources: some institutions have an embedded geriatric oncology team; others have a geriatric consultation service; other centres have combined outpatient visits by a geriatrician and an oncologist; in other settings, the only option might be for the medical team to add geriatric instruments to its oncologic evaluation.

Important domains in a GA are functional status, comorbidity, cognition, mental health status, nutrition, social status and support, fatigue, and assessment for polypharmacy and presence of geriatric syndromes. Various tools are available for assessing these domains.

There are strong general data on the effectiveness of geriatric interventions. What are the data specific to cancer patients? Here again, SIOG has published a recent update of its 2005 guidelines. Besides the ability of CGA to detect unidentified problems, there is now solid evidence that these problems affect prognosis independently from classic oncology predictors. CGA items can predict survival or treatment complications. More research still needs to be done on its ability to predict functional and QOL outcomes in cancer patients. There are now several studies demonstrating that a CGA/geriatric consultation modifies the management of cancer patients (Table 2).

Table 2. Treatment modifications by CGA. Studies reporting changes from a baseline oncology treatment plan.
<table>
<thead>
<tr>
<th>Author</th>
<th>Sample Size</th>
<th>Assessment</th>
<th>Outcomes</th>
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<tr>
<td>Aliamus</td>
<td>49</td>
<td>GA</td>
<td>44.9%</td>
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<tr>
<td>Aparicio</td>
<td>21</td>
<td>Mini GA</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>72% adaptation of non-oncological treatment</td>
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</tbody>
</table>
| Caillet  | 375         | Referral to geriatrician, extensive CGA, multidisciplinary meeting | 20.8% intensification of cancer treatment (n= 8, 10.2%), delayed cancer treatment to allow geriatric management (n= 7, 9.0%), and decrease in cancer treatment intensity (n= 63, 80.8%);
| Chaibi   | 161         | Full geriatric consultation | 79 pts (49%)
|          |             |            | Delayed therapy in 5 patients, less intensive therapy in 29 patients and more intensive therapy in 45.
|          |             |            | 76% of patients had a geriatric therapeutic intervention |
| Decoster | 902         | GA by trained nurse, filed in chart. | 42.2% oncologists modified treatment based on age (44.2% in the subgroup where they consulted the GA)
|          |             |            | Based on GA, 6.1% did extra modification. |
|          |             |            | The judgment as to whether the treatment was modified due to age or the GA was rated by the oncologists a posteriori. |
The average rate of modifications is 21.5% (range: 0-49%). This does not count ancillary interventions aimed at non-cancer geriatric problems. The changes may be either intensification or de-escalation of treatment. This might also allow effective prehabilitation or rehabilitation around oncology treatment.

**Tools to Help Decision Making**
An overall approach to treatment selection is illustrated in Figure 2.

Figure 2. Treatment approach based on levels of geriatric impairment
Some tools have been developed that may assist in decision making. Several are available online (Table 3) and cover GA, chemotherapy risk assessment, or life expectancy estimates.

Standard oncology tools, such as Adjuvant! Online, can be helpful but should be used with caution as their data estimates can be skewed in the elderly. In addition, published predictive assessments are available, for example for the risk of post-surgical complications: PACE/PREOP, Kristjansson.

The links provided in Table 3 are some of those found to be very useful by the author but in no way is this presented as an exhaustive list as such lists evolve rapidly.

With advancing age and comorbidity, patients may use increasingly diverse criteria to judge which treatment choice is “worth it”, and subjective estimates by both patient and physician become increasingly imprecise as case complexity increases. Therefore, one of the main goals of these tools is to provide accurate estimates of the benefits and risks of cancer and its treatment alternatives for discussion with the patient and other stakeholders.

Table 3. Useful links to online resources

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<th>Name</th>
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<td>Chemotoxicity risk</td>
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Practical tips
Establish relationships with colleagues and think through the referral pathways for positive screening in advance. Use preformatted orders when possible to simplify referrals. Integrate referrals and tools which help in onco-geriatric decision making in your clinical pathways. Integrate geriatric assessment recording in your electronic medical record. Seek training and regular input from experienced onco-geriatricians if you are developing a focus group or programme in your institution: this will avoid a lot of pitfalls, as the format of such programmes is still very much context-dependent.

Conclusion
Geriatric problems are frequent in older cancer patients. They affect prognosis and treatment outcomes, and should therefore be carefully evaluated and addressed in parallel with oncology treatment planning. Efforts should be made to build or develop multidisciplinary onco-geriatric teams in cancer centres and oncology practises.

Further Reading
**Chapter 04 – Frailty in the Elderly**

**Introduction**

Frailty is a physiological syndrome, which is characterised clinically by decreased reserve and diminished resistance to stressors, resultant of cumulative decline across multiple physiological systems during ageing. It places older people at risk for death and other adverse health outcomes.

Frailty can make routine care less effective, more dangerous and more costly if vulnerability is not identified and managed. However, there is little agreement on the best way to measure frailty although the evidence suggests that the frailty index (FI) may be the most suitable to capture and quantify frailty.

Theou et al (2015) analysed data of 4961 participants from The Irish LongituDinal study on Ageing (TILDA). They found that most characteristics of frailty are similar whether exclusively self-reported or when test-based measures are used to construct the FI. When only self-reported items are included in the index, levels of frailty are lower. A review of databases searched from January 1990 to October 2013 assess the “diagnostic test accuracy” (DTA) of simple instruments for identifying frailty in community-dwelling older people. They studied seven indexed tests including gait speed, timed up and go test, the PRISMA 7 questionnaire, self-reported health, general practitioner clinical assessment, polypharmacy and the Groningen frailty index. They found that the diagnostic test accuracy was greatest for

- Gait speed of <0.8 m/s (sensitivity 0.99 specificity 0.64),
- PRISMA 7 (sensitivity 0.83, specificity 0.83),
- Timed get up and go test of >10 seconds (sensitivity 0.93, specificity 0.62).

 Whilst these three commonly used assessments have high sensitivity for identifying an individual with frailty, these instruments cannot be used as single tests due to the many false positive results.

There is evidence that falls, disability, fractures and death in older women can be identified using two frailty indices. Ensrud (2008) compared one FI which included: weight loss, inability to rise from a chair five times without using arms and reduced energy level, with a second index which included components of unintentional weight loss, poor grip strength, reduced energy level, slow walking speed and low level of physical activity. The two models revealed no difference in discriminating falls, disability, non-spine fracture, hip fracture or death. Therefore, further research on a simple FI, with only three components, may be worthwhile. Although, this would have to be validated in an oncology environment.
Assessment of Frailty

Until recently, both geriatricians and oncologists developed assessment methodologies predominantly designed for their individual patient populations. A review of a clinical assessment of elderly people with cancer in 2005 highlighted many of the deficiencies of the different assessment methodologies. With more recent collaborative work between the two groups, the role of Comprehensive Geriatric Assessment (CGA) is now being well validated. The CGA has become increasingly accepted, and by using such assessment methodologies, Retornaz has validated the use of seven frailty markers (nutrition, mobility, strength, energy, physical activity, mood, and cognition) and found that nutrition, mobility, and physical activity were the most prevalent in a group of older individuals referred for chemotherapy. In addition, up to 42% of older cancer patients had areas of potential vulnerability that would not have been detected through the more traditionally used instrumental activity of daily living (IADL) and activity of daily living (ADL). While mobility and physical activity are well-known predictors of morbidity and mortality in frailty studies, the addition of nutrition is important, particularly in a cancer patient. It is gratifying to see both mood and cognition included since the latter is one of the “giants of geriatric medicine,” as described initially by Bernard Issacs. There is, however, little in the cancer literature about the role of sensory deprivation due to impaired vision and hearing, acute delirium, both faecal and urinary incontinence, and impaired gait and falls on the management of cancer.

Frailty as a Predictor

Frailty measured in a variety of ways is associated with a number of different clinical outcomes. In a UK study of over 11,000 emergency admissions in people aged over 75, the clinical frailty scale (CFS) was an independent predictor of inpatient mortality (Odds Ratio [OR] = 1.6), transfer to a geriatric ward (OR = 1.33) and length of stay > 10 days (OR = 1.19), but not a predictor of 30 day readmission. Its use as a predictor was demonstrated after adjustment for age, gender, Charlson Co-morbidity index and history of dementia and/or current cognitive issues. A limitation of this study by Wallis et al (2015) was that the CFS was completed within 72 hours of admission in 81% of cases but 23.5% of patients had missing CFS information.

A study from the USA, measuring frailty in almost 600 patients aged 65 or older and admitted for elective surgery, used a validated scale (0-5) which included weakness, exhaustion, low physical activity, slowed walking speed and weight loss (patients with a score ≥ four were classified as frail). Pre-operative frailty was associated with an increased risk of post-operative complications (OR = 2.54), prolonged length of stay (OR = 1.69) and discharge to a skilled or assisted living facility after previously residing at home (OR = 20.48). Those scoring two to three were classified as having intermediate frailty and were also found to have increased risk of post-operative complications, prolonged length of stay, and discharge to residential care.
Within oncology there have been varying results using frailty to predict outcomes. A 2010 pilot study from Canada studied 110 patients aged 65 or older. This study found those patients requiring cancer-related hospitalisations were more often those with colorectal or lung cancer and less often breast cancer. In addition, and not surprisingly, those with more advanced disease who had received more extensive treatment, were more likely to have cancer-related hospitalisations. However, they also found that none of the frailty markers predicted the outcome of cancer-related hospitalisation or GP visits. It is important to note that 60% of those included in the sample were under the age of 75, in addition 65% of the study sample were classified as fully active. With this in mind, it is not surprising that this relatively fit study group failed to identify frailty as a marker of adverse outcomes.

In a variety of specific tumour types, frailty is seen to be an independent predictor. Ommundsen et al (2014) categorised a cohort of 178 colorectal cancer patients, aged 70 years or older, into being frail or non-frail. The frailty was assessed through geriatric assessment and was found to be present in 43% of individuals and predicted both one-year and five-year survival post-surgery. In localised and regional disease, the impact of frailty on five-year survival was comparable with that of TNM staging. In this study the geriatric assessment took between 20 and 60 minutes and included a Barthel Index, a medication review, comorbidity, nutritional status, cognitive function and identification of depression.

A systematic review of the prevalence and outcomes of frailty in older cancer patients identified data from 20 studies including almost 3,000 participants. The median reported prevalence of frailty was 42% with a further 43% being pre-frail. A median of 32% of patients were classified as fit (range 11% to 78%). Frailty was independently associated with all-cause mortality (HR = 1.97) post-operative mortality in both frail (HR = 2.67) and pre-frail (HR = 2.33) patients. Both treatment complications were more frequent (OR = 4.86) and post-operative complications at 30 days (HR = 3.19) in those classified as frail. These studies were heterogeneous in that; only 16 used CGA for the diagnosis of frailty, in nine studies the member of the multidisciplinary team who completed the CGA was identified, and in nine studies there was a retrospective review of medical records to calculate the CGA. Seven studies carried out face to face interviews, two used telephone consultations and five used self-reported questionnaires. Studies either dichotomised patients into frail or fit (N=8); four used impairments in >2 GCA domains to define frailty; two used >3 as a cut off for frailty and one study defined frailty as >2 CGA impairments or cognitive impairment alone. A final study reported that two independent physicians defined frailty on the basis of CGA but this was not fully defined. In two studies a detailed description of the definition of frailty was not described. The majority of studies were from the US (7), Canada (2), Belgium (2), Norway (2) and Australia (2).

It is clear that frailty requires definition in a consistent manor and that its correlation with the results of CGA are defined. A systematic review by Hamaker et al (2012) identified a
number of screening methods for predicting those patients who need to have their frailty defined by a CGA. They showed a variety of sensitivity and specificity (Table 1).

Table 1. Sensitivity and specificity of comprehensive geriatric assessment

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity for predicting frailty</th>
<th>Specificity for predicting frailty</th>
</tr>
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<tbody>
<tr>
<td>Vulnerable Elders Survey (VE13)</td>
<td>68%</td>
<td>78%</td>
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<tr>
<td>Geriatric 8 (G8)</td>
<td>87%</td>
<td>61%</td>
</tr>
<tr>
<td>Triage risk screening tool (TRST 1+)</td>
<td>92%</td>
<td>47%</td>
</tr>
<tr>
<td>Groningen Frailty Index (GFI)</td>
<td>57%</td>
<td>86%</td>
</tr>
<tr>
<td>Emed Criteria</td>
<td>31%</td>
<td>91%</td>
</tr>
<tr>
<td>Barber</td>
<td>59%</td>
<td>79%</td>
</tr>
<tr>
<td>Abbreviated CGA (aCGA)</td>
<td>51%</td>
<td>97%</td>
</tr>
</tbody>
</table>

The G8 and TRST 1+ had the highest sensitivity for frailty, but poor specificity and negative predictive value. This review supports the fact that available screening methods have insufficient discriminative power to select patients for further assessment and therefore patients should receive a CGA.

**Conclusion**

There is little doubt frailty exists and its diagnosis is fraught with problems in cancer patients. Oncologists and geriatricians use different definitions of frailty, may measure functional status with different assessment tools, and also may see very different patients. Frailty may be reversible in some patients, and the oncologist needs to work toward identifying the presence of factors such as nutritional deficiency, poor mobility, incontinence, and delirium: both before and during therapy. Patients suitable for therapy require comprehensive assessment with validated tools, and the word “frail” should not exclude individuals from potentially life-saving therapy. Frailty is a continuum rather than a yes or no. Cancer may render a patient frail but treatment may reduce frailty if treatment is targeted. Best practice guidelines are now available and updates should frequently be sought by oncologists and surgeons.
Further Reading

Chapter 05 - Surgical Treatment

Introduction
The life expectancy of the population has doubled between 1982 and 2003. The United States census bureau projects the number of people over 65 years of age, in the USA, is going to be near 90 million by 2050. Cancer is a disease of the elderly, as the age of the population increases so will the incidence of cancer, resulting in more elderly patients, with complicated medical histories, needing surgical intervention. This increased number of patients with multiple comorbidities and impaired functional reserves will result in more frail, nutritionally imbalanced patients with polypharmacy, and psycho-social issues. Optimal post-operative management of these complex patients rests on identifying the appropriate multidisciplinary treatment plan. This is a complex decision making process, as there are multiple variables that need to be considered in order to ensure the best outcomes for these individuals.

Solid malignancies like gastrointestinal, lung, head and neck cancers and sarcoma are best treated with surgery. However, complication rates, mortality, length of stay and intensive care unit admissions increase with patient age, and these have a direct effect on oncological outcomes. One has to consider that surgery will impair the functional status of the individual, either temporarily or in some people permanently. When the impact of abdominal surgery was evaluated by measuring one’s functional exercise capacity, two-thirds of people were shown not to have recovered to preoperative levels, even 9 weeks after surgery. In older patients screening is controversial for various malignancies. This can result in a delayed cancer diagnosis and an increased likelihood of requiring emergency surgical intervention, which is associated with a higher morbidity and mortality. Unfortunately, there is no standard of care and no evidence based guidelines available for this age group, due to older people regularly being excluded from clinical trials. In the absence of clear guidelines and concerns about their ability to tolerate treatment, older patients are less likely to be offered standard surgical cancer treatments that have been shown to improve survival. A careful frailty assessment will allow the multidisciplinary team to compare result, audit institutional series, offer informed consent to patients and tailor surgical management.

Assessing Senior Patients
Older patients are unique and often have multiple medical problems. They can have multiple comorbidities, geriatric syndromes, and impaired physiological reserves, that may result in a decline of functional reserve and progressive restrictions in personal and social resources leading to a prolonged or reduced recovery after surgery. Frail elderly patients, who undergo surgery, are more likely to encounter postoperative complications (e.g. pneumonia, delirium, and urinary tract infection). They have longer hospital stays, and are often discharged to nursing homes or long-term care facilities. They also have amplified financial burdens and higher mortality rates, when compared to fit patients.
Surgical patients usually have a preoperative physical exam and laboratory work-up, ordered by a surgeon. Sometimes they will also have a preoperative assessment with a Cardiologist. The American Society of Anaesthesiologists physical status classification (ASA class) is a commonly used anaesthesiology tool. However, ASA class is not sensitive enough to identify patients who are at risk of developing post-operative complications. Geriatric surgical patients often have unique impairments that need further assessment beyond the traditional preoperative evaluation. Geriatricians use the Comprehensive Geriatric Assessment (CGA) in their evaluations, a multidisciplinary approach for the evaluation of the elderly population that often reveals information missed by routine history or physical examination alone. Its benefits include prolongation of life, prevention of geriatric syndromes, prevention of institutionalisation, and improved subjective well-being. CGA is a systematic approach that aims to assess physical functioning, co-morbidity, polypharmacy, nutrition, cognition and emotional status. Extensive and solid evidence supporting this approach is provided by randomised controlled trials demonstrating that a geriatric intervention guided by CGA has positive effects on health, functional status and mortality. CGA is still not routinely adopted in most practises as an assessment tool for treating elderly oncology patients. However, a large number of review articles advocate the introduction of CGA as a routine assessment in elderly patients with cancer. Some observational studies suggest that the evaluated domains have predictive value in elderly cancer patients receiving chemotherapy or undergoing surgery. There are still several validation studies in progress, to confirm the CGA-based approaches in older cancer patients. Krisjannson et al, studied the CGA on patients undergoing elective surgery for colorectal cancer. They did a prospective observation cohort study which confirmed a CGA-based stratification predicts complication in elderly patients. Frail patients had a significantly higher morbidity than patients in the fit and intermediate groups, but the rate of postoperative complications was not related to increasing age, ASA classification or tumour stage. Another study conducted by Sun Wook Kim et al, included patients undergoing intermediate or high-risk elective operations, in whom CGA had been performed beforehand. This study found the postoperative 1-year all-cause mortality rate, length of hospital stay, and likelihood of discharge to nursing facility can be predicted from particular components of the CGA in older surgical patients. The study concluded the predictive model based on CGA can predict unfavourable outcomes better than the conventional ASA classification. In addition, a higher score is correlated with a greater mortality risk.

CGA is difficult to adopt in a regular surgical oncology practice, the time needed to do these tests is extensive and there is no particular model to help the physician improve the outcomes. The prediction of morbidity or mortality is good but unless appropriate interventions are placed, the outcomes may not improve. The trend of declining 30-day morbidity and mortality in the face of increasing incidence of cancer among patients who are older with multiple comorbidities, underscores the important and significant advances in surgical and anaesthesia technique. Several organisations are now focusing on cancer survivorship and community reintegration after cancer treatment. Research is needed to
address the development and application of interventions that will prevent, or reduce, adverse outcomes of cancer and its treatment. There are a few studies which have analysed CGA-guided interventions, but they are rare. Two randomised studies evaluated the impact of a CGA in the outpatient care of older patients with cancer, who had undergone surgery. In the study by McCorkle et al, geriatric nurse practitioners conducted CGA in the home. In the one month period both patients and their caregivers received 3 home visits and 5 phone calls, for comprehensive clinical assessments, monitoring and teaching, including skill training. There was a definite survival advantage, with a 2-year survival rate of 67%, in the intervention group, compared with 40% in the control group. Goodwin et al, assessed the impact of nurse care management in the treatment of older women with breast cancer. They found patients in the CGA-directed interventions group were significantly more likely to return to normal functioning within 2 months after completion of surgery, compared with controls. It has been found that CGA-guided interventions have a positive impact on health outcomes, including prevention of disability progression, reduction in risk of falls, unplanned hospitalisation and nursing home admission, providing evidence a multidimensional approach is effective with older patients.

The CGA is very comprehensive but it has limitations, especially around the identification of frailty, this can result in functionally impaired elderly patients not being diagnosed as such. Therefore, it is important to develop screening tools (i.e. Groningen Frailty index, Vulnerable Elder Survey 13) to identify more vulnerable patients where treatment may result in long-lasting disabilities. Disability is associated with increased rates of adverse outcomes, preventable hospitalisation and utilisation of healthcare resources. Interventions should be designed to prevent disability to potentially generate large healthcare savings. These interventions must also lead to important reductions, for the patient, in the physical, emotional, social and financial hardships attributed to disability. Gill et al, in their prospective study that involved 188 frail older patients who were receiving home based physical therapy that focused on improving underlying impairments such as: balance, muscle strength, ability to transfer and mobility. They found prehabilitation was associated with less functional decline over a subsequent 12-month period. Prehabilitation may be especially useful in frail elderly patients who are undergoing cancer surgery. The essential requirements for prehabilitation are still being worked out. Four weeks of Prehabilitation has been shown to improve recovery after a total knee arthroplasty among patients 50 to 60 years of age. However the evidence is limited for oncologic series.

Malnourishment is known to be associated with post-operative adverse events such as chest infection, abdominal abscess, wound infection, urinary tract infection, bacteremia/septicaemia, wound dehiscence, anastomotic leak, renal dysfunction and hepatic failure. The percentage of patients experiencing major complications increased as nutritional status deteriorates and is more than double, even in the presence of mild nutritional impairment.
Surgical Resection

Inappropriately, chronological age is still considered to be a factor to decline surgery by some physicians. A large survey of primary care providers in France, showed that chronological age of the patient was highly associated with the decision not to refer patients with advanced cancer (not defined) to oncologic specialties (odds ratio 0.55; 95% confidence interval 0.35-0.86; p = 0.009). If elderly patients are referred to an oncologic specialty, age being a barrier to treatment may exist there too. In a survey of 1408 French medical and radiation oncologists, to whom breast cancer patients were referred, significant differences in treatment choice were observed based solely on patient age.

Surgical resection, when feasible, is one of the most successful modalities of therapy for solid cancers. Age is becoming less important when deciding if surgery is appropriate. The acceptance of this surgical philosophy is different throughout the world, as it is not uncommon in some countries for surgeons to routinely perform cancer resections on patients with multiple comorbidities and increased frailty. A study analysing data at the Eindhoven Cancer Registry has shown an acceptance rate of 95% for surgical resection in non-metastatic colorectal cancer patients who are elderly. This study involved 8,000 patients aged between 50 to 80 years old with colon, rectal and other cancers. A study comparing outcomes of colorectal cancer resection among 32,621 Veterans Administration patients, between temporal cohorts of 1987 to 1993 and 1994 to 2000, found significantly more patients aged 80 year or older received surgical resection in the 1994-2000 time period. A study by Nascimbeni R. et al, also looking at the temporal trends in patients undergoing colorectal cancer resection, compared outcomes between 1975 to 1984 and 1995 to 2004 and found surgical patients aged 75 years or more increased from 19% to 29%, furthermore those aged 85 years or older, doubled from 3% to 6%.

In addition to the increase surgical intervention in elderly cancer patients, doctors are also increasingly looking at the various curative options with multimodality therapy. The importance of targeting appropriate treatment does not diminish with age, because inadequate treatment in older cancer patients is associated with poor survival. A study reviewing the treatment and survival of older (>75 years of age) cancer patients, in a Danish national cancer registry, found the proportion of patients who were denied treatment, or received only palliative therapy, decreased by 35% from 19.8% in the period of 1977 to 1982 to 13.1% in the period of 1995 to 1999. This study also found that the proportion receiving “curative” therapy increased from 36% to 49.2% during these same time intervals.

When a decision to perform surgery is made and the basic assessments are in favour of a surgical intervention, the question to be asked is, with a curative intent operation in the elderly what sort of invasive procedure is to be performed? This is crucially relevant for those patients undergoing major surgical procedures, like thoracic and abdominal procedures, as they have the greatest risks associated with them.
Lung Cancer
Lung cancer is primarily a disease of the elderly. More than 65% of lung cancer patients are older than 65 years of age, when diagnosed. The standard of care for patients of any age, with resectable lung cancer, has been anatomic lung lobectomy (the relative risks and efficacy of lesser resections [i.e. segmentectomy] are being evaluated in clinical trials). In large randomised trials a lobectomy is associated with a mortality of 1.4%, no increased risk has been found to be associated with advanced age. However, these and several smaller studies have not characterised the elderly sufficiently well. Alternative therapies, such as ablation or radiation, have been used for patients who were not deemed fit for surgery, but the criteria used to identify such patients has not been clearly explained.

Colorectal Cancer
More than half of patients diagnosed with colon cancer are older than 65 years of age. Approximately 70% are diagnosed at an early stage, when surgical resection is the cornerstone of treatment. Curative resection of colonic carcinoma is well tolerated in the elderly. Age alone should not be an indication for less aggressive therapy. The elderly may have more comorbidities which can influence postoperative mortality and morbidity. Therefore, careful patient selection for surgical procedures is important. Frail elderly patients are at a higher risk of both mild and severe complications, compared to elderly patients who are who are not considered to be frail. Laparoscopic surgery seems to be associated with improved short-term outcomes. In a systematic review of comparative outcomes of elderly and non-elderly patients with rectal cancer, postoperative morbidity was as high as 40% in elderly patients, but not significantly higher than in younger patients. Patients who survived the first year after surgery showed similar outcomes as their younger counterparts.

Liver Tumours and Metastasis
Primary or secondary liver tumours are subject to liver resection even in senior patients. Improvements in anaesthesia, postoperative management, surgical techniques and technologies have resulted in better outcomes. However, morbidity and mortality remain high, when compared with those for other types of surgery. Several retrospective studies have shown that liver resection can be performed safely in elderly, but their length of hospital stay and their discharge to rehabilitation facilities is higher when compared to their younger counterparts. Two multi-institution series have evaluated outcomes of elderly patients undergoing liver surgery. One series reported on the outcomes of 856 patients who underwent major hepatectomy. The patients were divided into groups (>50, 50 to 64, 65 to 74, and ≥75 years) age was independently associated with surgical mortality (odds ratio 1.039; 95% CI, 1.021 to 1.058; p = 0.0029). Another large series evaluated 7,764 patients who underwent liver resection to treat colorectal liver metastases. Compared with patients younger than 70 years of age, those older than 70 years had an increased 60-day mortality (3.8% v 1.6%; p < 0.001), as well as increased postoperative complications (32.3% v 28.7%; p. < 0.001). However, patients do benefit
from surgery when they are fit. Therefore, surgical options should be considered as appropriate interventions, but caution is needed.

**Pancreatic Cancer**

Pancreatic resection, when feasible, is the mainstay of treatment for pancreatic cancer. Large population-based studies in the pancreatic literature suggest worse short-term outcomes in older patients, compared to younger patients. When large series of elderly patients undergoing major pancreatic or hepatobiliary operations are analysed, chronological age turns out not to be a meaningful risk factor, although the consensus is that physiologic age is essential to consider. When the contribution of chronologic age was isolated statistically, using logistic regression modelling with pseudo $r^2$ analysis in one of the world’s largest series of pancreaticoduodenectomy, age alone was found to contribute to less than 1% of morbidity and mortality. Much more important was chronic obstructive pulmonary disease and coronary artery disease, which had a nearly 4-fold and 5-fold increased impact, respectively.

Thus, liver and pancreas resections can be safely performed, although older patients are at higher risk for perioperative mortality, which reinforces the need for better assessment tools and perioperative interventions.

**Postoperative Care**

The postoperative management of the elderly is different from that of younger patients. The geriatric population is at an increased risk of complications such as: delirium, malnutrition, urinary incontinence, pressure ulcers, depression, falls, the use of restraints, infection, functional decline, adverse drug effects, and death. One third of hospitalised older adults develop delirium during hospitalisation. Elderly patients and their families have to be educated about postoperative delirium to prepare them with effective strategies to face it. It is important to screen individual for geriatric syndromes, such as dementia. Implementation of interventions that prevent delirium, accidental falls and acute functional decline in the hospital is vital. The 4AT tool has recently been reported as a useful and quick instrument to identify delirium and cognitive impairment in the postoperative setting.

**Tumour Biology**

Tumour behaviour in older age groups is poorly understood and there is a need for further studies. One report that looked into the SEER database revealed fewer cases of lymph node involvement in older patients with colon adenocarcinoma. When adequately staged ($\geq12$ lymph nodes harvested) the lymph node involvement decreased significantly as the patients got older, 33% in those <70 years old compared with 27% of 70 to 79 year olds and 23% in patients $\geq80$ years old.

Patients were divided into several groups: 20-49, 50-64, 65-74, 75-84 and $\geq85$ years of age. The relative risk of node positivity was 1, 0.95, 0.85, 0.80 and 0.74 respectively. This
study also showed that patients who had ≥12 lymph nodes harvested had a better prognosis. In addition, the number of lymph nodes harvested also decreased as age increased. As patients get older, curative cancer treatment will become more common in the elderly. Understanding how cancer behaves in these patients needs to be a priority, as this will lead to better treatment and outcomes in these individuals.

**Conclusion**

There are several challenges when planning individualised cancer treatment for elderly patients. We tend to consider elderly patients in terms of chronological age, as it is easier to define. It is important to understand that disparities with age should not happen. Patients should receive appropriate and adequate cancer treatment no matter what their age may be. The patient’s current physiological status should be respected, this is better understood with a geriatric assessment. The treatment modalities should be appropriately instituted with a multidisciplinary management. Perioperative interventions to improve the outcomes in the elderly should be strongly considered. Extensive research is needed to achieve a better understanding of tumour biology in the elderly, so appropriate individualised treatment can be offered. Outcome measures such as, functional decline and disability monitoring should be adopted in the future as survival alone may not appropriately tell the story of the elderly who are receiving cancer treatment.

**Further Reading**

Chapter 06 - Radiotherapy in the Elderly Cancer Patient

Indications for Radiotherapy in the Elderly

Compared with other treatment modalities like surgery and combination chemotherapy, radiotherapy has the advantage of less severe side effects, especially rare treatment-related mortality. This becomes of particular importance in elderly or frail patients who typically present with a considerable number of clinically relevant comorbidities, such as vascular problems (e.g., cardiovascular, cerebrovascular, or general arteriosclerotic vascular disease) or organ impairments [e.g., emphysema, chronic obstructive pulmonary disease (COPD), renal insufficiency, and diabetes mellitus]. Radiotherapy represents a local modality that—in solid tumours—can be aimed at the primary tumour (local disease) and involved regional lymph nodes (locoregional disease) as well as systemic points/regions of need (systemic metastases).

In locally confined disease (early stages I/II), excellent results are achieved with aggressive higher radiation doses with curative intent (60–70 Gy). Considerable local control can be observed after even higher and more focused doses [stereotactic radiotherapy (SRT)].

Locally advanced stages (e.g. III) in solid tumours are characterised by locoregional node involvement (N factor) or locoregional disease extension (T factor). Radiotherapy targets both the primary, where usually higher doses are needed because of bulky disease areas, as well as locoregional lymph node areas, where reduced doses can still eradicate nodal disease. Thus, some patients can be cured with this locoregional treatment strategy. Cisplatin-based chemotherapy given concurrently with radiotherapy, can induce even higher local efficacy/control in certain tumour types.

In metastasised, advanced stages, radiation doses of 30 to 50 Gy can still achieve excellent management for areas of need (e.g. brain, bone and soft tissue metastases). Reduction of clinical symptoms is the main palliative end point of these interventions.

While this simplified classification system describes a number of solid tumours (e.g. lung, rectal, prostate, breast cancer), haematological malignancies such as Hodgkin’s disease, non-Hodgkin’s lymphoma (NHL), and plasmocytoma have more specific treatment protocols where systemic modalities have gained increasingly important roles in curative management (e.g. innovative chemo immunotherapy in NHL). Indications for the use of radiation have decreased due to toxicity issues in some (Hodgkin’s disease), but it remains a valuable palliative and symptomatic care for others.

When prognostic factors such as performance status (PS) or pre-treatment weight loss are taken into account, older patients are usually treated with more intensive protocols when PS is excellent [Eastern Cooperative Oncology Group (ECOG) 0-1] and no
significant weight loss has occurred because of systemic cancer. A more reduced PS of ECOG 2 or 3 or significant weight loss at diagnosis may lead to more palliative radiotherapy protocols, with symptom control and reduced tumour-related complications being major end points in this setting.

**Side Effects of Radiotherapy in the Elderly (Acute and Late)**

Three major reviews of interactions between age at presentation and clinical outcome within European Organization for Research and Treatment of Cancer (EORTC) radiotherapy protocols have been performed in 1996, 1997, and 1998. They included 4,406 patients with head and neck, thoracic, and pelvic cancers demonstrating more severe functional acute reactions in older patients (mucositis and sexual dysfunction). In 2011, a retrospective review of 1,372 non-small cell lung cancer (NSCLC) patients investigated the influence of age on treatment selection and efficacy for stage III NSCLC. Elderly patients with lung cancer showed a trend toward increased weight loss following radical radiotherapy.

Patients older than 65 years and younger patients with NSCLC treated with curative intent, with nonsurgical bimodality therapy or trimodality therapy including surgery, had similar rates of grade 3/4 toxicity.

Another retrospective analysis of nine EORTC studies in pelvic tumours revealed no differences in acute toxicity between different age groups. Moreover, in most tumour sites, retrospective studies of older patients have demonstrated no differences in acute and late tolerance to radiotherapy compared with younger patients. In patients with ECOG PS 0 or 1, the intensity of acute reactions was similar in older and younger patients. Only duration of recovery from acute reactions seemed to be prolonged (four to seven weeks) in older patients.

A large review of the EORTC database of head and neck cancers observed no statistically significant difference between age groups in terms of acute and late side effects. But when evaluating age-related differences in toxicities, we have to admit that comprehensive data on chronic toxicities in individual cohorts are currently missing. The overall incidence and severity of all adverse effects seem to not be significantly increased in elderly versus younger ones. The elderly typically experienced longer hospital admission than younger patients, but age was not related to treatment interruption or grade of toxicity.

**Specific Side Effects**

With modern radiotherapy techniques, skin reactions are rarely observed unless skin areas lay within the clinical target volume (e.g. in advanced breast cancer).

Mucosal reactions remain greatly unavoidable (e.g. in head and neck, rectal and prostatic cancer). Healing of mucosal reactions to full recovery occurs at the same rate regardless of age. The secondary side effects of mucosal gland reactions are minimised (e.g. in head
and neck cancer) by sparing the contralateral side, preventing xerostomia by maintaining functional salivary glands on one side. In prostatic cancer, the organ volumes of bladder, small bowel, and rectal mucosa and the dose administered to these organs can be significantly reduced with modern planning techniques. Higher doses can now be delivered to target volumes in the elderly with good or acceptable tolerance.

There seems to be lower incidence of radiation-induced nausea/vomiting in the elderly receiving radiotherapy than in younger patients treated with the same protocol. But once nausea/vomiting occurs, the consequences can be worse in the elderly who more frequently tend to ignore symptoms of dehydration and develop electrolyte imbalance, if not properly supported during radiotherapy courses. In a prospective analysis of radiation-induced gastrointestinal side effects, typically, the frequency of developing nausea/vomiting was underestimated and thus frequently inadequate and inefficient antiemetic was prescribed. In treatments with high emetic potential (e.g. in abdominal and pelvic cancers) and in concomitant radiochemotherapy, 5-hydroxytryptamine-3 receptor antagonists should be administered prophylactically rather than symptomatically.

In conclusion, acute and late toxicities have developed at the same percentages amongst all age groups.

Prevention of Side Effects

Novel radiotherapy techniques including external megavoltage radiotherapy (EMRT), conformational intensity-modulated radiotherapy (IMRT), and SRT have benefited from individual 3-D image reconstruction of target volumes and neighbouring structures as well as respiratory cycle-gated radiation in organs moving with the respiration cycle (“4-D radiotherapy”). These innovations have allowed individualised calculations of doses delivered to critical organs and optimisation of dose delivery. As a result, acute tolerance to radiation in all patients has improved remarkably, whereas incidence and severity of late normal tissue damage have significantly decreased. Such progress has been observed in multiple sites, being of particular relevance for brain, head and neck, thoracic, abdominal, and pelvic malignancies.

The functional reserve of many vital organs typically declines with advancing age, and this alone can cause increased acute toxicity from radiotherapy. Increased damage to normal tissues can be associated with a reduced stem cell reserve in bone marrow, as well as in mucosa and with a reduction in the rate of normal tissue cell repopulation. The potential benefit from innovative radiotherapy techniques may be observed in all age groups.

Most of the early literature on increased radiotherapy toxicity in elderly patients stems from a series with standard fractionation schedules or un sophisticated treatment planning. In contrast, reports on age-independent tolerance are based on selected patient populations from clinical trials in high-level institutions. On the basis of positive selection effects (e.g. strict protocol eligibility criteria within prospective trials), these reports may
not be totally representative for the overall population. Therefore, the current literature gives biased reports about delivering aggressive treatments within clinical studies that sometimes have to be significantly modified because of acute treatment-related toxicities when given to patients outside the clinical trial setting.

**Efficacy and Outcome of Radiotherapy in the Ageing**

Most of the reports about the efficacy of radiotherapy in the elderly originate from university hospitals or dedicated cancer centres with a specific interest in aggressive approaches. Typically, elderly patients are often per se excluded from clinical trials, and prospective investigations for this selected group are rare. As a consequence, management of cancer in the elderly often cannot be based on first-level evidence.

Population-based data sets from cancer registries may represent alternate ways to gain insight into specific questions within this group. Results in regional and non-university hospitals are typically worse in outcome parameters. Often, radiation therapy in this setting is based on conventional fractionation of only moderate doses. Long-distance transportation to centralised radiotherapy units may be responsible for early discontinuation, significant treatment interruptions, and an increased overall treatment time leading to a worse outcome. However, population-based estimates of survival benefit associated with combined modality therapy (radiation and chemotherapy), in elderly patients with locally advanced NSCLC demonstrate that survival benefits associated with combined modality therapy can be extended to the elderly in routine care settings. However, mortality might be increased depending on the kind of therapy used (i.e. sequential or concurrent, induction or consolidation chemotherapy).

To increase overall compliance and delivery in patients, often dose/ fractionation compromises are made, by reducing the number of individual fractions and increasing the dose per single fraction. This hypofractionation approach, with fewer than five fractions per week or reduced overall fraction number has been investigated in older and frail patients, leading to overall lower biological doses. The consecutive outcome is generally poorer, at least compared with standard fractionation in most solid tumours. Inadequate doses may potentially compromise the chances of cure for elderly, but the use of novel radiotherapy techniques may significantly improve the quality of life and overall survival in the elderly.

There is no clear justification from radiation biology that radiation effects to the tumour tissue itself may be significantly different in older compared with younger patients. When looking at the literature, a subgroup analysis from several randomised trials with concurrent chemoradiotherapy protocols in solid tumours gave even more promising results in the older patients’ subset (e.g., Radiation Therapy Oncology Group (RTOG) study 94–10 in locally advanced NSCLC). Furthermore, good primary tumour control rates of patients with medically inoperable T1-T2 NSCLC have been replicated in patients aged at least 75 and over 80. Therefore, when cure is aimed for, no dose density or overall dose compromises should be allowed based solely on age alone.
Response depends on sensitivity of tumour cells to radiation with adequate tissue oxygenation and ongoing cellular proliferation. Ongoing cellular proliferation varies according to the neoplasm site, its histology, and individual tumour biology. Two neoplasms at the same anatomic site, and with the same histology, may show a different response when exposed to the same radiation dose because of differences in proliferation.

There is little information about the proliferative activity of tumours in the elderly, and there are no clinical data correlating tumour oxygenation with patient age. Experimental data in tumour-bearing mice have demonstrated that oxygenation of tumour cells decreased with age of the tumour-bearing animal. This correlation may be extrapolated to cancer patients, leading to a relevant age-related decrease in tissue perfusion. This, in return, may significantly affect sensitivity of some solid tumours to irradiation. But proliferative activity seems to be inversely correlated with age only for some neoplasms while in others, it remains independent. In several tumours, the H3-thymidine labelling index (TLI), a measure of cell proliferation, is decreased in elderly patients, suggesting that sensitivity of tumours to radiation may also be decreased compared with younger ones. Tissue hypoxia caused by age-related decrease in circulation and tissue perfusion might lead to reduced tumour sensitivity.

As for local control, there is currently no evidence that solid tumours show different outcomes between different age groups. In a retrospective analysis of nine European EORTC trials in patients with pelvic tumours and age over 70, it was concluded that there were no differences in local control and overall survival following radiotherapy based on patient age. In 1996, 1997, and 1998, three reviews have analysed the relationship between age at presentation and clinical outcome of patients treated within EORTC radiotherapy protocols. These reviews included 4,406 patients with different cancers [e.g. head and neck, thoracic (including breast and lung cancers), and pelvic cancers (including bladder and prostate)].

Age did not influence locoregional recurrences and overall survival for head and neck tumours after radical radiotherapy. In pelvic malignancies, analysis adjusted for T stage showed comparable local control and disease-free survival between different age groups for anal, prostate, and uterine cancers. In contrast, younger patients with rectal cancer survived significantly longer than older patients, possibly explained by increased treatment-related mortality in this setting. On the whole, patient age did not represent a limiting factor for radical radiotherapy in pelvic malignancies, excluding rectal cancer.

**Palliative Setting: Toxicity and Efficacy Ratio**

Once cure is no longer realistic because of large bulky tumours or advanced disease, palliative radiotherapy may still be administered with palliative intent. The predominant aims of radiation in this setting are symptom relief (e.g. bone pain in bone metastases, reduction of neurological symptoms in brain metastases, bleeding of mucosal tumours) and control as well as improvement of quality of life. Toxicity to normal tissues and
neighbouring organs has to be strongly considered and to be weighed against the overall benefits from palliation. The toxicity/efficacy ratio becomes of major importance, but significant improvements in radiation techniques (as outlined above) have led to more favourable treatment profiles, with a general reduction of toxicity for normal tissues surrounding the tumour.

**Curative Setting: Combinations of Chemotherapy and Radiotherapy**

Age itself should not hinder curative approaches in the absence of other significant exclusion criteria for aggressive protocols. Biological age and numerical age do not always correspond. Concurrent application of cisplatin-based chemotherapy to radiotherapy significantly improves local control and thus increases the curative potential of treatment in several solid tumours (e.g. lung cancer, head and neck cancer, oesophageal cancer and cervical cancer). Within the literature, there are several examples showing that dosing schedules of reduced individual cisplatin (CDDP) doses (e.g. 6 mg/m\(^2\) CDDP daily application; 20 mg/m\(^2\) CDDP q d1–d5; 30 to 50 mg/m\(^2\) CDDP once weekly) may be viable alternatives and result in significant benefits in to overall and long-term survival. Combinations of chemotherapy and radiotherapy may have a significant impact on organ preservation (e.g. rectal cancer, laryngeal cancer and cancer of the floor of the mouth). Therefore, concurrent chemoradiotherapy may be an important alternative to extensive surgical intervention, with underlying higher patient risks in the elderly. When deciding on individual treatment protocols in an elderly patient, these alternatives should be acknowledged and discussed within the multimodality team that includes at least a radiation oncologist, medical oncologist, and preferably also a geriatric physician.

Comorbidities responsible for impaired organ function in the tumour-bearing region can affect treatment tolerance, may lead to significant side effects or even late complications, and may be important patient-related selection factors. Additionally, general comorbidities (e.g. cardiovascular and pulmonary) are significant factors that influence treatment decisions.

Increased side effects, following radiation in the elderly with less tolerance to aggressive treatments, are often considered as major contraindications to radiotherapy. Thus, many elderly patients are either not treated at all or treated with reduced intensities because of expected treatment-related toxicities (e.g. radiation mucositis). These increased treatment-related toxicities may be related to significant comorbidities, such as chronic cerebrovascular and/or cardiovascular disease, arterial hypertension, diabetes, or significant cardiac, renal, and hepatic dysfunction. However, these comorbidities may differ widely in severity, and even when present in combination, they usually do not implicate a strict contraindication to radiotherapy, unless they significantly impact on the overall survival prognosis of the patient compared with the spontaneous course of the disease.
In most patients, comorbidities alone do not justify confining indications of radiotherapy. After correction for physiological and biological risk factors, a large proportion of elderly patients can still have access to radiation comparable to that in younger ones. However, these considerations are valid for the elderly with adequate PS only and, unfortunately, little evidence based on clinical trials and prospective data sets is available to date. Moreover, often at the time of diagnosis, comorbidities are insufficiently controlled. Proper management of comorbidities prior to treatment decisions may allow a full-dose radiotherapy delivery even with more aggressive concurrent chemoradiotherapy protocols or application of higher radiation doses alone.

Unfortunately, older patients are less frequently intensively investigated with regard to pulmonary, cardiopulmonary, or vital organ reserve. As a consequence, they may receive less aggressive therapy based on a general assumption that they have a higher vulnerability to treatment, less tolerance to intensive protocols and a presumed limited life expectancy.

Another selection criterion for specific patients in everyday clinical practice may be the overall treatment time of radiotherapy. Importantly, some neurological comorbidities like Parkinson’s disease or senile dementia can prevent patients from maintaining a reproducible position during treatment over several days. This may significantly hamper radiotherapy compliance and tolerance. Furthermore, the distance between the patient’s home and treatment site can be a selection criterion, which may make outpatient treatment difficult. Access to local hosting/housing facilities during treatment periods may be unaffordable or even completely unavailable for older patients.

**Conclusions**

Historically, elderly cancer patients were considered to tolerate aggressive radiation protocols less well based on increased toxicities observed in early clinical trials. Recent improvements in radiotherapy techniques and delivery, have significantly reduced side effects. There is currently no clear evidence for treating elderly patients generally different from younger ones.

The available data on normal tissue tolerance to radiotherapy in the elderly strongly suggest that those with good functional or PS can tolerate modern schedules comparably to younger ones. As a consequence, more intensive radiotherapy techniques with curative intent should not be withheld from patients based on their numerical age alone.

However, in the individual patient, clinically significant comorbidities may sometimes hamper intensive treatment protocols and lead to decisions for more palliative and less aggressive approaches.
Further Reading

Chapter 07 - Hormonal Anti-Cancer Treatment in the Senior Cancer Patient

Introduction
About 50% of women with breast cancer and approximately 70% of men with prostate cancer are diagnosed after the age of 65. Hormonal therapy rarely causes acute side effects and is often recommended in patients with breast and prostate cancer. However, hormonal agents are associated with chronic toxicities that can sometimes be life threatening. Thus, before recommending hormonal therapy to elderly patients, the benefits of treatment should be balanced against potential harms and competing risks of morbidity and mortality.

Breast Cancer
In women older than 65 years (and in men with breast cancer), up to 85% of cancers are oestrogen receptor (ER) and/or progesterone receptor (PR) positive.

Hormonal agents used commonly are as follows:
- Selective oestrogen receptor modulator (SERM): tamoxifen
- Third-generation aromatase inhibitors (AIs): anastrozole and letrozole (nonsteroidal), and exemestane (steroidal)
- ER downregulator: fulvestrant
- Progestins: megestrol acetate and medroxyprogesterone

(Neo)adjuvant Hormonal Therapy
The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that five years of adjuvant tamoxifen reduces the annual rate of death from ER+ breast cancer by about 30%, an effect that appears to be independent of age.

Several phase III clinical trials have evaluated the role of AIs given either up front (e.g., ATAC, BIG 1-98) or sequenced/switched after two to three years of tamoxifen (e.g., BIG 1-98, IES, TEAM), and the EBCTCG reported recently the results of a meta-analysis of trials comparing AIs with tamoxifen. The meta-analysis demonstrated improved disease-free survival (DFS) and overall survival (OS) rates for AIs compared with tamoxifen, but the absolute difference in survival is very small for women with low-risk disease.

As a result of a prolonged risk of relapse of hormone receptor positive breast cancer, aromatase inhibitors (e.g., MA.17) and tamoxifen (e.g. ATLAS and aTTom) have been evaluated as ongoing therapy after five years of tamoxifen (extended hormonal therapy). These trials have shown a reduced risk of breast cancer recurrence with prolonged therapy, but again the absolute benefit is small, especially in low-risk patients. In older patients any benefit might be counter-balanced by the risk of death due to the accompanying comorbidities and/or the long-term adverse effects of hormonal therapy.
• An AI should be used at some point during adjuvant therapy in older women with intermediate- or high-risk breast cancer. Five years of treatment with an AI does not give superior survival to a sequenced strategy, which has the advantage of splitting exposure to toxic effects.

• Up-front use of an AI is the preferred option for postmenopausal women with high-risk breast cancer and in women with contraindications to tamoxifen (e.g., history of thromboembolic disease). There is no basis for continuing AIs beyond five years when used up-front or after switching from tamoxifen.

• In most women with low to moderate risk breast cancer, five years of tamoxifen remains appropriate. Furthermore, in selected women with a very low-risk ER-positive tumours (e.g. small, low grade, node negative), especially in very old women it may be reasonable to omit adjuvant hormonal therapy.

• For postmenopausal women with high-risk disease who complete five years of adjuvant tamoxifen, extended treatment with an AI or tamoxifen should be recommended. Unless contraindicated, extended adjuvant AIs are preferred due to an earlier reduction in risk of recurrence compared with extended tamoxifen. There is as yet no information about the role of extending treatment in those who received upfront AI or sequencing strategies, although data from ongoing studies will better determine the optimal duration of endocrine therapy in such patients.

In the neoadjuvant setting, randomised clinical trials (e.g., IMPACT and PO24) showed that AIs lead to higher rates of response and breast conservation and should be considered in older women with locally advanced breast cancer who have hormone receptor – positive breast cancer and in women with contraindications to chemotherapy (Table 1). Although most of the trials investigated neoadjuvant hormonal therapy for 3-4 months only, longer duration of neoadjuvant hormonal therapy can lead to further reduction in tumour size.

Some differences in efficacy between AIs and tamoxifen may be explained by inactivation of or genetic polymorphism in the enzyme cytochrome P450 (CYP) 2D6, which converts tamoxifen into its active metabolites. However, post-hoc analyses of the BIG 1-98 and ATAC trials found no associations between CYP2D6 genotype and clinical outcomes and therefore routine testing for genetic polymorphism of CYP2D6 is not recommended. Use of strong and moderate CYP2D6 inhibitors (e.g., the antidepressants bupropion, fluoxetine or paroxetine) should be discouraged in women who receive tamoxifen; the weak CYP2D6 inhibitors venlafaxine and citalopram are preferred antidepressants in this setting.

Adjuvant therapy with tamoxifen for five years should be recommended to men with early breast cancer. Use of AIs in men has little rationale since 20% of circulating oestrogen is produced in the testicles independently of aromatase (Table below).
## Role of Hormonal Therapy in Breast Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Therapy</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Early breast cancer (adjuvant therapy)</td>
<td>Monotherapy with tamoxifen (5 year)</td>
<td>• Preferred option in older women with low-risk breast cancer (e.g., small tumour size, N-, and HER-2-)&lt;br&gt;• Women who cannot tolerate AIs or have relative contraindications for their use&lt;br&gt;• Men with early breast cancer</td>
</tr>
<tr>
<td>Early breast cancer (adjuvant therapy)</td>
<td>Monotherapy with AIs (5 year)</td>
<td>• An option in women with high-risk breast cancer (e.g., large tumour size, N+, or HER-2+)&lt;br&gt;• Women who cannot tolerate tamoxifen or have contraindications for its use</td>
</tr>
<tr>
<td>Early breast cancer (adjuvant therapy)</td>
<td>Sequenced hormonal therapy (AI 2-3 years after initial use of tamoxifen for 2-3 years, or vice-versa in total for 5 years)</td>
<td>• Women with moderate/high risk breast cancer, in whom AI was not used up-front</td>
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<tr>
<td>Early breast cancer (adjuvant therapy)</td>
<td>Extended hormonal therapy with AI or tamoxifen –after 5 years of tamoxifen)</td>
<td>• Women with high-risk breast cancer (e.g., N+ disease)</td>
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<tr>
<td>Early breast cancer (adjuvant therapy)</td>
<td>Neoadjuvant hormonal therapy with AIs/tamoxifen (3-4 months or preferably longer if response)</td>
<td>• Women with strongly endocrine-responsive locally advanced breast cancer, especially important for senior women&lt;br&gt;• Women with endocrine-responsive breast cancer, in whom chemotherapy is not possible because of contraindications</td>
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</table>
Advanced breast cancer
Tamoxifen, non-steroid AIs, steroid AIs, fulvestrant, progestins

- Sequential administration of available hormonal agents due to incomplete cross-resistance (not appropriate for women who have endocrine-resistant disease (as per ABC2 guidelines)

Abbreviations: AI, aromatase inhibitors; N, lymph node.

Hormonal Therapy in Advanced Breast Cancer

Hormonal therapy is the treatment of choice for older women with metastatic hormone receptor – positive tumours with metastases predominantly to bone and soft tissues and/or with asymptomatic slowly progressive visceral disease. Women with endocrine-responsive breast cancer may benefit from sequential administration of hormonal agents because of incomplete cross-resistance between them: tamoxifen, AIs, fulvestrant and progestins can lead to tumour response and relief of symptoms.

In randomised clinical trials, AIs demonstrated better response rates and progression-free survival (but not overall survival) as compared with tamoxifen or megestrol acetate. The addition of the mTOR inhibitor everolimus to the steroidal AI exemestane has been shown to significantly prolong progression-free survival (PFS), but does not improve overall survival. Everolimus substantially increases toxicity with almost 1 in 4 patients discontinuing the drug, so this strategy has questionable therapeutic benefit. After second-line hormonal treatment, there is no high-level evidence to assist in selecting the optimal agent. When fulvestrant is used after previous hormonal therapies, ~30% of women derive clinical benefit. According to the results of a meta-analysis, use of high dose fulvestrant monotherapy in first line or in patients with limited prior exposure to adjuvant endocrine therapy may delay progression compared with an AI. A recent study showed substantial improvement in PFS when fulvestrant was combined with the cyclin-dependent kinase inhibitor palbociclib, which is well tolerated, but data are too immature to accurately evaluate overall survival.

Women diagnosed with metastatic endocrine-responsive breast cancer who did not receive adjuvant hormonal therapy or had a long disease-free interval after such therapy have a high chance of response to hormonal therapy at the time of recurrence. In contrast, women recurring during adjuvant hormonal therapy have a lower probability of response to further hormonal manipulations.

Although not recommended in the adjuvant setting in male patients, AIs can cause protracted stability and objective responses in some men with advanced breast cancer.

False negative determinations of ER and PR status may occur. Thus, hormonal therapy may be active in some women who were reported to have ER-negative and PR-negative
tumours, especially in soft tissue and/or bone predominant disease. Further, differences in hormonal status between primary and metastatic sites are reported, and biopsy for determination of hormonal status should be encouraged at time of recurrence.

Side Effects of Hormonal Therapy in Breast Cancer

Major side effects of tamoxifen, AIs, and other hormonal agents used in the treatment of breast cancer are summarised in the Table below. Tamoxifen increases the risk of rare adverse events such as uterine cancer (including uterine sarcoma) and thromboembolic disease, and elderly women are at higher risk to develop these toxicities. Women receiving an AI have a lower risk of uterine cancer and thromboembolic events compared with women on tamoxifen but a higher likelihood of developing arthralgias, fractures, urogenital atrophy and ischemic cardiac events. Bone loss and fractures are of particular concern in older patients, especially those with pre-existing osteopenia or osteoporosis: all women receiving an AI should be encouraged to exercise and given calcium and vitamin D supplementation; their bone density should be assessed annually, with a bisphosphonate or denosumab prescribed if bone loss is documented. Randomised data show similar frequency of cerebrovascular disease between AIs and tamoxifen. Observational data suggest that the prevalence of AI-related joint symptoms is higher than reported in phase III clinical trials. In unselected patients, fulvestrant monotherapy is associated with similar efficacy, but reduced arthralgia compared with other endocrine therapy options. Side effects can be an important cause of noncompliance with treatment and should therefore be actively sought and addressed during treatment with hormonal therapy.

**Major Side Effects of Hormonal Therapy in Breast Cancer**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Major Side Effects</th>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td>• Hot flashes</td>
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<td></td>
<td>• Venous thromboembolism, stroke</td>
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<td></td>
<td>• Vaginal discharge, uterine hyperplasia/polyps endometrial cancer</td>
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<td>• Fluid retention, muscle cramps</td>
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<td>• Cataract, retinopathy</td>
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<td></td>
<td>• Increased triglycerides (but favourable effect on cholesterol)</td>
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<td></td>
<td>• Other (tumour flare, alopecia, gastrointestinal intolerance, headache)</td>
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<tr>
<td>Aromatase inhibitors</td>
<td>• Hot flashes</td>
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<td>• Vaginal dryness/atrophy</td>
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<tr>
<td></td>
<td>• Joint pain/stiffness, muscular pain, carpal tunnel syndrome,</td>
</tr>
</tbody>
</table>
Prostate cancer is predominantly a disease of older men. In the era of screening with prostate-specific antigen (PSA), most men are diagnosed with localised disease. Older men with prostate cancer usually die of other causes, with cardiovascular disease being the leading cause of death. In a subset of men with aggressive tumours and without major comorbidity, prostate cancer can progress rapidly to an advanced stage and cause death if not adequately treated.

The aim of androgen deprivation therapy (ADT) is to deprive prostate cancer of its predominant growth signal. Hormonal agents used in men with prostate cancer are as follows:

- Gonadotropin-releasing hormone (GnRH) agonists (goserelin, buserelin leuprolide) or antagonists (degarelix); alternative is bilateral orchiectomy
- Nonsteroid anti-androgens: bicalutamide, nilutamide, flutamide, enzalutamide
- Androgen synthesis inhibitors: ketoconazole, abiraterone acetate
- Oestrogens: diethylstilbestrol (DES)
- Miscellaneous: prednisone, dexamethasone

ADT in Men with Localised and Locally Advanced Prostate Cancer

Decisions regarding treatment should consider the patient’s tumour risk, treatment preferences, comorbidity, and life expectancy rather than chronologic age. Depending on
the disease status and life expectancy, senior men with localised prostate cancer can be managed with the following treatment options:

- Conservative (watchful waiting or active surveillance)
- Brachytherapy
- External beam radiotherapy
- Radical prostatectomy

Each of these options can be used with or without ADT.

- Randomised clinical trials have demonstrated improved prostate cancer–specific and overall survival from radiation therapy in combination with ADT as compared with radiation therapy alone in men with locally advanced prostate cancer. GnRH agonists should be started before or concurrent with radiotherapy and given for up to three years.
- Use of ADT in combination with brachytherapy or radical prostatectomy has not demonstrated improved overall survival.
  - One small, randomised clinical trial demonstrated that adjuvant ADT after prostatectomy in men with node-positive disease and other high-risk features (e.g., positive margins, involvement of seminal vesicles) might be beneficial, but more evidence is required to support its use in this setting (Table 3).

### Role of ADT in Various Clinical Settings of Prostate Cancer

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Role of ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>External radiotherapy for localised/locally advanced</td>
<td>In combination with external radiotherapy, ADT improves overall survival in men with locally advanced or intermediate and high-risk localised prostate cancer.</td>
</tr>
<tr>
<td>Brachytherapy for localised/locally advanced prostate</td>
<td>Neoadjuvant therapy with ADT has not been shown to improve overall survival</td>
</tr>
<tr>
<td>prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Radical Prostatectomy for localised/locally advanced</td>
<td>Neoadjuvant ADT does not improve overall survival. Adjuvant ADT in men with N0 disease does not improve overall survival.</td>
</tr>
<tr>
<td>prostate cancer</td>
<td>Adjuvant ADT in men with N+ disease (and other adverse histopathologic factors such as positive margins, involvement of seminal vesicles) may improve overall survival, but further clinical trials are needed.</td>
</tr>
</tbody>
</table>
Biochemical (PSA only) recurrence in advanced prostate cancer

No proof from randomised clinical trials that ADT in men with biochemical recurrence is beneficial. However, some men with recurrence at high risk for cancer specific death (e.g., Gleason score 8-10, PSA doubling time ≤ 3 months) may benefit from immediate ADT.

Asymptomatic disease

Optimal timing (immediate vs. deferred) of ADT remains controversial. In men who remain asymptomatic for a long time, ADT can be deferred.

Symptomatic cancer

ADT should be given immediately to palliate symptoms and prolong overall survival.

Abbreviations: ADT, androgen deprivation therapy; N, lymph node; PSA, prostate-specific antigen.

Older men are less likely to receive radical treatment for prostate cancer as compared with younger men, but there is a general trend for increasing use of primary ADT. Data from randomised clinical trials and large observational studies show that primary ADT may improve cancer-specific mortality but does not improve overall survival in older men and may even be detrimental (Table above).

**ADT in Advanced Prostate Cancer**

To optimise treatment with ADT in men with advanced prostate cancer, the following two principles should be followed:

- **Monotherapy with a GnRH agonist** can be recommended initially. A patient-based meta-analysis of more than 8,000 men demonstrated that addition of an anti-androgen [maximal androgen blockade (MAB)] did not improve overall survival significantly as compared with a GnRH agonist or bilateral orchidectomy alone. Monotherapy is also cheaper and less toxic.

- **Intermittent androgen blockade** may be an option if the serum PSA falls to a low level. Results from several small randomised clinical trials support non-inferiority of intermittent ADT as compared with continuous ADT in men with advanced prostate cancer. Recently, results of two large randomised trials, which evaluated intermittent hormonal therapy were published. While non-inferiority of intermittent hormonal therapy was demonstrated in men who had PSA relapse after radical radiotherapy, non-inferiority was not confirmed in men with metastatic prostate cancer when compared to continuous hormonal therapy. Literature-based meta-analyses suggest that these strategies lead to equivalent survival in men with initial reduction in PSA to low levels. The main advantages of intermittent ADT are less time on a potentially toxic therapy, better quality of life, and decreased costs of treatment. However, most of the randomised clinical trials evaluated MAB, which cannot be considered standard
of care, and future clinical trials should address intermittent versus continuous monotherapy.

Biochemical Relapse
Every third man after radical prostatectomy or radiotherapy experiences biochemical (PSA-only) relapse: only a subset of them will develop overt metastases, and an even smaller subset will die of prostate cancer. Radiation therapy is a potentially curative therapy for men with biochemical recurrence after radical prostatectomy if the source of increasing PSA is local recurrence. ADT is not curative, and there is no evidence from randomised clinical trials to support its use in men with biochemical recurrence. Results of a recent population-based outcome study shows no survival benefit of immediate ADT (started within 3 months of PSA relapse) when compared with deferred ADT initiation (started at least two years after PSA relapse or at clinical progression and short PSA doubling time) among prostate cancer patients with PSA-only relapse. It may be reasonable to consider treatment with ADT only in a subgroup of men with PSA relapse, who have a high risk for cancer-specific death (e.g., PSA doubling time ≤ 3 months, Gleason score 8–10, and short time from primary local treatment to the development of recurrence) (Table above).

Metastatic Prostate Cancer
Men with symptomatic metastatic prostate cancer should be treated with ADT. However, many men with metastases diagnosed by computed tomography or bone scan remain asymptomatic for a long time: it is reasonable to offer ADT to men with asymptomatic metastatic disease and rapidly rising PSA but not to those with slow progression.

Initially, more than 80% of patients respond to GnRH agonists or bilateral orchidectomy, but their disease will eventually progress after a median of 18 to 20 months. Three trials (GETUG-AFU-15, CHAARTED and STAMPEDE) have evaluated the upfront use of docetaxel in combination with ADT for men with metastatic prostate cancer. Two of these trials showed improved survival in the group given docetaxel. Most of the patients on these trials had high volume metastases at diagnosis and docetaxel should be recommended with ADT for fit men with a high burden of metastatic disease at time of diagnosis. ADT alone should remain standard for men with low burden disease and for those presenting with metastases several years after diagnosis of localised prostate cancer.

At progression, about one-third of men respond to the addition of an anti-androgen, and about 10 - 20% of those patients who respond and then progress will respond to withdrawal of the anti-androgen. Some men may respond to further hormonal therapies including dexamethasone, ketoconazole, or oestrogen (Table 3); their activity can be explained by (i) suppressed production of adrenal androgens (e.g., ketoconazole and dexamethasone) and (ii) direct anticancer effects (e.g., oestrogens and dexamethasone). However, none of these agents has demonstrated improvement in survival. In the light of new, more effective hormonal agents (i.e. abiraterone acetate and enzalutamide) further
hormonal therapies such as dexamethasone, ketoconazole and oestrogen can be recommended only in countries where abiraterone acetate and enzalutamide are not available. Results of trials evaluating these agents in chemotherapy-naïve men with mCRPC also show delayed progression and improved survival. These agents can now be recommended at time of progression after initial ADT, whether or not this is given with docetaxel chemotherapy.

There is evidence that the androgen receptor remains a valid target in men with metastatic castrate-resistant prostate cancer (mCRPC). Abiraterone acetate and enzalutamide are effective new hormonal agents with a favourable benefit-risk profile. While abiraterone acetate blocks production of androgens in the adrenal gland and in metastases by the inhibition of the CYP17A1 enzyme, enzalutamide potently blocks the androgen receptor and signalling from it. In pivotal trials both agents have been shown to improve overall survival and quality of life of men with mCRPC who were previously treated with chemotherapy.

**Side Effects of ADT**
The risk of treatment with GnRH analogues needs to be assessed carefully in older men with prostate cancer. Well-recognised side effects include hot flashes, muscle loss, anaemia, sexual dysfunction, and gynecomastia, all of which can decrease quality of life. ADT can also increase risk for more serious and potentially life-threatening side effects such as metabolic syndrome, cardiovascular disease, and bone fractures. These toxicities can appear after a short period (e.g., months) of therapy with GnRH agonists and are particularly salient for a senior population. All men receiving ADT should receive calcium and vitamin D supplementation and should have evaluation of bone density periodically; annual treatment with zoledronic acid or treatment with denosumab every 6 months can prevent bone loss in those at risk. Health professionals should also evaluate cardiovascular risk when prescribing ADT to older men with prostate cancer, especially in settings without compelling evidence for its use (Table below).

Concurrent use of prednisone with abiraterone acetate decreases the risk for development of symptoms related to mineralocorticoid excess (hypokalaemia, hypertension and oedema). Some men experience severe fatigue with the newer hormonal agents, especially enzalutamide.

**Major Side Effects of Androgen Deprivation Therapy**

<table>
<thead>
<tr>
<th>Androgen deprivation therapy</th>
<th>Major side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH agonists</td>
<td>• Male menopausal symptoms</td>
</tr>
<tr>
<td></td>
<td>• Muscle loss</td>
</tr>
<tr>
<td></td>
<td>• Bone loss/fractures</td>
</tr>
<tr>
<td></td>
<td>• Loss of libido, impotence, gynecomastia</td>
</tr>
</tbody>
</table>
| Anti-androgens (major drug-specific side effects) | Metabolic syndrome, diabetes, cardiovascular disease  
|  | Anaemia  
|  | Male menopausal symptoms  
|  | Gastrointestinal disturbance (bicalutamide, flutamide)  
|  | Gynaecomastia/mastodynia (bicalutamide)  
|  | Occular toxicity (nilutamide)  
|  | Pulmonary toxicity (nilutamide)  
| Miscellaneous | Cardiovascular disease (oestrogens)  
|  | Liver toxicity, gastrointestinal disturbance (ketoconazole)  
|  | Dermatologic toxicity (ketoconazole)  
|  | Diabetes (prednisone)  
|  | Hypertension (prednisone)  

Abbreviation: GnRH, gonadotropin-releasing hormone.

**Further Reading**

Chapter 08 – Cytotoxic and Targeted Anti-Cancer Treatment in the Senior Cancer Patient

Introduction
Systemic anti-cancer therapy is a mainstay in the fight against cancer. Chemotherapy is highly effective in attacking tumour cell spread all over the body. However, chemotherapy is sometimes related with significant toxicity.

- In some settings such as large-cell non-Hodgkin lymphoma (NHL), the benefits of chemotherapy can be much greater than the potential side effects.
- In other settings such as in many metastatic solid tumours, the absolute benefits are less extensive, and side effects and quality of life are of utmost importance.

In senior individuals, the potential for harming patients with chemotherapy is even higher than that in the younger population. It is hoped that the upcoming targeted therapies will have a better therapeutic index and can be more beneficial in older cancer patients. However, clinical experience shows that caution is also warranted with targeted therapy in older patients.

Chemotherapy in Senior Adults
Indications
In principle, the same indications for chemotherapy are present in older and younger cancer patients. There may, however, be specific concerns.

- In curative settings, such as treatment of large-cell NHL, chemotherapy dose intensity is crucial. This type of NHL is aggressive with very poor prognosis if untreated. Soft/low-dose regimens have been shown to be clearly inferior to standard therapy but can still provide benefit to patients if standard therapy is too toxic.
- In adjuvant settings of solid tumours, such as colorectal and breast cancer, the absolute benefits of chemotherapy are usually rather small and generally limited to 5% to 10% of patients, while all patients are exposed to potential toxicity. Moreover, the risks of chemotherapy increase with age, such as the risk of myelosuppression or cardiac failure with anthracyclines. It has also been shown that lowering the dose or dose intensity or choosing “soft” chemotherapy such as capecitabine for breast cancer is inferior to standard therapy. The decision of giving adjuvant chemotherapy is thus a delicate decision integrating the absolute risk of recurrence (based on tumour characteristics) and based on patient characteristics such as life expectancy, comorbidity, and the patient’s desire. If the decision is made to administer adjuvant chemotherapy, adequate dosing and regimens are warranted.
In metastatic settings of solid tumours, the goal is palliation and tumour control without causing excessive toxicity. Chemotherapy can be helpful, but continuous monitoring is required to ensure that toxicity is not taking the upper hand.

Considerations in the Use of Chemotherapy in Older Individuals
If the decision to give chemotherapy is made, it is important to keep in mind some specific age-related aspects summarised throughout this chapter.

Side Effects in Older Individuals
Elderly patients have a decreased tolerance to chemotherapy in general, with increased incidence of various toxicities. Some side effects are rather drug specific, such as cardiac failure with anthracyclines, or neuropathy with taxanes/cisplatin.

- Myelosuppression is a more general side effect and is the major dose-limiting toxicity of many modern chemotherapeutic drugs. Initial retrospective analyses of data from clinical trials in patients with solid tumours showed no correlation between age and myelosuppression.

Considerations When Using Chemotherapy in Senior Individuals
- Treatment individualisation: Senior adults are the utmost example of heterogeneity, and adaptation to the individual situation is always required
- Geriatric assessment: Geriatric assessment is the best way to obtain a more global view on the general health situation of the patient and is advised in all cancer patients > 70 years of age
- Supportive or protective agent: Antiemetics, growth factors, pain killers, and anti-diarrhoeal drugs can be crucial to continue treatment
- Risk of drug interactions: Polypharmacy is frequent in senior adults, and there is a great risk for drug interactions and potentially increased toxicity
- Compliance: Compliance can be an important issue undermining the efficacy of chemotherapy (mainly for oral cytostatics) or potentially increasing toxicity (if supportive drugs are not taken appropriately at home)
- Possibility of less toxic therapy: There might be good alternatives in some situations for chemotherapy, such as hormonal therapies, local radiotherapy, or surgery for localised problems
- Maintain adequate hydration: Elderly patients have a tendency to drink less, especially when feeling ill, and are more intolerant of hydration. Poor hydration can lead to decreased clearance and increased toxicity, especially for drugs subject to renal excretion
- Define the aim of chemotherapy: It is crucial to realise why chemotherapy is given. The need for maintaining dose and dose intensity can be very different depending on the setting
• Renal function: Renal function declines continuously with ageing, and comorbidity can even further compromise renal function in the elderly. Moreover, many cytostatic drugs are renally excreted. If renal function declines and the same dose of chemotherapy is given, global exposition [e.g., as defined by area under the curve (AUC)] can markedly increase with accompanying increased toxicity. Dose adaptation, according to renal function, is thus mandatory to avoid excessive toxicity. The International Society of Geriatric Oncology (SIOG) has made specific guidelines on the determination of renal function in elderly, as well on dose adaptation of specific chemotherapeutic agents in renal dysfunction.

• Be aware of pharmacological and clinical data for specific chemotherapy drugs: For most classical chemotherapeutic drugs, at least some data are available on age-related pharmacokinetics and dosing (see also Tables below). Oncologists should be aware of these data, and take them into account when prescribing chemotherapy to older individuals. However, it should be stated that dose adaptation based on age-related pharmacological changes is an unvalidated approach since clinical trials prospectively testing the efficacy and toxicity of age-related dose adaptation versus standard dosing are lacking.

Severe selection bias was present in these studies however, limiting the generalisation of these conclusions to the whole geriatric population. More recent data clearly show that the risk of neutropenia increases with age, for instance in NHL or breast cancer. Because of the increased risk of neutropenia and related complications in senior adults, and the potential for better outcomes when maintaining dose intensity in certain settings, prophylaxis with a colony-stimulating factor starting in the first cycle should be considered in elderly patients.

• Mucositis (intestinal and/or oral) is a common side effect of several chemotherapeutic drugs, for example, irinotecan and 5-fluorouracil. Older persons appear to be more susceptible to this side effect, and aggressive and effective management of these and other side effects is crucial in senior adults.

**Pharmacokinetic Parameters That Might Change with Ageing and Might Influence Efficacy/Toxicity of Chemotherapy**

<table>
<thead>
<tr>
<th>Parameter changes</th>
<th>Clinical consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption: decreased</td>
<td>Oral chemotherapy (e.g., capecitabine) might be less effective in elderly</td>
</tr>
<tr>
<td>Volume of distribution: decreased</td>
<td>Serum concentrations and toxicity of several chemotherapeutics might increase (e.g., cisplatin, taxanes, etoposide, irinotecan)</td>
</tr>
</tbody>
</table>
Hepatic metabolism: decreased | Not well known, may affect serum concentrations of chemotherapeutics eliminated by hepatic metabolism (e.g., taxanes, cyclophosphamide, anthracyclines)
Renal excretion: decreased | Dosing should be adapted to present recommendations to avoid excessive serum concentrations and toxicity from renally excreted chemotherapeutics (e.g., carboplatin, topotecan, methotrexate)

Targeted Therapies in Senior Adults

Targeted therapies do not induce classical side effects of chemotherapy in general (e.g., hair loss, deep neutropenia, nausea, and vomiting) and are certainly promising for elderly individuals, but care is warranted since specific side effects might also occur.

- In HER-2/neu-positive breast cancer, trastuzumab was the first modern “targeted therapy” established with a favourable safety profile. However, age was a documented risk factor for congestive heart failure in patients receiving trastuzumab although this probably depends more on pre-existing comorbidities than on age by itself.
- Angiogenesis inhibitors can cause thrombosis and hypertension, and age is an important risk factor.
- For instance, a pooled analysis of bevacizumab-treated patients with all types of cancer from five randomised trials demonstrated that patients >age 65 are at increased risk of arterial thromboembolic events, particularly when bevacizumab was given in combination with chemotherapy.
- With small-molecule tyrosine kinase inhibitors of angiogenesis, a higher incidence of cardiac failure has been demonstrated and is of great concern for the senior population that often has cardiac comorbidity.

A major problem is that most clinical trials only include “healthy” senior patients, so results and toxicity data cannot be extrapolated to the general senior population. It is crucial that upcoming targeted therapies are also studied in senior patients to establish the safety and efficacy in that particular population.

Besides efficacy and toxicity, also the costs and cost-effectiveness of new (mostly expensive) drugs is becoming more and more of an issue. It should be acknowledged that benefits of new drugs might not be the same in old and young people. Competing risks of death in senior adults (i.e. dying from another cause without relation to the cancer) can decrease the cost-effectiveness of expensive therapies. On the other hand, older...
people should not be systematically denied new therapies, and the avoidance of both undertreatment and overtreatment remains the major challenge for oncologists treating older cancer patients.

**Age-Related Effects on Pharmacokinetics of Frequently Used Chemotherapeutics and Consequences**

*Topo-isomerase inhibitors*
- **Etoposide** (topo II)
  - High variability in oral absorption.
  - Increased AUC and toxicity in elderly.
  - Dose adaptation according to albumin, bilirubin, and renal function should be considered.
- **Irinotecan** (topo I)
  - Increased AUC and diarrhoea in elderly.
  - A lower dose (e.g., 300 mg/m² q3w instead of 350 mg/m² q3w) could be considered for age >70.
- **Topotecan** (topo I)
  - Adapt to renal function.
  - Consider weekly regimens (less myelosuppression).
  - Antimetabolites
- **Methotrexate**
  - AUC possibly increased.
  - Adapt to renal function.
- **Fluorouracil**
  - PK and toxicity not majorly influenced.
- **Capecitabine**
  - Lower dose such as 1000 mg/m² bid instead of 1250 mg/m² seems equally effective with less side effects.
  - Adapt to renal function.
- **Gemcitabine**
  - Unpredictable PK.
  - Generally good tolerance in elderly.

*Antitumour antibiotics*
- **Doxorubicin**
  - Increased peak plasma concentrations.
  - Increased myelosuppression and cardiotoxicity.
  - At full dose (e.g., CHOP, AC) relatively toxic.
  - Possible solutions:
    - Dose reduction if being given in palliative setting
    - Alternative administration regimens: e.g., weekly
• Liposomal forms
• Removal of doxorubicin in lymphoma regimens
• Growth factors

Abbreviations: PK, pharmacokinetics; AUC, area under the curve; PD, pharmacodynamics; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; AC, doxorubicin and cyclophosphamide.

Source: Courtesy of Elsevier.

Further Reading

Chapter 09 - Diffuse Large B-Cell Lymphoma in the Elderly: R-CHOP or Adapted Strategy?

Introduction
Life expectancy has been increasing dramatically in the last century and it is thought that it will reach a median of 85 years for women and 80 years for men by 2030. Non-Hodgkin's Lymphoma (NHL) represents the fifth most frequent cancer in men and the sixth in women. Diffuse large B cell lymphoma (DLBCL) is the most frequent NHL in developed countries and its incidence increases with age: more than 50% of patients with DLBCL are older than 60 years and almost one third of patients are over 75 years. DLBCL will be the cause of death for these patients unless an adapted treatment strategy with a curative intent is applied. In the absence of comorbidities, patients with DLBCL older than 70 years survive as long as younger patients. Therefore, the poor outcome of elderly patients may partially be due to the presence of concomitant disease that may alter the possibility of receiving a full-dose chemotherapy regimen. Another reason may be because of the subtypes of DLBCL seen in older patients: the germinal centre-like (GC) subtype, associated with a better outcome, is usually seen in patients 8 years younger than those with the activated B cell (ABC) subtype.

Although there is no established age limit used to define elderly patients, most studies classify patients over 65 or 70 years as elderly. Chronological age is not a good definition of elderly. A better definition is the presence of another active disease that contraindicates high-dose chemotherapy for patients over 65 years who may therefore not tolerate the standard R-CHOP and this could be used as an alternative definition of elderly patients with DLBCL.

Initial Clinical and Biological Evaluation of Patients and the Disease

Disease Evaluation
As for younger patients, the initial staging of the lymphoma includes clinical evaluation, relevant laboratory tests, bone marrow biopsy, positron emission tomography scans (whenever possible) and computed tomography scans. Electrocardiography and echocardiography must be performed to exclude a contraindication to anthracyclines, i.e. a left ventricular ejection fraction (LVEF) < 50%.

The International Prognostic Index (IPI) predicts survival better than the Ann Arbor (AA) staging system. The age adjusted IPI (aaIPI) (Table 1), a simplified score based on lactate dehydrogenase (LDH), AA stage and ECOG-performance status (PS), has been developed and is now currently used to stratify patients for therapeutic choice.

Table 1: Age-adjusted IPI score:
### Age-adjusted International Prognostic Index (IPI)

<table>
<thead>
<tr>
<th>Age-adjusted Index (IPI)</th>
<th>International Prognostic Score</th>
<th>5-year relapse-free survival (%)</th>
<th>5-year overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>86</td>
<td>83</td>
</tr>
<tr>
<td>Low-intermediate</td>
<td>1</td>
<td>66</td>
<td>69</td>
</tr>
<tr>
<td>High-intermediate</td>
<td>2</td>
<td>53</td>
<td>46</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>58</td>
<td>32</td>
</tr>
</tbody>
</table>

Adverse risk factors for age-adjusted IPI are: stage III or IV disease, elevated LDH, ECOG performance status ≥ 2.

IPI, international prognostic index; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group


### Patient Evaluation

Comorbidities should be evaluated using scales such as the Charlson Index or the Cumulative Illness Rating Scale (CIRS-G). Patients presenting with comorbidities are more likely to experience treatment toxicity. Alterations in kidney or liver function and other frequent concomitant medication modify drug pharmacokinetics, pharmacodynamics and tolerance. Haematopoietic reserve capacity decreases with age and myelotoxicity increases.

Another consequence of aging is the possible alteration of functional capacity, which is a very heterogeneous phenomenon. The comprehensive geriatric assessment (CGA) is a multidimensional scoring process used to estimate the medical, psychological and functional status of older patients. It has been shown to predict survival and tolerance to chemotherapy independently from PS. The instrumental activities of daily living (IADL) and activity of daily living (ADL) scales evaluate the ability to perform the fundamental functions required to allow an individual to live independently in a community setting (termed “instrumental activities of daily living”). Among the alterations associated with aging, nutrition is one of the most important.

The presence of DLBCL is sufficient to alter the functional capacity of elderly patients and chemotherapy with intent to cure (in this case, R-CHOP) is the best way to improve this. It is often difficult to differentiate between alterations in functional capacity arising due to the lymphoma or as a secondary effect of diseases already present in the patient.
Treatment: First-Line Strategy
Therapeutic decisions in elderly patients should be based on the aaIPI score and a CGA. Many of these patients present with a good PS, allowing the administration of standard-dose chemotherapy regimens. Several studies agree that, with an optimal treatment strategy, elderly patients can have a similar outcome to younger patients. There is now a consensus that most patients, in the absence of specific contraindications and regardless of their age, should be treated with regimens that include anthracyclines. Active supportive care, such as nutrition, neutropaenia prophylaxis, and, if absolutely necessary, reduced dose intensity, should always be combined with chemotherapy.

Treatment of Fit Elderly Patients with Localised DLBCL
In the population of elderly patients with localised disease and no adverse prognostic factors (aaIPI = 0), the question of radiotherapy efficacy has been raised in a randomised trial performed by GELA (Groupe d'Etudes des Lymphomes de l’Adulte). The results did not show any benefit of adding radiotherapy to the CHOP regimen for these patients (Bonnet et al, 2007).

In the immunochemotherapy era and based on results from a phase III prospective trial, 6 cycles of R-CHOP every 3 weeks is the recommended regimen. Central nervous system (CNS) prophylaxis is not recommended and lumbar puncture can be stopped after a normal initial evaluation.

Treatment of Fit Elderly Patients with Poor-Risk Disease
In 1998, GELA conducted the first phase III study that randomised fit elderly patients (i.e. 60 to 80 years, median 70 years) with stage II to IV disease to receive either 8 cycles of CHOP or rituximab plus 8 cycles of CHOP. The trial successfully showed that the R-CHOP regimen improved complete response (CR) rate, progression-free survival (PFS) and overall survival (OS), with a benefit still present after 10 years. Additional phase III studies confirmed these results, without any increase in benefit shown for R-CHOP every 2 weeks compared to every 3 weeks.

A phase II study of lenalidomide plus R-CHOP conducted by the Fondazione Italiana Linfomi (FIL) in patients 60 to 80 years with diagnosed and untreated AA stage II-IV DLBCL showed an overall response (OR) of 92% and a CR of 86% without grade 4 haematological toxicities or toxic deaths. These results have been confirmed by another study carried out at the Mayo Clinic.

Maintenance strategies have also been evaluated in this population of patients. Rituximab maintenance did not show any benefit. However, it might improve outcome in the subgroup of male elderly patients, as shown in the NHL13 study. A maintenance strategy with lenalidomide is currently being evaluated in the LYSA REMARC trial (NCT01122472).
If there is no initial CNS involvement, prophylaxis should be reserved for patients with high risk of CNS relapse (those who present with aalPI>1) or special localisation (vertebra, testis or breast, cavum, sinus and ethmoid).

Treatment with a Regimen Adapted to the CGA
Few studies have investigated the results of adapting the treatment strategy according to the outcome of an initial evaluation including a CGA. An Intergruppo Italiano Lymphoma (IIL) prospective study of 100 patients (aged ≥70 years) aimed to evaluate the feasibility of chemotherapy dose modulation based on ADL and IADL scales, evaluated by a CGA (Spina et al, 2012). Treatment resulted in a CR rate of 81%, and OS was 60% at 5 years. Overall, this study showed that chemotherapy dose modulation based on a CGA is associated with manageable toxicity and excellent outcomes in elderly patients with DLBCL. Results from other studies underlined the fact that frail patients who received less intensive regimens have a poorer outcome. The benefits of adapting treatment regimens according to the outcomes of a CGA are difficult to evaluate as the different studies included a variable, and frequently low, number of frail patients. Therefore, dose modification conditions cannot yet be standardised.

Very Elderly Patients (> 80 years)
This population is the one with the most important unmet medical need. A retrospective analysis in 278 patients aged over 80 years with NHL from the GELA group reported a similar clinical and biological presentation as observed in younger patients but huge differences in terms of disease management, with only 32% of patients treated with anthracyclines. Comorbidities were found in 87% of patients, but only 14% had a high Charlson Index. The decision to not treat the patient relied on a subjective estimation of physiological age in 19% of cases. The median OS was 2.2 years and NHL remained as the main cause of death. In multivariate analysis, the presence of comorbidities was not a relevant prognostic factor.

GELA conducted the first prospective phase II trial in patients older than 80 years with DLBCL using an attenuated regimen containing an anthracycline and rituximab: R-miniCHOP (doses of doxorubicin, vincristine, and cyclophosphamide reduced by 50%). The study included 150 patients with a median age of 83 years. Two-year PFS and OS were 47% and 59%, respectively, with 20% of deaths related to toxicities and 60% to lymphoma. The full planned dose regimen was administered to 72% of patients. Serum albumin level was the strongest prognostic factor for survival.

The same group recently published a retrospective analysis of lymphoma occurring in patients over 90 years of age. The median age was 92 years and more than 80% had DLBCL. The OS in patients who received a systemic treatment (57%) was longer compared to untreated patients in the group of patients with aggressive lymphoma but not for indolent lymphoma. Low albumin level was a strong prognostic factor.
Based on these different studies, R-miniCHOP without CNS prophylaxis is the standard of care for very elderly patients. An initial prephase with prednisone or vincristine may be considered.

Different studies have evaluated the efficacy of regimens with a reduced dose intensity (described in Table 2). These regimens show acceptable results for the very elderly or for frail elderly with comorbidities, although the evaluation of the studies is not easy as they included different percentages of frail patients and very elderly patients.

Table 2: Prospective studies with a reduced dose intensity in the rituximab era

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>regimen</th>
<th>RDI</th>
<th>CR</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peyrade (2011)</td>
<td>149</td>
<td>83 (80-95)</td>
<td>R-miniCHOP</td>
<td>Doxorubicin 50%</td>
<td>63%</td>
<td>2y 47%</td>
<td>2y 59%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Endoxan 53%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spina (2012)</td>
<td>100</td>
<td>75 (70-89)</td>
<td>RCHOP</td>
<td>Fit 100% Frail 75%</td>
<td>70-80y: 83% &gt;80y: 80%</td>
<td>5y 60%</td>
<td>5y 80%</td>
</tr>
<tr>
<td>Olivia (2012)</td>
<td>91</td>
<td>74 (65-92)</td>
<td>RCHOP RCDOP miniCHOP</td>
<td>RCHOP 100% Comorbidities: RCDOP, LD 40% Frail: Endoxan 50% Doxorubicine 50% Vincristine 40%</td>
<td>81% 64% 50%</td>
<td>2y 72% 2y 65% 2y 52%</td>
<td>2y 70% 2y 48%</td>
</tr>
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<tr>
<td>Gimeno (2011)</td>
<td>35</td>
<td>76 (61-88)</td>
<td>RCMyOP</td>
<td>NPLD 40% Vincristine 24%</td>
<td>69%</td>
<td>2y 58%</td>
<td>2y 70%</td>
</tr>
<tr>
<td>Meguro (2012)</td>
<td>61</td>
<td>70+</td>
<td>R-CHOP</td>
<td>70%</td>
<td>75%</td>
<td>3y 45%</td>
<td>3y 58%</td>
</tr>
<tr>
<td>Musolino (2011)</td>
<td>23</td>
<td>77 (70-90)</td>
<td>DA-POCH-R</td>
<td>Doxorubicin and endoxan 20% based on NADIR</td>
<td>57%</td>
<td>3y 54%</td>
<td>3y 56%</td>
</tr>
<tr>
<td>Shin (2012)</td>
<td>85</td>
<td>60+</td>
<td>RD-RCHOP</td>
<td>Endoxan 20% Doxorubicin 60% Vincristine 40%</td>
<td>67%</td>
<td>72%</td>
<td>83%</td>
</tr>
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</tr>
<tr>
<td>Merli (2012)</td>
<td>224</td>
<td>72 (64-86)</td>
<td>RminiCEOP vs RCHOP</td>
<td>Epirubicin, vinblastine 0%</td>
<td>68%</td>
<td>73%</td>
<td>5y 46%</td>
</tr>
</tbody>
</table>

RDI: % of reduced dose intensity  
CR, complete response; EFS, event-free survival; OS, overall survival  
CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone  
RCHOP, rituximab plus CHOP  
RCDOP: doxorubicin replaced by pegylated liposomal doxorubicin (LD) at 30 mg/m²  
R-miniCEOP: cyclophosphamide, epirubicin, vinblastine, prednisone, rituximab  
RCMyOP: intermediate dose of non-pegylated liposomal doxorubicin  
R-miniCHOP, doses of doxorubicin, vincristine, and cyclophosphamide reduced by 50% compared with RCHOP  
NPLD, non-pegylated liposomal doxorubicin  
DA-POCH-R, rituximab plus dose-adjusted infusional CHOP  
RD-RCHOP, reduced-dose CHOP plus rituximab

### Treatment of Patients with a Contraindication to Anthracyclines

The main contraindication to anthracyclines is cardiac dysfunction (LVEF<50%). A recent American study from the SEER medicare database suggests that elderly patients with DLBCL and contraindication to anthracyclines can be efficiently treated.

A non-pegylated liposomal doxorubicin may be an option in this patient population, as it seems to induce less cardiotoxicity than doxorubicin. A recent Italian phase II study evaluated the R-COMP regimen, in which doxorubicin is replaced by non-pegylated liposomal-encapsulated doxorubicin (NPLD) in untreated elderly patients with poor-risk DLBCL and moderate to high 'life threat' impact NIA/NCI cardiac comorbidity. Results were similar or slightly inferior to those obtained with R-CHOP in the study by Coiffier et al: the CR rate was 68% compared to 76%. Cardiotoxicity was not prevented: the incidence of cardiac events was 17%, making this drug less appealing.

Other analogues of doxorubicin, such as piparubicin, have also been evaluated, although no differences in outcome were observed in these studies. These results must be taken with caution as the CR rates observed with the R-CHOP regimen were lower than in other studies.

Different chemotherapies have been tested as a replacement for doxorubicin. Doxorubicin was substituted for etoposide in the CHOP regimen in a trial by the British
Columbia group. This resulted in a 5-year OS of 49%, which is certainly lower than that observed with R-CHOP but satisfying in this patient population. In this indication, bendamustine showed disappointing results in association with rituximab.

Finally, the use of dexrazoxane (an iron chelator) with anthracyclines to prevent the risk of congestive heart failure is not universally recommended due to concerns over its efficacy and safety.

**Treatment: At Relapse**

It is generally recognised that the prognosis of elderly patients at relapse is very poor, with few therapeutic possibilities and a median OS of a few months. There is a benefit of high-dose therapy with autologous stem cell transplantation (ASCT) for younger patients who respond to salvage therapy. However, the majority of elderly patients will not be fit enough to tolerate such intensive treatment, although it should be considered (see below).

The outcome of re-treated patients was described in the initial R-CHOP trial performed by GELA. Of the 399 patients included in the trial, 202 (50.6%) experienced relapse or progression, including 125 (63%) in the CHOP arm and 77 (38%) in the R-CHOP arm. Salvage chemotherapy regimens were mainly dexamethasone, cisplatin, and cytarabine (DHAP); etoposide, cytarabine, cisplatin, and methylprednisolone (ESHAP); or ifosfamide, carboplatin, and etoposide (ICE). The 2-year survival rate of re-treated patients was similar between the two arms: 26% and 31% for the CHOP and R-CHOP arms, respectively. Relapsing patients who received a salvage regimen including rituximab had a better 2-year survival rate than those who received a salvage regimen without rituximab (58% versus 24%). Nevertheless, patients who were refractory to initial therapy, with an initial PFS of less than 1 year, did not show a difference in survival according to the presence or absence of rituximab in their salvage treatment.

The immunomodulator lenalidomide could also be an option for elderly patients who relapse as data are emerging on its efficacy for treating relapsed-refractory DLBCL. Zinzani et al. recently conducted a phase II trial to evaluate the efficacy of lenalidomide plus rituximab followed by lenalidomide maintenance in elderly patients with relapsed or refractory DLBCL. Among the 23 patients included in the trial, 7 achieved a CR and one patient with a partial response (PR) after induction converted to a CR with lenalidomide maintenance therapy. The median duration of the response was 32 months and estimated OS at 18 months was 55%.

Less toxic regimens with a continuous administration of low-dose chemotherapy and/or rituximab may also be proposed. Finally, palliative care alone might be an option for patients with a poor PS, with the intention of maintaining the best quality of life at home for as long as possible.
As for initial treatment, age itself should not be a contraindication to ASCT. The European Blood and Marrow Transplantation group conducted a retrospective study of 463 patients aged over 60 years of whom 23% were in first CR and 71% in second or more CR or in PR at time of ASCT. The non-relapse mortality rate was higher in elderly patients when compared to the younger patients included in the study (n=2149): 4.4% versus 2.8% at 100 days of ASCT and 10.8% versus 6.5% at 3 years, respectively. The risk of relapse was also higher for elderly patients when compared with younger patients: 38% with a median follow-up of 12 months for the elderly surviving patients and 32% at 15 months for the younger group. Consequently, PFS and OS were longer in the group of younger patients (PFS at 3 years 51% versus 62% and OS at 3 years 60% versus 70%, for elderly and younger patients respectively). In multivariate analysis, factors associated with non-relapse mortality were: age over 60 years, two or more lines of therapy prior to ASCT, poor PS, and refractory disease at ASCT.

These results indicate that ASCT is possible in elderly patients, but with a higher treatment-related mortality than in younger patients.

**Conclusion**

All the prospective studies performed in NHL show that age itself should not be a reason to move away from conventional therapy. The standard immunochemotherapy used for this malignancy, R-CHOP, should also be the recommended strategy for elderly patients with DLBCL. The main question is: which elderly patients can or cannot receive this regimen? As life expectancy for these patients is superior to 5 years, the aim of the physician must be to restore the same quality of life to the patient that they were experiencing prior to the DLBCL. A palliative intent in first line must be reserved for those patients with major organ failure preventing any administration of chemotherapy or immunotherapy.

Among the comorbidities or alterations in physiological functions, the nutritional status, simply evaluated with serum albumin, and a poor or decreased mobility capacity seem to be key factors that influence which patients can receive R-CHOP. In the rituximab era, a reduction in chemotherapy dose, mainly regarding anthracyclines, can still provide very good results.

**Further Reading**

- Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard


Chapter 10 - Management of Chronic Myeloproliferative Neoplasia (MPN) in Elderly Patients

Diagnosis and Classification of Myeloproliferative Disorders

Myeloproliferative neoplasia (MPN) are relatively rare chronic haematologic malignancies that include the classic myeloproliferative disorders, such as the Philadelphia chromosome-negative essential thrombocythemia (ET), polycythaemia vera (PV), primary myelofibrosis (PMF) and Philadelphia chromosome-positive chronic myelogenous leukaemia (CML). Typical myeloproliferative disorders include molecularly defined platelet-derived growth factor (PDGFR) A-rearranged eosinophilic/mast cell disorders; PDGFR B-rearranged eosinophilic disorders; systemic mastocytosis associated with c-kit mutation; 8p11 myeloproliferative syndrome; and juvenile myelomonocytic leukaemia with recurrent mutations of RAS.

Ph-negative MPD are usually diagnosed later in life, at a median age of 60 years of age, which is also the median age of CML diagnosis. A considerable proportion of this patient group is above 60 years of age at diagnosis, including a relevant proportion over 70 years of age. The median survival of patients with MPN is relatively long, resulting in a comparatively high prevalence of elderly patients with MPN. Despite this clinical reality, specific treatment considerations in the era of targeted therapies, within this patient population, have not been sufficiently addressed in clinical trials.

Independent of patient age, since 2008 MPNs have been classified according to the revised World Health Organization (WHO) classification (for diagnostic criteria see Table 1). The required diagnostic procedures are outlined as follows: physical examination, examination of a blood sample, a bone marrow biopsy including molecular biology (analysis of classical cytogenetics, fluorescence in situ hybridisation [FISH] for detection of the Philadelphia chromosome and mutation analysis for diagnosis of JAK-2, and if needed mutations in the Calreticulin Exon 9 or the MPL gene). An enlarged spleen is often detected by physical examination, but ultrasound or computed tomography (CT) scans may occasionally be necessary to define spleen size in more detail. These are particularly helpful to follow spleen size reduction during therapy with novel drugs, such as JAK-inhibitors.

Table 1. Diagnostic criteria for myeloproliferative disorders according to the revised World Health Organization (WHO)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>CML</th>
<th>ET</th>
<th>PV</th>
<th>PMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>1. BM biopsy showing hyperplasia of</td>
<td>1. Sustained platelet count ≥ 450 x 10^9/L</td>
<td>1. Haemoglobin &gt; 18.5 g/dL in</td>
<td>1. Presence of megakaryocyte proliferation and</td>
</tr>
</tbody>
</table>

ESMO Handbook on Cancer in the Senior Patient
2. Detection of Philadelphia chromosome by conventional cytogenetics and by FISH

3. Detection of the BCR-ABL fusion transcript by PCR

during work-up period

2. BM biopsy showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes; no significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis

3. Not meeting WHO criteria for PV, PMF, CML, MDS, or other myeloid neoplasm

4. Demonstration of JAK2617V>F or other clonal marker, or in the absence of a clonal marker, no evidence for reactive thrombocytosis

men, 16.5 g/dL in women or other evidence of increased red cell volume

2. Presence of JAK2617V>F or other functionally similar mutation such as JAK2 exon 12 mutation

atypia, usually accompanied by either reticulin and/or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterised by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)

2. Not meeting WHO criteria for PV, PMF, CML, MDS, or other myeloid neoplasm

3. Demonstration of JAK2617V>F or other clonal marker (eg, MPL515W>L/K), or in the absence of a clonal marker, no evidence of BM fibrosis due to underlying inflammatory or other neoplastic diseases
<table>
<thead>
<tr>
<th>Minor</th>
<th>1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation</th>
<th>1. Leukoerythroblastosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Serum erythropoietin level below the reference range for normal</td>
<td>2. Increase in serum lactate dehydrogenase level</td>
<td>2. Increase in serum lactate dehydrogenase level</td>
</tr>
<tr>
<td></td>
<td>4. Palpable splenomegaly</td>
<td>4. Palpable splenomegaly</td>
</tr>
</tbody>
</table>

Abbreviations: BM, Bone Marrow; FISH, fluorescence *in situ* hybridisation; PCR, polymerase chain reaction; WHO, World Health Organization; PV, polycythemia vera; PMF, primary myelofibrosis; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome

**For Diagnosis of PV**  
The presence of both major and 1 minor criterion or the presence of the first major criterion together with 2 minor criteria is required.

**For Diagnosis of ET**  
All 4 major criteria are required.

**For Diagnosis of MF**  
Diagnosis requires meeting all 3 major criteria and 2 minor criteria.
Treatment Strategies of Chronic Myeloid Leukaemia (CML) in the Senior Patient

Nowadays, elderly patients generally get access to targeted therapeutics. Imatinib is most frequently used in this patient population. Only limited data on second or even third generation tyrosine kinase inhibitors (TKI) in elderly patients are available. Recent data from large multicentre studies from the German CML study group, as well as the Italian GIMEMA CML Working Party, have addressed this particular issue in more detail.

Efficacy of Imatinib in Senior Patients

Both studies compared patients enrolled in phase III trials, below 65 years of age versus those patients ≥65 years of age. The median daily dose was not different between both groups. In the German CML study IV, older patients achieved complete cytogenetic responses (CCR) and major molecular responses significantly later than younger patients (12.3 vs. 10.7 months and 24.1 vs. 15.9 months, respectively). Interestingly, when looking at the German data in more detail, the group recently reported that patients >65 years of age may have a particular benefit from higher imatinib doses (i.e. 800 mg QD). Elderly patients treated with high dose imatinib, respond similarly to younger high-dose imatinib-treated patients. In contrast, the Italian cooperative group (which also included patients receiving 800 mg daily, which is not the standard dose) was not able to detect any statistically significant differences in response rates between young and elderly CML patients (cumulative CCR rate 88 vs. 84% and 82 vs. 81%, respectively). The rate of treatment failures, progression and rate of CML-related deaths were also comparable, according to the European LeukemiaNet (ELN) guidelines.

The German CML IV trial also provided important insights regarding co-morbidities in CML patients, and how they may be drastically underestimated. As co-morbidities are more frequent in elderly patients, this topic is of particular importance for senior patients. Susanne Saussele and her co-workers demonstrated that rating the co-morbidity burden by means of the Charlson Co-Morbidity Index, allows survival predictions (during treatment with a TKI) to be made. Importantly, co-morbidity burden does not affect the response rate, but it does affects the likelihood of a patient dying from reasons not related to CML. It is therefore, of the utmost importance to focus (in addition to CML therapy) on the optimal management of co-morbidities. This data is supported by the Italian GIMEMA group. They demonstrated, in a large retrospective analysis that included 2784 adult CML patients, that CML-specific survival is comparable between different age groups (i.e. 18-29 vs. 30-59 vs >60 years). However, when focusing on overall-survival analyses, they also demonstrated a clearly lower survival rate in elderly patients, which nicely fits with the data from the German CML IV trial.

Efficacy of second generation TKI in senior patients

Similar to Imatinib (at least for the higher dose), the other second generation TKIs (dasatinib, nilotinib and bosutinib) are all equally effective when comparing response data from elderly with younger CML patients. Data from the BELA, ENESTnd and DASISION...
studies all provide clear evidence that age is not a factor that predicts lower response rates. Thus all second generation TKIs can be considered for treatment of elderly CML patients. It should be noted that, in contrast to nilotinib and dasatinib, bosutinib is not approved for first line therapy. However, it is of particular importance (due to their specific side effect profile) that the optimal TKI selection is based on the co-morbidity burden, which an individual presents with, for example:

- Physicians should use nilotinib carefully in patients with pre-existing arteriosclerosis, as the compound increases the risk of peripheral artery occlusive disease (PAOD). In addition, nilotinib also affects metabolic parameters, such as lipids and blood sugar. Therefore, patients with diabetes and hyperlipidaemia have to be carefully monitored during nilotinib therapy.
- Dasatinib, may induce pulmonary hypertension and pleural effusion. Therefore, in patients with pre-existent pulmonary dysfunction it may not be the drug of choice.
- Bosutinib, mainly affects the gastrointestinal tract by inducing diarrhoea, and the liver by inducing elevated liver parameters. Bosutinib should (if possible) be avoided in patients with pre-existing GI or hepatic diseases.

Generally, in elderly patients, personalised selection of the most appropriate TKI is of the utmost importance to guarantee long-term safety and also compliance. When mutations are detected and only one second generation TKI is appropriate, surveillance and optimal side effect management are important to allow continued long-term therapy, and minimise time periods between stoppages.

Toxicity of Imatinib in senior patients
In the German trial, a higher proportion of older patients discontinued treatment (12.4% vs. 8.4%). Various differences were observed in the profile of grade III/IV adverse events (AEs). Haematologic AEs were more common in older patients compared to the younger patient cohort (leukopenia <2000 leukocytes/µl 4.2% vs. 2.8% and thrombocytopenia <50000/µl 4.2% vs. 2.8%, respectively). Most non-haematologic AEs were not different between the two age groups (gastrointestinal 29% vs. 28%, myalgia 17% vs. 16%). Oedaema and neurological symptoms were even higher in younger than older patients (17% vs. 23% and 6% vs. 15%, respectively), whereas dermatologic side effects were more frequent in the older patient population (17% vs. 13%).

Toxicity of Second Generation TKIs in Senior Patients
In the Dasision trial tolerability of dasatinib was evaluated in a post-hoc analysis grouping patients in the following age cohorts: <46, 46-65 and >65 years of age. Dasatinib exerts higher rates of fluid retention (13 vs 25 vs 35%), nausea/vomiting (10 vs 8 vs 35%) and rash (9 vs 12 vs 20%, respectively). Other haematological and non-haematological toxicities were not affected by age. However, age itself may not be the sole factor determining tolerability, as age is linked to co-morbidity. A report presented at ASH 2010 by Khoury and colleagues supports this idea, by demonstrating that toxicities are linked
to a higher co-morbidity burden. Thus, dasatinib is effective and safe also in older patients.

In the nilotinib clinical trials, approximately 30% of patients were older than 65 years of age. No major differences in safety were observed in patients >65 years of age compared to patients <65 years. Bosutinib, another second generation TKI, was tested in Phase 1-3 clinical trials. In those trials up to 20% were more than 65 years of age with 4% older than 75 years of age. No overall differences in safety or effectiveness could be observed between the younger and elderly patients. Other reported clinical experiences, have not identified any differences in responses between elderly and younger patients.

**Treatment Strategies of Polycythemia Vera (PV) in the Senior Patient**

In PV the increased number of red blood cells or platelets can cause bleeding problems and induce clot formation in blood vessels. This can cause serious complications such as stroke or heart attack. In patients older than 65 years, the risk of stroke and heart attack is clearly higher, and PV is more likely to transform into acute leukaemia or PMF. Without treatment, patients with PV usually die from bleeding or blood clotting. In contrast, median survival is about 10 years in older patients when appropriately treated. Many patients can reach their normal life expectancy, if they do not develop marrow fibrosis or transform to leukaemia.

Currently, there are no studies available specifically addressing the question of how senior PV patients should be treated. However, the treatment options currently available for this disease are generally well tolerated and (after careful evaluation of relevant co-morbidities of the individual patient) can be applied to elderly patients, for example:

- Periodically removing erythrocytes by phlebotomy represents a safe and very effective way to treat low-risk PV patients. The seminal CYTO-PV study provides clear evidence that haematocrit should be kept below 45% in both men and women.
- Due to platelet activation, patients should also receive low dose aspirin (i.e. 100 mg per day), which can also be easily prescribed to elderly patients who have no contraindications against aspirin (major side effects are gastrointestinal intolerance and bleeding).
- Patients with a higher risk of clotting (i.e. those who have risk factors such as leukocytosis, age >65 years and/or a previous thrombotic event) should receive additional cytoreductive therapy, such as hydroxyurea. This drug has relatively few side effects, and its beneficial effects in terms of prevention of vascular complications outweigh its potential harm (i.e. induction of leukaemia), which may not be as relevant in the elderly population when compared to younger patients.
- In the case of insufficient response or intolerance to hydroxyurea or high symptom burden, the JAK1/2 inhibitor ruxolitinib is now also approved for PV therapy. Other
off-label options comprise interferon-alpha or anagrelide (especially when thrombocytosis is present). Interferon-alpha may be particularly difficult to tolerate, as its side effects include flu-like symptoms (e.g. fever, chills, postnasal drip and poor appetite), fatigue, weight loss, depression, insomnia, memory loss, and nausea. So far interferon-alpha is the only drug known to induce a substantial reduction of the clonal disease burden, which may be of importance in very fit elderly patients. However, in highly symptomatic patients or individuals with a very large spleen, ruxolitinib is a valuable option, as it drastically reduces symptoms and shrinks spleen size. But the compound also induces an increased rate of infection, which has to be considered.

- Finally, radioactive phosphorus still represent a possible option for elderly patients who are unable to take oral medication or who are not expect to need many years of treatment. In 80–90% of patients, this treatment can suppress the disease symptoms for months or even up to several years.

**Treatment Strategies of Essential Thrombocytosis (ET) in the Senior Patient**

In ET, the increased number of platelets in the blood can cause thrombotic and haemorrhagic complications. Currently, no randomised clinical studies are available that provide the optimal point for treatment initiation. However, the number of thrombocytes, age, history of thromboembolic complications and vascular risk factors allow a risk categorisation, which then prompts treatment initiation.

Platelet-lowering treatment is indicated for patients over 60 years of age, or with platelet counts over 1.5x10⁶/µL, or either bleeding or thromboembolic complications associated with ET.

- Hydroxyurea and anagrelide are equally effective in WHO True-ET in the reduction of total vascular events.
- Very high platelet counts may induce a secondary von Willebrand-deficiency leading to an increased bleeding risk. This fact has to be considered when giving low-dose aspirin to patients with platelets >1x10⁶/µL.
- Interferon-alpha is not approved, but may also be an option for patients not sufficiently responding to or not tolerating hydroxyurea or anagrelide.

Due to the fact that age >60 years is a major risk factor for thrombosis or bleeding events, all senior patients should be treated with cytoreductive treatment, given that no contraindications for those treatment modalities exist. Treatment-decision includes careful evaluation or relevant co-morbidities to prevent treatment-related side effects (i.e. advanced renal insufficiency or chronic heart failure are relative contraindications for anagrelide).
Treatment Strategies of Primary Myelofibrosis (PMF) in the Senior Patient

Currently, despite allogeneic stem cell transplantation, which is in principle only applicable to patients <65 years of age with a suitable donor, no curative treatment option is available for patients with PMF. Studies specifically addressing the question of the optimal treatment strategy in elderly patients are not available. However, approval of the JAK-inhibitor ruxolitinib has dramatically improved quality of life (QoL) and overall survival (OS) in PMF patients. When treating an elderly patient with PMF the attending physician should take the following considerations into account:

- Symptomatic patients (e.g. B-symptoms, abdominal discomfort due to splenomegaly) should be treated with ruxolitinib 20 mg BID. With dose adjustment due to haematological toxicity, as this is the most prevalent side-effect of this compound (i.e. anaemia and thrombocytopenia). Moreover, the drug induces an increased risk of infections (urinary tract infection, herpes zoster reactivation), which should be discussed with patients.
- In the hyperproliferative phase in patients with high thrombocyte counts and thromboembolic complications, cytotoxic treatment with hydroxyurea should be started. This may also be combined with ruxolitinib, if the JAK inhibitor is not sufficient to control hyperproliferation but controls symptoms.
- In the phase of bone marrow insufficiency, erythrocytes should be substituted when haemoglobin is <8 g/dl and thrombocyte transfusions should be applied when thrombocytes are <10 x 10⁹/L or bleeding signs appear.
- In patients with low endogenous Epo-level (<500 U/ml), erythropoiesis can also be stimulated with erythropoietin 3x10000 IE/week.
- Alternatively, androgens (e.g. danazol 400-800 mg/day) can be initiated to stabilise haematopoiesis. Danazol may also be combined with ruxolitinib, if a JAK inhibitor is needed to control symptoms but anaemia is clinically significant side effect or erythropoiesis is not sufficient due to an advanced disease status.
- In cases when excessive splenomegaly cannot be controlled with a JAK-inhibitor and serious clinical symptoms are present, PMF may be treated with irradiation or splenectomy. It is essential to perform a bone marrow biopsy before spleen removal or irradiation, to define the bone marrow reserve and to prevent long-term pancytopenia.

Conclusions

- Given the limited literature available, so far all approved TKIs have a comparable safety and efficacy profile in elderly CML patients when compared to younger CML patients. Its clinical efficacy is also far superior to other treatment modalities, which
underscores the central role of TKIs as standard first-line treatment in senior CML patients.

- Low risk PV patients should be managed with low-dose aspirin and if necessary phlebotomy (target haematocrit <45%). Special precautions for aspirin should be taken in the case of patients with greater bleeding risk or allergies. Cytoreductive therapy should be considered as an option for high-risk PV patients. Hydroxyurea and Interferon-alpha are the preferred agents and should be administered to maintain a platelet count of less than 450 x 10^9/L. Of note, interferon-alpha is the only known compound so far that includes a significant reduction of the JAK2 V617F allelic burden, and may be of particular interest for fit elderly individuals. If treatment with hydroxyurea is not appropriate, ruxolitinib is now approved, especially in patients with high symptom burden and/or splenomegaly.

- All seniors with WHO-ET are at risk for thrombotic events and should be treated with anagrelide or hydroxyurea and low-dose aspirin.

- Only very few selected and fit senior MF patients qualify for allogeneic stem cell transplantation, which is the only curative approach. Ruxolitinib is the standard for most symptomatic elderly MF patients. In the hyperproliferative phase, hydroxyurea can reduce thrombocytosis-associated vascular events. When haematopoiesis becomes insufficient, supplementation of blood products, erythropoietin, or androgens can be applied to stabilise haematopoiesis.

Further Reading

Chapter 11 - Myelodysplastic Syndromes in the Senior Patient

The Relevance of Myelodysplastic Syndromes in the Elderly

Myelodysplastic syndromes (MDS) represent a typical disease of the elderly. MDS are a heterogeneous group of clonal haematopoietic stem cell diseases characterised by a dysplastic and ineffective haematopoiesis. The clinical course is highly variable ranging from mild symptoms caused by anaemia, thrombocytopenia or granulocytopenia to the transition to overt acute myeloid leukaemia (AML). MDS are preferentially diagnosed in the elderly. The median age at diagnosis is 70+ in epidemiological studies (72 years in the Düsseldorf registry; 76 in the Tyrol registry and 74 in the European Leukemia Net registry). The incidence of MDS increases dramatically with advanced age revealing age specific incidences of 9, 25, and 31/100.000/year for the age groups 60-70, 71-80, and 80+, respectively. Moreover, therapy-related MDS (t-MDS) is observed preferentially in elderly cancer survivors following successful cytotoxic chemotherapy and/or radiation therapy. The large and increasing proportion of elderly MDS patients and the availability of more and more treatment options, imposes an urgent need to develop strategies and algorithms for optimal management and treatment.

Classification and Risk Scoring in MDS

Based on morphologic features MDS are classified according to the FAB (French-American-British) or World Health Organization (WHO) proposal. These classifications are based on the morphological examination of dysplastic features in haematopoietic cells, the presence of ring sideroblasts and the percentage of bone marrow blasts. Presently, the WHO-classification is most widely used.

The WHO Classification of Myelodysplastic Syndromes 2008

- Refractory cytopenias with unilineage dysplasia (RCUD)
  - Refractory anaemia (RA)
  - Refractory neutropenia (RN)
  - Refractory thrombocytopenia (RT)
- Refractory anaemia with ring sideroblasts (RARS; ≥15% BM ringed sideroblasts)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Myelodysplastic syndrome unclassified (MDS-U)
- MDS associated with isolated del(5q)
- Refractory anaemia with excess of blasts-1 (RAEB-1, 5–9% BM blasts)
- Refractory anaemia with excess of blasts-2 (RAEB-2, 10–19% BM blasts)

As the overall survival and the rate of transformation into AML vary quite considerably among patients with MDS, even within morphological subgroups, much attention has focused on the identification of additional prognostic parameters. The International
Prognostic Scoring System (IPSS) published in 1997 has become the most widely used risk assessment tool for MDS (Table 1). A revised IPSS (IPSS-R) was developed in 2012 (Table 2). Improvements include a refined classification of cytogenetic abnormalities. More detailed cut-offs for bone marrow blast counts and cytopenias, weighted for their severity, are integrated. Age has been included resulting in the IPSS-RA (Table 3). The IPSS-R has been validated in several studies and represents the gold-standard for clinical risk assessment in patients with primary MDS. Based on the IPSS patients are divided into lower-risk (Low to intermediate-1 IPSS; very low, low to intermediate IPSS-R) and higher-risk (Intermediate-2 to high IPSS; high to very-high IPSS-R) MDS. These prognostic subgroups differ significantly in survival and rates of leukemic transformation and maintain their prognostic significance even in MDS patients aged 70+. Both, IPSS and IPSS-R have improved risk stratification in clinical trials and are widely used for decision-making in clinical practice. However, IPSS and IPSS-R were established in primary MDS at initial diagnosis. Thus, limitations of both scores are the lack of data on dynamic aspects and therapy-related MDS. Moreover, molecular abnormalities, which are emerging as one of the most relevant clinical prognosticators, have not yet been integrated in IPSS/IPSS-R at all.

Age-Adjusted Models and Assessment in Elderly MDS Patients

Age has a significant negative impact on overall survival in most analyses performed in MDS. In general, the relevance of age in prognostication is more pronounced in low-risk MDS than in high-risk disease. As shorter overall survival in older persons is logical, prognostication in the elderly should include age-adjusted parameters like the standardised mortality rate (SMR) or age-adjusted survival based on local survival statistics. Thus the survival in a given MDS patient is compared with an age- and sex-matched population. Analyses in representative cohorts of MDS patients achieved a SMR of around 5, implying a 5-fold increased risk of death for MDS. Addressing various age groups, younger patients revealed an SMR of 10 and elderly an SMR of 3.4. Even in elderly persons, MDS represent a relevant disease with a greater than threefold risk of disease-related death, resulting in a significant loss of life years in the majority of prognostic subgroups. However, in the prognostically excellent subgroup of elderly patients (70+ years of age), life expectancy was not different from the general population, pointing out the relevance of age-matched prognostic scoring systems for designing age and risk-adapted treatment strategies.

Whereas the scoring systems established so far are based on disease-specific prognostic factors like bone marrow blasts, karyotype or cytopenias, patient-related factors namely functional capacities or co-morbidities including cardiac insufficiency or tolerance to chemotherapy are less well defined. The integration of structured co-morbidity scores to classify and quantify co-morbid conditions has revealed a relevant prognostic impact of comorbidities in several studies. The haematopoietic stem-cell transplantation-specific co-morbidity index (HCT-CI), was found to be a significant prognostic factor for overall
survival as well as for event-free survival in MDS patients in uni- and in multivariate analyses and predicts non-leukaemic deaths.

The systematic evaluation of the scores of the geriatric assessment in MDS has just started. The prognostic relevance of functional capacities, mood and cognition has been demonstrated in MDS recently and forms the basis for further analyses. The inclusion of patient-reported outcomes (PROs) including health-related quality of life (HR-QoL) by assessing and integrating the patient’s wishes and needs, will further improve individualised decision-making in MDS.

The performance and integration of scores of the geriatric assessment in MDS has just started but will considerably improve individualised therapy-planning in clinical studies and in medical practise.

**Treatment Options in Elderly MDS Patients**

**Transfusion Therapy, Growth Factors and Iron Chelation**

An essential goal in the treatment of senior MDS patients is to manage and to counteract the consequences of cytopenias and to maintain and increase the quality of life (QoL).

- Anaemia is present in the vast majority (80-90%) of MDS patients and results in an impaired HR-QoL. In addition, a high red blood cell (RBC) transfusion frequency represents an unfavourable risk factor for survival. Transfusion therapy using RBC aims to reach a range of 80-100 G/L in cardio-respiratory healthy persons and >100-120 G/L in elderly and in persons displaying co-morbidities. RBC-transfusions should be kept to a minimum. Erythropoiesis-stimulating agents (ESAs) with or without granulocyte-colony stimulating factor (G-CSF) represent the standard of treatment for transfusion-dependent anaemia in lower-risk MDS (Figure 1).

- ESAs represent an effective treatment of anaemia in MDS to improve haemoglobin levels, to reduce transfusion need and to increase QoL. As low endogenous erythropoietin (EPO) levels as well as a low transfusion need result in an increased response rate, predictive models for ESA treatment have been developed. The Nordic Score identifies patients with low, intermediate and high probability of response (Table 5). Moreover, G-CSF is administered in combination with ESAs in low/intermediate risk patients to augment the erythroid response, which is particularly effective in patients with an increase of ring sideroblasts (RARS). ESAs have been used safely in larger numbers of MDS patients with no evidence for negative impact on survival or AML evolution. Moreover, ESAs even seem to improve survival in treated patients. Despite their widespread use in MDS, ESAs are so far not registered in this indication. Prospective, randomised clinical studies are ongoing. When applying ESAs the increased risk of thromboembolic complications should be considered. Whereas the majority of MDS-patients suffer from iron-overload, iron deficiency should be assessed at the start and during the course of an ESA-therapy.
by analysing serum ferritin levels, transferrin saturation and corrected by iron supplementation orally or i.v.

- In neutropenic infections in MDS the interventional use of G-CSF is recommended.
- In thrombopenic patients platelet transfusions are given to prevent bleeding. However, due to immunisation, frequent transfusions might cause a poor response. Thrombopoietic agents like romiplostim or eltrombopag, which are approved for the treatment of immune thrombocytopenic purpura (ITP), have been introduced in MDS and are currently evaluated in clinical trials. First reports promising results show that romiplostim results in a decrease in the number of bleeding events and platelet transfusions. Although the study drug was discontinued because of an initial concern of AML risk, survival and AML rates were similar with romiplostim and placebo.
- Frequent RBC transfusions result in iron overload and may cause transfusion-related hemochromatosis, which primarily affects the heart and the liver. As the risk of events becomes apparent when RBC transfusions exceed 20 and serum ferritin levels exceed 1500-2000 ng/mL, treatment with iron-chelating agents such as desferoxamine (applied either subcutaneously or intravenously) or deferasirox (orally), should be considered. In most guidelines a reasonable expected survival (at least more than one year) is anticipated. Renal function has to be monitored carefully in elderly patients treated with deferasirox.

Immunomodulating Agents
- Lenalidomide represents an immunomodulating drug (IMiD) which is highly active in MDS with 5q-. Lenalidomide produces major clinical and even cytogenetic responses that formed the basis for EMA and FDA approval. Lenalidomide also reveals activity in non-del5q- lower risk MDS (phase III studies to evaluate the relevance of lenalidomide in non-del5q- lower-risk MDS are ongoing). Relevant side effects of Lenalidomide are neutropenias and thrombocytopenias.
- Immunosuppressive strategies using combinations of anti-thymocyte globulin (ATG) and Cyclosporin-A (CyA) are effective in subgroups of younger patients in hypoplastic MDS and with a HLADR15 phenotype. As ATG is poorly tolerated in elderly patients, a CyA monotherapy is generally preferred. Due to nephrotoxicity renal function has to be monitored closely.

Epigenetic Therapies
The hypomethylating agents 5-azacitidine and decitabine have shown encouraging results in higher-risk MDS patients. 5-azacitidine (AZA) is already considered to be the standard of therapy in elderly higher-risk MDS, who are not eligible for intensive therapies such as AML-induction or hematopoietic stem cell transplantation (HSCT) (Figure 2). AZA has received EMA approval in MDS for this indication. In low risk patients, these drugs are analysed in clinical studies and might so far only be considered when signs of progression occur. AZA was demonstrated in a phase III study to significantly extend
overall survival in higher-risk MDS in comparison with a conventional care regimen. Effectiveness of AZA in response and survival prolongation was demonstrated in a subgroup analysis even in elderly MDS patients (≥75 years). As patients respond often after several courses, at least six cycles of AZA are recommended. In the absence of unacceptable toxicity or disease progression, continued AZA treatment might further improve responses in MDS. Besides induction of a complete remission (CR) or a partial remission (PR), hematologic improvement of anaemia or thrombocytopenia including stable disease, might be clinically relevant as they have shown to be associated with prolonged survival. Actually studies are ongoing to improve the effectiveness of AZA by addition of lenalidomide or histone deacetylase inhibitors.

- Decitabine and azacitidine show similar response rates and toxicities, azacitidine significantly improved overall survival and time to acute myeloid leukaemia transformation. These benefits were not found with decitabine (Xie M et al. 2014). Therefore, azacitidine is recommended as the first-line hypomethylating agent for MDS, especially in elderly patients or those with high risk.
- Valproic acid (VPA) was used as an anticonvulsant for decades and might be effective in myeloid neoplasms by the inhibition of histone deacetylase. As VPA causes an erythroid response in about 50% of patients in low-risk MDS, treatment with valproic acid might represent a useful alternative in low-risk MDS patients with a low probability of erythropoiesis-stimulating factors (ESF) response (Figure 1). In senior patients monitoring of VPA serum concentrations is essential.

**Intensive Therapies in elderly MDS: Current Standards**

Allogeneic HSCT represents so far the only curative treatment approach in MDS. As this therapy is associated with a relatively high risk of transplant-related morbidity and mortality, a HSCT with reduced intensity conditioning (RIC-HSCT) can only be offered to a small cohort of elderly patients, who are characterised by an excellent performance status and the lack of relevant co-morbidities. Similarly to HSCT, intensive AML-like polychemotherapy can restore normal polyclonal haematopoiesis in subgroups of patients, but induces long-term disease-free survival only in a minority of patients. In a given elderly patient, the final decision to apply intensive therapies must be based on multiple parameters including karyotype, functional capacities, co-morbidities and patient preference (Figure 2).

**Future Perspectives**

As a result of the development of innovative therapeutic options in MDS including epigenetically active drugs, immune modulating agents, thrombopoietic agents and effective iron chelators, the treatment of elderly MDS patients has become more successful, but also more complex. The results of relevant clinical phase III studies, which might change daily practise, are expected in the near future. To choose the appropriate treatment for an elderly MDS patient, not only chronological age but also aspects of age-
adjusted life expectancy, co-morbidities and capacities, as defined by geriatric assessment, have to be integrated, to achieve an individualised therapy-planning and to optimise clinical outcome.

Further Reading

Chapter 12 - Breast Cancer in the Senior Patient

Introduction
The median age for breast cancer diagnosis in Europe and in the United States is approximately 65 years. The incidence rises with increasing age. Major difficulties in defining treatment strategies in elderly breast cancer patients are the limited data coming from clinical trials and the heterogeneity of the older population, compounded by the insufficient information available for treating unfit patients. There is increasing agreement that patient and tumour biology, not chronological age, should drive treatment decisions in healthy women with breast cancer. Personalised methods of estimating the risks and benefits of various treatment strategies, in specific groups and settings are essential in older cancer patients.

Early Breast Cancer

Surgery
The surgical approach in older patients with breast cancer should not differ from that in younger women. Depending on the clinical situation, breast conserving surgery (BCS) or mastectomy combined with sentinel node biopsy or axillary dissection are suitable options. Two randomised trials, conducted in patients with clinically node-negative, hormone receptor-positive (HR+), early breast cancer who received tamoxifen, have shown that the omission of axillary clearance did not affect breast cancer specific survival and disease free survival (DFS), and was associated with a very low local relapse rate. This approach remains exploratory and should be reserved for patients who present with contraindications to or refuse sentinel node biopsy.

Primary Endocrine Therapy
Primary endocrine therapy alone has been shown to be inferior to surgery in fit women, and should only be offered to elderly individuals with HR+ tumours who have short estimated life expectancy (<2–3 years), who are considered unfit for surgery despite optimisation of medical conditions, or those who refused surgery.

Radiotherapy
Post-mastectomy chest wall radiation should be considered in selected elderly women with a high risk for relapse, i.e. ≥4 positive nodes or large tumours (pT3/T4). The cost-benefit ratio of post-mastectomy radiotherapy should be discussed in patients with limited life expectancy (<5 years).

For early invasive breast cancer, postoperative whole breast radiotherapy (WBRT) is considered the standard of care for fit patients following BCS. WBRT was associated with an 8% absolute improvement in the 10-year locoregional recurrence (CALGB 9343). However, omission of WBRT in patients with HR+ early stage breast cancer who received tamoxifen, caused no disadvantage in terms of overall survival (OS), distant DFS, or breast preservation. Based on these findings, adjuvant endocrine treatment alone may
be a reasonable therapeutic option for some women after BCS. Hypofractionated radiation schedules have similar locoregional control and DFS benefits as standard WBRT. Accelerated partial breast radiotherapy with multicatheter brachytherapy in patients with low risk \([pT1-2a \ (T\leq3cm), \ pN0/pNmi,M0]\) early breast cancer is not inferior to adjuvant WBRT with respect to 5-year local control, DFS, and OS. European and US guidelines indicate that patients with good prognosis can be treated with perioperative radiation only to the tumour bed.

**Adjuvant Endocrine Treatment**

Endocrine therapy is the standard of treatment for elderly patients with HR+ tumours. The benefits of tamoxifen and aromatase inhibitors (AIs) are age-independent, although the efficacy is slightly greater with aromatase inhibitors. However, elderly patients are more vulnerable to toxicities, and competing comorbidities must be considered when planning the treatment strategy. AIs are generally preferred to tamoxifen because of the lower risk for thrombosis and endometrial cancer. Bone loss, a typical side effect of AIs, is a critical issue in elderly patients, since pre-existing decrease in bone mineral density and osteoporosis are prevalent. Although, appropriate use of bone-modifying agents may be a solution (with possible survival benefit as indicated by the bisphosphonate meta-analysis).

Initial treatment should either be with tamoxifen or an AI. It is recommended to consider patients started on tamoxifen to switch to an AI after 2–3 years. The extended approach, defined as administration of AI after five years of treatment with tamoxifen, is associated with a significant DFS advantage, but only in patients younger than 60 years (trial MA.17). Nevertheless, the study showed no interaction between treatment and age, indicating a probable similar effect of the AI among all age groups. Omission of endocrine therapy may be an option for patients who have a tumour with a very low risk \((pT1aN0)\) for recurrence or have life-threatening comorbidities.

**Adjuvant Chemotherapy**

The benefit of adjuvant chemotherapy is often perceived to progressively decrease with increasing age. However, patients aged 70 years and older achieve similar advantage as those aged 50 to 70 years. Patients with hormone receptor–negative (HR-) tumours gain significantly more from chemotherapy than HR+ tumours.

Two retrospective studies, based on the Surveillance, Epidemiology, and End Results (SEER) database, have shown an OS advantage from adjuvant chemotherapy in elderly patients with oestrogen-receptor negative tumours. The benefit was observed only in patients with node-positive tumours in one of the two studies.

Polychemotherapy, doxorubin and cyclophosphamide \((AC) \times 4\) cycles or classical cyclophosphamide, methotrexate, and fluorouracil \((CMF) \times 6\) cycles, is superior to single-agent adjuvant chemotherapy \((capecitabine)\). Four cycles of an anthracycline-containing regimen are usually preferred over CMF. Taxanes are associated with increased toxicity.
in older patients compared with younger women, but can be added to anthracyclines in high-risk healthy elderly patients, or replace anthracyclines to reduce the cardiac risk. Adjuvant docetaxel and cyclophosphamide (TC) is superior to AC even in older patients (≥65 years). TC-related febrile neutropaenia has been reported in 8% of elderly patients in a clinical trial. However, higher rates have been reported in actual clinical practice, supporting the use of primary prophylaxis with granulocyte colony stimulating factor (G-CSF), as indicated by the guidelines.

Tumour biology, risk of relapse, and patient’s life expectancy, rather than age, must influence clinical decision-making and determine the appropriateness of adjuvant chemotherapy for an elderly woman with breast cancer. Healthy older patients with node-positive, HR- tumours derive the largest benefit from adjuvant chemotherapy. There is no evidence that unfit patients will benefit from adjuvant chemotherapy, as the dose-intensity needed cannot be maintained. Paclitaxel monotherapy failed to show non-inferiority over combination AC in a randomised phase III study (CALGB 40101). However, paclitaxel was better tolerated, and the estimated absolute difference for OS was only 1%. These features might justify the use of single agent paclitaxel in high-risk patients who are unfit for standard polychemotherapy.

**Trastuzumab**

Although only a few patients aged ≥70 years have been included in trials evaluating the role of trastuzumab in the adjuvant setting, it is recommended that all fit HER2-positive elderly breast cancer patients without contraindications (i.e. cardiac disease) should be offered trastuzumab in combination with chemotherapy. The cytotoxic partners should preferably be anthracycline-free to diminish the risk of cardiotoxicity associated with trastuzumab. A cost‐benefit ratio evaluation is needed for elderly women with low risk HER2 small tumours (i.e. T<1cm). Currently, no clinical data is available to support treatment with trastuzumab alone. However, in certain situations when chemotherapy is not suitable, giving trastuzumab monotherapy may be justifiable.

**Locally Advanced Breast Cancer**

The approach in healthy older patients with locally advanced breast cancer should not differ from that in younger women. The choice of the chemotherapy regimen is influenced by each patient’s clinicopathological characteristics. The approach to using trastuzumab in this group is similar to the adjuvant setting. When neoadjuvant endocrine therapy is necessary, an AI may be the agent of choice.

**Metastatic Breast Cancer**

**Endocrine Therapy**

Endocrine therapy is the treatment of choice for women with HR+ and non-life-threatening metastatic disease. In patients with durable response or prolonged disease stabilisation from hormonal therapy, the use of a subsequent line of non-cross-resistant endocrine therapy is considered an adequate strategy at the time of disease progression. Several
treatment options are available: tamoxifen, AIs (including a switch from a nonsteroidal to a steroidal AI in the setting of progression), fulvestrant, progestins, and androgens.

Everolimus in combination with exemestane is an active treatment option, but toxicity has to be carefully monitored since more on-treatment deaths in older patients were reported in the BOLERO-2 trial subgroup analysis.

Palbociclib in combination with letrozole (PALOMA 1) or fulvestrant (PALOMA 3) improves PFS in comparison to endocrine treatment alone. This effect is age-independent. The PALOMA-1 trial per age subgroup analysis has reported that the combination of palbociclib + letrozole is well tolerated in older patients (aged ≥ 65 years) despite the higher incidence of grade 3-4 neutropaenia and fatigue.

Chemotherapy
Chemotherapy is the treatment of choice in patients with HR-, endocrine-resistant, or rapidly proliferating disease. Single-agent chemotherapy is generally preferred to combination regimens, as they are usually more toxic and provide, at most, a limited survival gain.

Cytotoxic agents with favourable safety profiles such as weekly taxanes or anthracyclines, liposomal doxorubicin, capecitabine, or vinorelbine are recommended.

Retrospective data suggest that eribulin and weekly nab-paclitaxel are safe and active in older patients. Metronomic chemotherapy combines good tolerability with acceptable activity. Although there are limited data on using polychemotherapy in elderly patients, combination oral chemotherapy (vinorelbine and capecitabine) was effective and well tolerated when assessed in patients older than 70 years with advanced cancers, including breast cancer. Dose reductions and schedule modifications are controversial, but should be considered based on organ reserve, pharmacology, and toxicity. As a general rule, elderly patients have reduced tolerance to treatment and therefore, close monitoring of toxicity is recommended.

Biological Agents
In the absence of cardiac contraindication, trastuzumab can be safely administered to elderly patients with HER2-positive, metastatic breast cancer. In fit patients, concurrent administration of trastuzumab and chemotherapy is recommended. Trastuzumab monotherapy with or without endocrine therapy depending on HR status, is a reasonable option in patients with no life-threatening disease, but are unfit for chemotherapy.

New anti-HER2 agents, i.e. pertuzumab in combination with trastuzumab and taxane, and TDM-1 can be offered to fit elderly patients. In a pre-specified subgroup analysis of PFS according to age (<65, n= 681 vs. ≥ 65 years, n=127) of the CLEOPATRA trial, combination of pertuzumab, trastuzumab, and docetaxel benefitted both age groups, when compared with placebo, trastuzumab and docetaxel. However, diarrhoea, fatigue,
asthenia, decreased appetite, vomiting and dysgeusia were reported more frequently in the ≥ 65 years subgroup. In contrast, neutropaenia and febrile neutropaenia were reported less frequently in the older age group (where docetaxel dose and cycles were reduced more frequently).

In the EMILIA trial, T-DM1 significantly prolonged PFS and OS with less toxicity than lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and taxane. This benefit was consistently observed across clinically relevant subgroups, albeit less so among patients aged ≥ 75 years (n=25). When T-DM1 was compared to physician’s chemotherapy of choice (THERESA trial), the PFS benefit was noted across all age groups, including aged ≥75 years. The subgroup study of T-DM1 safety and efficacy in the elderly (KAMILLA trial) showed that the overall incidence of ≥grade 3 adverse events and treatment discontinuations were higher in patients ≥65 years. Although the proportion of T-DM1 associated adverse events was similar across all age groups.

Bevacizumab is active in elderly patients in terms of increased PFS over chemotherapy alone. However, in real practice, complications resulting from bevacizumab are significantly higher than what had been reported in randomised clinical trials.

Bisphosphonates and Denosumab
The use of bisphosphonates and denosumab in patients with metastatic bone lesions is indicated irrespective of age, but with caution in patients with decreased renal function.

Conclusion
There is increasing evidence that a selected population of elderly breast cancer patients may benefit from specific anticancer therapies both in the adjuvant and metastatic settings. Data supporting adjuvant chemotherapy or trastuzumab in unfit patients are lacking, and the benefit of adjuvant endocrine therapy in unfit patients or older patients at very low risk of relapse is uncertain. A personalised approach that takes into account the tumour and the patient’s characteristics (e.g., tumour burden, presence of symptoms), as well as patient's preferences, should be considered in unfit patients with advanced disease. The patient’s age should not limit access to new treatment options. However, it is difficult to translate the results of trials conducted in selected patients to the overall older adult population, especially to those with comorbidities and increased susceptibility to adverse events.

Further Reading


Chapter 13 – Lung Cancer in the Elderly

Introduction
Lung cancer is the most common cancer in the world, and the majority of lung cancer patients are above the age of 65 years. The changing demographics will result in an even higher number of senior people who will develop lung cancer and are in need of subsequent cancer treatment and care. This patient population may suffer from other comorbid conditions or geriatric syndromes, complicating their treatment and care.

While there are some data from randomised trials including fit senior patients, there is only a limited amount of information regarding vulnerable or frail elderly.

Early Non-Small-Cell Lung Cancer in the Elderly
Without treatment, the five-year overall survival (OS) rate in patients with stage I non-small-cell cancer (NSCLC) is between 6% and 14% with a five-year disease-specific survival rate of 23% for T1 tumours. Anti-cancer treatment can improve these figures but should be used carefully in the elderly.

Lung Cancer Surgery
Age alone should not be an exclusion criterion for surgery. Retrospective studies have shown no consistent differences in OS between elderly (≥70 years) and younger patients undergoing surgery for NSCLC and higher rates of surgery were associated with improved survival in elderly patients (>66 years) and early-stage disease. There are discrepancies in morbidity and post-operative mortality when comparing results from patients aged <70 years with those from patients aged >70 years due to risk factors. These risk factors include greater age, male gender, resections of multiple lobes, advanced stage, greater tumour size and certain comorbidities.

All elderly patients require a pre-operative assessment including a comprehensive geriatric assessment (CGA) and evaluation of comorbidities with correction of reversible conditions. In addition, pre- and post-operative pulmonary rehabilitation should be offered to improve functional status and quality of life (QoL).

Lobectomy is often considered the best curative option for early-stage NSCLC. Minimally invasive techniques may offer efficacy generally comparable with traditional thoracotomy procedures while reducing perioperative morbidity. Video-assisted thoracic surgery (VATS) allows lobectomy or limited surgery and may reduce the morbidity and perioperative mortality of elderly patients.

Wedge resection resulted in elderly patients with T1aN0 tumours in a similar OS compared with lobectomy, although there is a higher loco-regional recurrence rate in patients aged ≥75 years. Extended lung resection has long been associated with poorer outcomes in elderly (≥70 years) compared with younger patients and higher
mortality rates are also associated with pneumonectomy, particularly right pneumonectomy.

After adequate selection, senior patients can undergo lung cancer surgery, although a slight increase in mortality should be anticipated.

**Definitive Radiotherapy**
Radiotherapy is a valid treatment option in patients unfit for or unwilling to undergo surgery. However, conventional radiotherapy results in local recurrence rates as high as 40% (range 6-70%), and three-year overall and cause-specific survival rates of 34% and 39%, respectively. Stereotactic radiotherapy has a local control rate of 90% and a five-year OS rate of 70.8%, but at a cost of acute (e.g. fatigue, nausea, and chest pain) and late toxicities (<10% of patients; radiation pneumonitis which is higher in elderly patients, rib fractures, chronic pain syndromes), which may impair QoL.

Stereotactic body radiotherapy (SBRT) may be preferable to external beam radiation therapy. Newer approaches such as radiofrequency ablation may find a place for patients with peripheral small tumours.

Radiotherapy should be proposed to patients with local disease who are not candidates for surgery.

**Adjuvant Chemotherapy**
Several large phase III randomised trials and meta-analysis have established the role of adjuvant cisplatin-based combination chemotherapy in early-stage NSCLC with an improvement of 5.3% in five-year survival in patients with stages II to IIIA disease.

However, there are no data of prospective, elderly-specific trials, but retrospective analysis of these studies showed a mixed picture with a benefit in some, a poorer outcome in OS in the eldest patient groups who had an increase in adverse events.

These retrospective data support the use of adjuvant chemotherapy in fit elderly patients, although data are insufficient to draw conclusions in patients aged >75 years.

In selected elderly patients, adjuvant chemotherapy might be of benefit, although there is a need for elderly-specific, prospective trials.

**Adjuvant radiotherapy**
Post-operative radiotherapy in resected lung cancer with negative surgical margins showed no impact on survival, although some benefit has been seen in patients with pN2 disease.

In the elderly population, there are no indications that adjuvant radiotherapy is beneficial.
Chemoradiation

In patients with inoperable or unresectable NSCLC, chemoradiation is superior to radiotherapy alone. There are limited data from retrospective studies that show similar survival benefits in elderly patients compared with younger ones, although short-term haematological and non-haematological toxicity is significantly increased in elderly patients.

Even though specific data regarding sequential treatment in elderly patients are lacking, this approach is better tolerated than concurrent chemoradiation. The EORTC Elderly Task Force and Lung Cancer Group and SIOG, recommend that concurrent chemoradiation should be offered to elderly patients with unresectable locally advanced NSCLC but the treatment decisions should be based on close individual patient evaluation.

Advanced Non-Small-Cell Lung Cancer in the Elderly

When choosing a treatment strategy in elderly patients with advanced NSCLC, several options are available such as palliative care without chemotherapy, single-agent chemotherapy with a third-generation drug, non-platinum-based combination chemotherapy, platinum-based combination chemotherapy, and new biological agents.

First-line Treatment in Epidermal-Growth Factor Non-Mutated Cancer

Single-Agent Chemotherapy

Single-agent chemotherapy with vinorelbine, gemcitabine, and taxanes (paclitaxel and docetaxel) are first-line treatment options supported by prospective, elderly-specific clinical data (Table below).

Randomised Trials in Elderly Patients with Advanced Non-Small Cell Lung – First-line treatments

<table>
<thead>
<tr>
<th>Author (yr)</th>
<th>Treatment</th>
<th>Number of patients</th>
<th>Response rate (%)</th>
<th>Median overall survival (wk)</th>
<th>Quality of life/Toxicity</th>
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<tbody>
<tr>
<td>Elvis (99)</td>
<td>Best supportive care</td>
<td>78</td>
<td></td>
<td>21</td>
<td>Better with vinorelbine</td>
</tr>
<tr>
<td>Elvis (99)</td>
<td>Vinorelbine</td>
<td>76</td>
<td>20</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Frasci (00)</td>
<td>Vinorelbine + gemcitabine</td>
<td>60</td>
<td>15</td>
<td>18</td>
<td>Better with vinorelbine + gemcitabine</td>
</tr>
</tbody>
</table>
Single-agent vinorelbine prolonged OS and improved the control of tumour-related symptoms compared with best supportive care (BSC) in patients aged ≥70 years and induced low toxicity.

Gemcitabine was equally effective compared to vinorelbine or the combination of gemcitabine and vinorelbine in terms of response rate (RR) and median OS.

Docetaxel improved RR and progression-free survival (PFS) compared with vinorelbine, but at the cost of higher grade 3 and 4 neutropenia. In phase II studies, paclitaxel given either in a weekly or 3-weekly schedule also showed efficacy in the elderly population compared to younger patients.

Based on these findings, single-agent therapy (docetaxel, gemcitabine or vinorelbine) is recommended as first-line NSCLC treatment in most elderly patients.

**Combination Chemotherapy**

To improve the results obtained with single-agent chemotherapy in elderly patients, combination therapy with different agents were tested.

**Non-platinum-based combinations**

Non-platinum doublets have been compared with single agent schedules in predominantly elderly patients (generally ≥70 years) and showed either significant advantages for doublet therapy or no significant differences compared to single-agent therapy.

A meta-analysis of trials including patients aged 65–79 years indicated a significantly increased RR with gemcitabine-based regimens over single-agent chemotherapy but a
non-significant improvement in 1-year survival. However, single agent gemcitabine is not registered for this indication.

**Platinum-based combinations**

Several trials of cisplatin- and carboplatin-based chemotherapy, comparing the outcomes in younger and elderly patients (generally aged ≥70 years) with NSCLC showed the feasibility of these schedules in the elderly with similar findings in relation to outcome.

Randomised trials of platinum-based regimens have also been conducted in elderly patients. A combination of carboplatin and paclitaxel in fit patients aged 70–89 years with NSCLC was compared with single agent vinorelbine or gemcitabine and showed a longer median OS of 10.3 months compared to 6.2 months for monotherapy but at a cost of more toxicity.

A recent systematic review and meta-analysis that evaluated outcomes with doublet chemotherapy versus single agent cytotoxic treatment in patients aged ≥65 years with NSCLC, confirmed platinum-based doublet therapy to be superior to single-agent therapy in terms of OS, time to progression, 1-year survival rate and objective RR. Grade 3/4 anaemia, thrombocytopenia and neurotoxicity were seen more frequently in the doublet therapy group.

Based on these findings, single-agent therapy (docetaxel, gemcitabine or vinorelbine) is recommended as first-line treatment of epidermal growth factor receptor (EGFR) non-mutated NSCLC in the elderly. The combination of carboplatin and paclitaxel might be considered in fit elderly patients.

**Second-line Treatment in Epidermal-Growth Factor Non-Mutated Cancer**

Retrospective analysis of a randomised phase III trial comparing pemetrexed in combination with folic acid and vitamin B12 with docetaxel in pre-treated patients with NSCLC showed that objective RRs, median PFS, median OS and toxicity findings were not significantly different between younger and elderly (aged ≥70 years) patients in either treatment group. Pemetrexed was superior compared to docetaxel in non-squamous histologies.

**Targeted Therapy**

**Anti-angiogenic agents**

Elderly patients (≥ 75 years) appear not to benefit from the addition of bevacizumab to carboplatin/paclitaxel based on subgroup analysis of clinical trials evaluating these combinations with increased toxicity with the addition of bevacizumab.

**Tyrosine kinase inhibitors**

The use of tyrosine kinase is indicated as first-line treatment in patients with EGFR gene-mutated tumours. Both gefitinib and erlotinib have been used in elderly patients and there
are no comparative data to recommend one or the other, while gefitinib appears to have a slightly more favourable toxicity profile.

Second- or third-line treatment with gefitinib or erlotinib may be beneficial in older patients with advanced, non-EGFR-mutated NSCLC but elderly patients have more grade ≥3 toxicity and were more likely to stop treatment earlier that younger patients. This may be due to concomitant medications that interfere with cytochrome P450 3A4 activity.

**Immunotherapy - Immune checkpoint inhibitors**

Recently, drugs targeting the programmed death-1 (PD-1) pathway, inhibiting the immunosuppressive activity of cancer cells have been developed in the treatment of metastatic non-small cell lung cancer.

Nivolumab, a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2 has been registered in Europe as a second-line treatment to be given after prior chemotherapy. Nivolumab use in second-line treatment is based on an open label phase 3 randomised study comparing nivolumab with docetaxel in 272 patients of whom 44% were ≥65 years of age and 11% ≥75 years of age. There was a consistent OS benefit in favour of nivolumab (hazard ratio 0.59; 96.85% confidence interval 0.43-0.81; p 0.0002).

This study included a limited number of patients ≥ 75 years, in this age group nivolumab showed numerically less effect on OS (HR 1.85; 95% CI: 0.76-4.51). Because of the small sample size, no definitive conclusions can be drawn from these data.

In elderly patients, no dose adaption of nivolumab is necessary and no overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from patients 75 years of age or older are too limited to draw conclusions.

**Small-Cell Lung Cancer in the Elderly**

The standard therapy for limited-disease (LD) small-cell lung cancer (SCLC) is four to six cycles of a platinum-based chemotherapy regimen (Cis- or carboplatinum plus etoposide) combined with concurrent thoracic radiotherapy of the tumour region and the mediastinum. Chemotherapy remains the only treatment for patients affected by extensive-disease (ED) SCLC. After response, prophylactic cranial irradiation results in a survival benefit in both LD and ED SCLC.

In elderly the standard cisplatin-based regimens lead to substantial toxicity, and these regimens are only indicated in the very fit senior patients.

Older patients (> 70 years) treated with optimal chemotherapy had response rates and OS rates similar to those in younger patients, although the elderly received less chemotherapy than the planned protocol and experienced more toxicity.
In the group of elderly patients treated with chemotherapy, 6-month median survival was better than in the group not receiving chemotherapy.

The combination of carboplatin plus etoposide has a good activity, with response rates ranging from 59% to 81% and a median survival time ranging from 7.9 to 11.6 months but with substantial myelotoxicity in elderly patients.

The addition of radiotherapy to chemotherapy should be carefully considered: a meta-analysis showed that thoracic radiotherapy moderately improved survival (5.4% ± 1.4% at three years), but this effect was lost in patients > 70 years of age.

Alternative treatments in elderly patients are single-agent treatments or non-platinum-containing combinations. Single agent oral etoposide, intravenous epirubicin and carboplatin induces responses but have a worse treatment outcome when compared with combination therapy.

**Palliative Treatment in Elderly Lung Cancer Patients**

Palliative radiotherapy is commonly employed in the treatment of lung cancer. This is particularly true for older patients who may not be suitable for definitive or curative treatment approaches. Several symptoms including haemoptysis, dyspnoea, and cough and chest pain are best palliated by short-course radiotherapy. This also prevents disease progression with lung collapse or other consequences. Poor prognostic factors such as performance status, age, or stage have little impact on achieving palliation. Therefore, palliative treatment should be offered to all, irrespective of poor prognostic factors since the benefits of palliative radiotherapy are similar in the elderly compared with younger patients.

All patients with incurable lung cancer should receive palliative care for symptom control.

**Conclusion**

Senior patients with lung cancer should receive optimal anticancer treatment. When fit, most of them will support standard treatment with some modification or extra supportive care. Data on anticancer treatment in the elderly lung cancer population are increasingly available, and treatment decisions can be made on evidence-based data.

However, for vulnerable and frail elderly, treatment strategies should be developed and adapted to these patients to ensure an optimal treatment and care and improvement of their quality of life.

**Further Reading**

Chapter 14 – Treatment of Colorectal Cancer in the Senior Patient

Introduction
In a constantly ageing population, an increase in cancer incidence is anticipated in the next decades. It is estimated that by 2030, approximately 70% of all cancers will be diagnosed in older patients. Colorectal cancer (CRC) is the second most commonly diagnosed cancer in Europe, with almost half a million new cases per year. The highest incidence is among older patients, between 65 to 85 years of age, with a median age at diagnosis of around 70 years. Indeed, more than 10% of new cases concern patients above the age of 84. However, the representation of the over 70’s in clinical trials is low. Therefore, there is a lack of generalisability of existing clinical trial data to the general older patient. Moreover, the referral of older patients for consideration of cancer treatment as well as their inclusion in multidisciplinary meetings is limited. Thus, older patients are less likely to be properly assessed and treated on an evidence-based setting. Factors such as increased co-morbidities and impaired organ function are quite often put forward as arguments for low rates of specialist referral.

Adjuvant Treatment
The benefit of adjuvant chemotherapy in stage III CRC is unquestionable, with an impact on both disease free (DFS) as well as overall survival (OS). On the other hand, the routine use of adjuvant chemotherapy in patients with stage II disease is more controversial. Single agent 5-Fluorouracil (5FU) modulated by leucovorin (LV) provides a survival benefit when administered in the adjuvant setting for both younger and older patients. At the same time, the toxicity profile appears to be similar, at least for those older patients fit to enter clinical trials. An alternative to intravenous 5FU is the oral fluoropyrimidine Capecitabine. Randomised clinical trial data suggest that capecitabine is at least as good as bolus 5FU/LV, in all age groups, including those over 70. However, since Capecitabine is predominantly cleared by the kidneys, the administration is contraindicated in patients with severe renal impairment (creatinine clearance [CrCl]< 30 ml/min) and dose modifications are necessary in patients with -CrCl between 30-50 ml/min. This of course is very relevant in older age groups.

The use of combination chemotherapy with a fluoropyrimidine plus oxaliplatin is considered the standard of care for stage III CRC patients. The MOSAIC (Multi-Center International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) evaluated the combination of oxaliplatin and infusional 5-FU (FOLFOX) versus single-agent infusional 5-FU in the adjuvant setting, establishing FOLFOX as a standard treatment option for stage III colon cancer. A pre-specified subgroup analysis of patients older than 65 years (30% of enrolled patients) though, did not show a reduction in recurrence risk. Interestingly, during the early years of follow up, older patients (70-75 years) shared a similar oxaliplatin benefit as their younger counterparts. This benefit was
diminished after the third year of follow up mostly due to deaths from other causes. The ACCENT (Adjuvant Colon Cancer Endpoints) database, which combined data from 6 large randomised clinical trials in the adjuvant setting, evaluated the benefit of adjuvant oxaliplatin-based therapy (with oral or intravenous fluoropyrimidine) in older patients (age > 70 years). No benefit in disease-free or overall survival was seen among older patients with the addition of oxaliplatin to 5-FU for the whole cohort or for patients with stage III disease. Cancer Registry-based retrospective data from patients above the age of 75 diagnosed with stage III colon cancer, showed that survival for patients who received adjuvant chemotherapy was substantially better than for non-receivers. However, the addition of oxaliplatin only added an incremental survival benefit as compared to that conferred by 5FU monotherapy.

Based on these reports and the higher rate of toxicity with the addition of oxaliplatin, combination regimens are used less frequently in the treatment of older patients with stage III disease. Overall, single-agent 5-FU seems to provide benefit for older patients in the adjuvant setting, mainly those with stage III disease, whereas the magnitude of benefit from combination chemotherapy with a fluoropyrimidine plus oxaliplatin remains uncertain. The decision to use single agent or combination chemotherapy should be individualised, based on the patient's functional status, needs and expectations, as well as the presence or absence of other medical conditions that are likely to impact on physiologic reserve and tolerance of therapy.

Metastatic Disease
Over the last two decades we have witnessed a rapid evolution in the management of metastatic colorectal cancer. The increasing use of biologic targeted agents and the implementation of advanced surgical techniques have changed the management approach. Nowadays, it is not rare to switch the treatment aim from palliative to curative. The possibility of metastasectomy- liver or lung - should always be considered at the initial evaluation regardless of age, as this will be the only opportunity for achieving long term survival or even cure. The proportion of older patients undergoing liver resection has increased over the last twenty years. Even though the postoperative mortality and morbidity is somewhat worse in this group, the benefit of long term outcomes appears to be similar to their younger counterparts. Patients considered unfit for such major surgery, should be considered for alternative procedures like radiofrequency or microwave ablation.

Although combination regimens are considered more effective than single agent 5FU in the metastatic setting, it is important to note that older patients are grossly under-represented in clinical trials, and those included are subjected to selection bias. Therefore, care should be taken when extrapolating results from clinical trials to these older patients. Recent data generated from elderly specific trials in frail older patients with metastatic CRC suggest that combination chemotherapy does not confer significant advantages when compared to the use of single agent fluoropyrimidines. Indeed, it is
suggested that intensive chemotherapy should be used with caution in patients ≥75 years with low autonomy and cognitive impairment, and support the importance of the evaluation of risk factors for toxicity in older cancer patients being considered for chemotherapy (eg comprehensive geriatric assessment).

Increasingly, combination chemotherapy plus a targeted agent (bevacizumab, cetuximab, and panitumumab) is being used to treat mCRC patients. Fit older patients selected for inclusion in clinical trials appear to derive a similar benefit to younger patients in terms of RR and PFS from the use of bevacizumab plus full-dose combination chemotherapy. However, the data are lacking as to whether this leads to significant patient-relevant gains such as improved survival with an acceptable QoL. Bevacizumab has a side-effect profile that needs careful consideration when treating older patients, with a modest increase in the risk of arterial thrombotic events in addition to side-effects seen also in younger patients such as hypertension. The addition of Bevacizumab to single agent capecitabine in patients over 70 (“AVEX” trial) achieved encouraging results with a significant PFS improvement over single agent capecitabine. For those older patients for whom intensive combination therapy would be inappropriate, such a lower dose capecitabine plus bevacizumab regimen can therefore be considered. Evidence for the use of epidermal growth factor receptor (EGFR) inhibitors is less abundant. Based on limited data from pooled analyses, it seems that the use of Cetuximab in combination with FOLFIRI or FOLFOX, according to K-ras status, may provide a PFS and OS benefit in patients over 70 as well. The commonest toxicity observed is skin rash. Although the prevalence of this side effect is similar between all age groups, older patients may appear with higher grades and duration of skin toxicity. Data for the use of panitumumab and newer agents like regorafenib and aflibercept in older patients are still limited.

Overall, older patients with mCRC may gain survival benefit and symptomatic relief from 5U/LV or capecitabine monotherapy. Cytotoxic combination treatment with irinotecan, oxaliplatin or targeted agents may benefit more fit older patients. Compromising doses with combination chemotherapy in less fit patients on the other hand may not have a clear impact on symptoms, QOL improvement or survival extension. For such patients, less intensive regimens may be used such as the “stop and go” approach, where treatment is given intermittently according to the patient’s condition and wishes.

**Rectal Cancer**

Total mesorectal excision and rectal surgery in general are technically demanding, especially in older patients. Postoperative mortality and severe complications are higher than in younger patients. Aggressive surgical treatment or permanent stoma can come at the expense of reduced functional status for older patients, and therefore the risk of local recurrence with regards to life expectancy must be considered before any therapeutic decision is taken.
Preoperative chemoradiation (CRT) and short course preoperative radiation (SCPRT) are standard modalities in the treatment of rectal cancer, especially for the moderate risk and locally advanced tumours. Patients that are candidates for radical surgery, can have preoperative short course radiation (5x5 Gy) and immediate surgery or long course chemoradiation followed by surgery with an interval of 6-8 weeks. If the tumour is inoperable or the mesorectal fascia is involved (<1mm on MRI imaging) then long course CRT is the appropriate choice. If the fitness of the patient is questionable, then a decision to omit the concomitant chemotherapy part of the long course radiation can be considered. For patients that are frail, a short course of preoperative radiation with delayed surgery (6-8 weeks) can be an alternative approach. Intensity-modulated radiotherapy (IMRT), if available, can reduce acute toxicity expected with standard radiation. The use of postoperative adjuvant chemotherapy is still controversial.

For early stage disease of the mid and distal rectum, endocavity contact radiation is an alternative option for radical treatment, with high response rates and local disease control. High dose rate intraluminal brachytherapy could be offered instead of surgery-is also useful in the palliative setting. Finally external beam radiation could be used in the palliative setting for the management of inoperable low rectal tumours and in advanced disease.

**Conclusions**

Therapeutic decisions for older patients with CRC should be made in the context of a multidisciplinary team, which could include a geriatrician. All older patients should be considered for comprehensive geriatric assessment. The notion of chronological age as a factor for unfitness should be abandoned. Adjuvant and palliative chemotherapy should not be denied to patients because of age. There is a clear benefit for the adjuvant use of 5FU/LV or capecitabine monotherapy in the adjuvant setting for stage III CRC. The magnitude of benefit for the addition of oxaliplatin in patients above 70 on the other hand is questionable. For patients with metastatic disease, liver metastasectomy, if applicable, should not be discouraged, especially if there is a potential for cure. Fit older patients can benefit from palliative combination chemotherapy and biologic agents. However, the balance of toxicity/benefit must be considered. Less fit patients can be treated with lower intensity regimens like reduced-dose FOLFOX, fluoropyrimidine monotherapy or capecitabine and bevacizumab. Constant evaluation of the performance status, monitoring for toxicity and early intervention in the case of adverse events are an essential part of the management for older patients with CRC.

**Further Reading**

- McCleary MJ, Dotan E, Browner I. Refining the Chemotherapy Approach for Older Patients With Colon Cancer, J Clin Oncol 2014:32;2570-2580.


Chapter 15 - Prostate Cancer

Introduction and General Background
Prostate cancer is predominantly a disease of senior adults (i.e. men aged 70 years or older); yet, no specific guidelines exist for this population.

Guidelines for the management of prostate cancer make reference to senior adult patients and age-related factors that may affect treatment decisions. The first guidelines were published by the International Society of Geriatric Oncology (SIOG) in 2010. These guidelines were updated in 2014. The European Association of Urology (EAU) guidelines have recently included a chapter on prostate cancer in senior adults. It is noteworthy that reference to the concept of life expectancy, which depends on many components of a patient’s well-being, is often misinterpreted by physicians. Instead it is better to refer to health status. Nevertheless, guidelines for assessing the health status of senior adults have been published and some of them can be applied to patients with prostate cancer. In summary, treatment decisions should be based on the patient’s actual health status rather than on chronological age, and also on patient’s preference.

Epidemiology
Prostate cancer is the most frequently diagnosed male cancer in Europe and represents the third cause of cancer-related death in men. The median age at diagnosis is 68 years; over 60% of new cases are diagnosed in men > 65 years of age and 25.7% in men > 75 years of age. Interestingly median age in the metastatic patients group is 80 years (70% of patients are aged > 75 years).

The overall growth and “ageing” of the world population are expected to increase the burden of prostate cancer, particularly in senior adults. In more developed regions of the world, the proportion of men aged > 70 years is expected to increase from 0.8% in the year 2000 to 17.2% by 2050.

Diagnosis and Staging
The diagnosis of prostate cancer is often made on the occasion of an individual screening examination. Otherwise, it is made when urological symptoms occur or when metastatic disease to bone becomes painful. The diagnosis is made on prostate biopsy. Extension of the disease is evaluated based on prognostic factors and relies on abdominal and pelvis computed tomography (CT) scan, prostate magnetic resonance imaging (MRI), and bone scan.

Prognosis
Prognostic factors of localised prostate cancer are clinical TNM stage, initial serum prostate-specific antigen (PSA) value, and tumour grade (Gleason score). This evaluation allows the classification of the patients into prognostic groups, as described by D’Amico.
Treatment

Curative treatments for localised, good and intermediate prognostic groups are radical prostatectomy, conformal radiotherapy and, in some cases, brachytherapy. In patients of the good prognostic group, active surveillance is a treatment option with curative intent. Sometimes a “Watchful Waiting policy” is proposed without a curative intent.

Patients with poor prognostic characteristics are likely to receive external radiotherapy with androgen deprivation therapy (ADT) or even palliative treatment with transurethral resection (TUR) and ADT.

Metastatic disease is treated first by ADT, but all tumours progress to castration-resistant prostate cancer (CRPC).

Several trials have shown a benefit of adding docetaxel to ADT upfront in patients with metastatic disease, especially those with high-volume disease. The European Society for Medical Oncology (ESMO) recommends ADT plus docetaxel as first-line treatment of metastatic, hormone-naive disease in men fit enough for chemotherapy.

There are now several options for mCRPC. Abiraterone acetate, enzalutamide and docetaxel can be offered as first line treatment. The choice of treatment depends on the presence of symptoms or not, the presence of visceral metastases or not, the rapidity of progression, patients’ comorbidities and patients’ preference.

Radium 223 can be used in patients with metastatic CRPC with symptomatic bone metastases without visceral disease: it can decrease pain and analgesic consumption.

Standard approved treatments when progression is observed while on or after docetaxel chemotherapy are cabazitaxel, enzalutamide and abiraterone acetate. Palliative symptomatic treatments are also useful.

There are no prospective studies aimed at establishing standard treatment in senior adult prostate cancer patients. However, multivariate analysis of prognostic factors in clinical trials which established the activity of the different drugs in metastatic CRPC (mCRPC) has demonstrated that age was not an adverse prognostic factor for response to treatment. Retrospective studies have been performed in the setting of both localised and metastatic disease. The SIOG Prostate Cancer Task Force has published recommendations for the management of senior adult prostate cancer patients (Droz JP et al. 2010, and updated Droz JP et al. 2014) (Figure 1). These are used as a basis for the following recommendations for patient management. Updated guidelines are scheduled in 2016.

Figure 1. Principles of the decision tree (International Society of Geriatric Oncology Prostate Cancer Task Force).
Treatment of Localised Prostate Cancer in Senior Adult Patients

Evidence suggests that only a minority of senior adults with localised prostate cancer receive curative therapy. The 2014 SIOG and EAU guidelines recommend that “Older men with prostate cancer should be managed according to their individual health status, which will be directed mainly by the needs of any associated comorbidities and not according to chronological age.” Panel members did not select a specific chronological cut-off point for treatment recommendations.

Alibhai and colleagues have evaluated treatment efficacy in men aged > 65 years with localised prostate cancer by using a decision model that integrates patient’s age, comorbidity, Gleason score, patient’s preference, and treatment efficacy data (from three complementary data sources including modern radiotherapy results). Their results show that prostatectomy and radiotherapy significantly improve life expectancy and quality-adjusted life expectancy in older men with little comorbidity and moderately or poorly differentiated localised prostate cancer. As healthy men in their 70s or 80s with localised prostate cancer are often managed conservatively, they conclude that “curative therapy should be seriously considered in men up to age 80 years who have high-grade disease.”
Retrospective and cohort studies have demonstrated that the presence of comorbidities in patients receiving a prostatectomy significantly and independently increases the risks of 30-day postoperative complications, long-term incontinence, and overall and non-prostate cancer death. However, the risk of incontinence is known to increase proportionally with age. It is therefore recommended to limit the indication of prostatectomy to patients younger than 75 years.

Several studies have reported that senior adult patients undergoing radiotherapy can achieve outcomes in terms of cancer control and treatment-related late comorbidity similar to those achieved by younger patients. A population-based study of non-metastatic prostate cancer patients aged 65 to 85 years treated with radiotherapy has shown improved long-term survival rates for patients with locally advanced stage receiving adjuvant ADT, but no survival advantage for men with low-risk disease. These findings are consistent with practice guidelines. However, the survival advantage achieved by combining radiotherapy and ADT in high-risk prostate cancer patients may apply only to those with no or minimal comorbidities (i.e. fit patients).

Brachytherapy is indicated in patients with low-risk prostate cancer. This technique does not appear to be a suitable treatment choice for older prostate cancer patients because its clinical benefit is not established.

Older prostate cancer patients with low-risk disease are more likely to be eligible for a “Watchful Waiting policy” or active surveillance (i.e. delayed curative intervention on progression).

The SIOG Task Force conclusion was as follows:

- A two-step decision making is performed:
  - 1- Systematic use of the G8 health status screening tool.
  - 2- If G8 ≤ 14 assessment of comorbidities (Cumulative Illness Score Rating-Geriatrics [CISR-G] scale), dependence status (Instrumental Activities of Daily Living [IADL] and Activities of Daily Living [ADL] scales), nutritional status (weight loss estimation), and screening for neuropsychological problems should be made, as well evaluation of the reversibility of health impairment.

- Patients can be classified into three health status categories (fit, vulnerable, and frail):
  - Healthy or fit patients are those with a G8 score of more than 14: they are expected to tolerate any form of standard cancer treatment.
  - Vulnerable patients are those with a G8 score of 14 or lower, and should be considered for further geriatric intervention (reversibility of their health impairment) and standard cancer treatment.
  - Frail patients with irreversible health impairment should receive both geriatric intervention and adapted cancer treatment.
• “Fit” and “vulnerable” senior adults in the “high-risk” group of the D'Amico risk classification, with a chance of surviving >10 years, are likely to benefit from curative treatment.
• Senior adults in the “low-risk” and “intermediate-risk” groups of the D'Amico risk classification are likely to benefit from active surveillance. There are only a few indications of minimally invasive therapy in these patients.

Treatment of Metastatic Prostate Cancer in Senior Adult patients

Castration-sensitive disease
ADT is the standard treatment for patients with metastatic prostate cancer.

It delays progression, prevents potentially catastrophic complications, and effectively palliates symptoms. Surgical castration and castration by luteinizing hormone–releasing hormone agonists and antagonists are the standard of care.

Adding docetaxel to ADT is recommended in patients, who are fit enough, as first-line treatment of metastatic, hormone-naïve disease. In the CHAARTED trial, the benefit was seen irrespective of age.

ADT is associated with a significant number of side effects, including osteopaenia with increased risk of fractures, and metabolic alterations with increased risk of cardiovascular events.

Bone mass decreases with age, and men > 75 years of age are at particularly high risk of developing fractures. The National Comprehensive Cancer Network (NCCN) recommendations and ESMO guidelines state that men receiving or starting ADT should be evaluated for their risk of osteoporosis.

• All men receiving ADT should receive calcium and vitamin D supplementation, and baseline bone mineral density should be determined.
• The routine use of bone targeted therapies in patients undergoing ADT is not recommended unless there is documented evidence of the presence or a risk of osteoporosis or CRPC with skeletal metastases.

Castration-resistant disease
There are no prospective studies aimed at establishing standard treatment in senior adult mCRPC patients. However multivariate analysis of prognostic factors in clinical trials which established the activity of the different drugs in mCRPC has demonstrated that age was not an adverse prognostic factor of response to treatment.

The standard procedure for second-line hormonal treatment is as follows:
• Cessation of anti-androgen if complete androgen blockade was given as first-line treatment. The addition of an anti-androgen when ADT was used as monotherapy in the first-line setting has no proven survival impact.

• Abiraterone acetate is registered in this indication (in patients without visceral metastases and non- or mildly symptomatic patients). Enzalutamide is also approved in this indication. It was studied in patients with or without visceral metastases and non- or mildly symptomatic patients.

• Docetaxel is a chemotherapy treatment that has demonstrated a survival benefit in patients with mCRPC. The tolerability of the 3-weekly docetaxel regimen has not been specifically studied in frail senior adults. The place of weekly and 2-weekly docetaxel in mCRPC should be considered in frail patients.

• New chemotherapy (cabazitaxel) and hormonal agents (abiraterone acetate and ezalutamide) are now available for second-line therapy of mCRPC, but careful monitoring is needed in older patients. The order in which these therapies should be given is a topic for further research.

• Palliative symptomatic treatments are useful and include radiotherapy, radiopharmaceuticals, bone-targeted therapies, surgery, and medical treatments for pain and symptoms.

Conclusion
Senior adult patients with prostate cancer should be managed according to their individual health status, which is mainly related to the severity of associated comorbid conditions and not to chronological age. Evidence-based medicine guidelines must be applied in senior adults with prostate cancer. Therefore, the standard and universally accepted EAU guidelines have included a specific chapter on elderly prostate cancer management. The decision making must be thereby applied according to the actual health status of each individual patient as published by the SIOG and EAU.

Further Reading


• EAU prostate cancer guidelines. Available at: http://www.uroweb.org/ Date last accessed June 3rd 2016
**Chapter 16 – Bladder Cancer in the Elderly**

**Incidence and Mortality**

Bladder cancer (BC) is the 11th most common cancer in the world. The annual incidence rate is 27/100,000 men and 2.2/100,000 women, with a corresponding mortality of 3.3/100,000 and 0.4/100,000, respectively. The incidence varies within Europe (highest in Spain, lowest in Finland). It is increasing in women, with the increasing smoking habit. BC is fatal in about one-third of men and half of women, thus explaining the social interest of the disease. The frequency of diagnoses reaches a peak at 65 years of age, and two-thirds of BC patients are older than 65 years. Since the average age of the population is increasing, the incidence of BC is expected to increase accordingly.

**Aetiology and Risk Factors**

Tobacco smoking is responsible for 65% of all cases of BC in the male and 30% in the female population. The relative risk of developing BC in smokers is two to four times that of non-smokers. Aromatic amines including naphtylamines and specifically benzinides, and derivatives, are likely to be present in tobacco smoking as well as in the occupational environment (i.e. industrial manufacturing of chemicals, hair dyes, rubber, metal). Schistosomiasis is a major cause of BC in some countries such as Egypt.

**Pathology**

BC is represented by transitional cell carcinoma (TCC) in about 90% of cases, mostly papillary. Metaplasia are frequent (adenocarcinoma, squamous cells). Some variants such as the micropapillary have been recognised as more aggressive. About 90% of TCCs are observed in the urinary bladder, 8% in the renal pelvis or calyx, and the remaining 2% within the ureter. Finally, this disease can also be located at the posterior urethra. Pure adenocarcinoma, squamous cell carcinoma, and small cell carcinoma account for the remaining 10% of BC.

**Natural History and Tumour Biology**

At presentation the disease is limited to the mucosa or submucosal layer through the lamina propria in about 75% of cases, referred to as non-muscle-invasive bladder cancer (NMIBC). Infiltration into the muscular wall is present in the remaining cases (MIBC). NMIBC shows an intrinsic tendency toward recurrence and/or progression to MIBC, depending on risk factors (see below).

NMIBC most likely represents three distinct diseases:

- papillary urothelial neoplasia of low malignant potential (PUNLMP), which has the lowest incidence of relapse
- intermediate-risk papillary malignancy that usually recurs without progression
• high-risk disease that might recur and/or progress to MIBC with the associated risk of nodal and visceral metastases.

Carcinoma in situ (Cis/Tis) consists of high grade flat, intraepithelial lesion. It can be isolated or associated with NMIBC or MIBC. Its presence bears a substantially negative influence on prognosis.

**Signs and Symptoms**
Macroscopic, asymptomatic haematuria is the most frequent and only sign of BC. Urgency, painful bladder, lower urinary tract symptoms, or prostatism in the male, can be the only presenting symptom associated with BC.

**Imaging, Cystoscopy, and Urinary Cytopathology**
Ultrasonography is used in the presence of gross or microscopic haematuria. If normal, it does not exclude BC. BC is suspected as an additional non mobile image on the bladder wall, and is often associated with vascularisation on Doppler. Endoscopy is the imaging process which best allows characterisation of the lesions: number, location, size, aspect of the lesions and the base. Cis might be suspected by velvety reddish spots but it is not consistently recognised. If negative, endoscopy can be optimised with fluorescence (especially for detection of Cis). Abdomen and pelvic computed tomography (CT) scans are mandatory in high risk NMIBC and in MIBC for local staging and to rule out upper urinary tract lesions. Magnetic resonance imaging (MRI) might also be helpful. Both examinations underestimate or overestimate the infiltration depth in up to 50% of cases. In MIBC, a thoracic CT is needed. A bone scan is only performed if symptoms suggest bone metastases.

Tumour cells are excreted in the urine. Urinary cytology (UC) is mandatory, with a better sensitivity for high grade lesions, and an excellent specificity. This might be the only tool to detect Cis.

**Staging**
The most widely accepted staging classification is the TNM system (UICC 2009).

It is clinical (T) and pathological (pT). After a transurethral resection of the bladder (TURB), the pT stage must be only considered as minimal.

T or primary tumour:

* Clinically (pelvis examination under anaesthesia)

  • T1: normal pelvis
  • T2: mobile pelvic mass no longer present after TURB
  • T3: mobile pelvic mass still present after TURB
• T4: fixed mass

* Pathology

• Tx: primary cannot be assessed.
• T0: no evidence of primary.
• pTa: non-invasive, limited to the mucosa.
• pTis: (Cis), flat tumour limited to the mucosa.
• pT1: infiltration of the basal membrane and limited to the sub-epithelial connective tissue.
• pT2: muscle invasive;
  o T2a: inner half;
  o T2b: outer half.
• pT3: invasion of the perivesical fat;
  o T3a: microscopic invasion;
  o T3b: macroscopic invasion.
• pT4: invasion of neighbouring structures;
  o T4a: prostate, uterus, vagina;
  o T4b: pelvis or abdominal wall.

N or regional nodes:

The nodes located within the true pelvis are considered as regional lymph nodes.

• Nx: no information on nodal status.
• N0: no evidence of tumour within the nodes examined.
• N1: tumour present in a single node
• N2: metastasis in multiple nodes in the true pelvis
• N3: metastases in the common iliac nodes

M or distant metastasis:

• Mx: no information on M.
• M0: absence of distant metastasis.
• M1: distant metastasis.

Histopathological grading (G): 2 classifications co-exist, overlap, and may be used (see Figure 1).

Figure 1. Histopathological grading

2004 WHO classification: urothelial papilloma (benign lesion), PUNLMP, low grade, high grade carcinoma.

Additional descriptors include lymphatic vessel invasion (L) and venous invasion (V).

Accurate pathological diagnosis and staging of BC represent the cornerstone for treatment strategy.

**Treatment of Bladder Cancer**

**Treatment of NMIBC**

TURB always represents the first step of treatment of BC. It is performed under anaesthesia and consists of removal of all the papillary lesions as well as deep muscle below the papillary lesions and all lesions suspicious of Cis. Lack of muscle in the specimen is an imperative indication for repeat TURB. The use of fluorescence might be helpful, especially if Cis is suspected based on positive cytology. It is a surgical procedure that deserves surgical application. Relapse and progression are linked to the disease itself but also to the quality of the TURB.

An immediate post-operative instillation (IPOP) of chemotherapy is mandatory in the absence of bladder perforation.

This will allow for pT staging and grading, allowing risk-adapted treatment (Table 1)

**Table 1. Risk groups**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Characteristics</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Primary solitary &lt; 3 cm, PUNLMP, No Cis</td>
<td>IPOP. Nothing more</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>All lesions not defined in the 2 other groups</td>
<td>Bladder instillations: chemotherapy (such as mitomycin C weekly for 8 weeks followed by maintenance) for up to 12 months or BCG (weekly for</td>
</tr>
</tbody>
</table>
6 weeks, followed by 3 weekly instillations at months 3, 6 and 12)

<table>
<thead>
<tr>
<th>High risk</th>
<th>T1 or high grade (or G3) or Cis or multiple and recurrent and large (&gt; 3 cm) Ta G1-2</th>
<th>An early repeated TURB is mandatory.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BCG instillations for 3 years (weekly for 6 weeks, followed by 3 weekly instillations at months 3, 6 and every 6 months up to 3 years)</td>
<td>For the highest risks (T1G3 + Cis, micropapillary lesions, multiple large pT1G3): an immediate cystectomy must be discussed</td>
</tr>
</tbody>
</table>

PUNLMP, papillary urothelial neoplasia of low malignant potential; Cis, carcinoma in situ; IPOP, immediate post-operative instillation; BCG, Bacillus Calmette–Guérin; TURB, transurethral resection of the bladder.

These instillations might lead to severe toxicities and require strict follow up procedures and well-defined and sometimes urgent standardised treatment to optimise their tolerance and efficacy. Complications must be prevented with the implementation of strict rules: no instillations under pressure, sterile urine culture before each instillation, no macroscopic haematuria for BCG, no bladder perforation for chemotherapy.

After treatment, follow-up is based on repeated cytology and endoscopy, usually every 6 months, and upper tract exam (CT-based). Patients must be advised and helped to stop smoking.

**Prognosis of NMIBC**

Tumour recurrence and progression are the clinically relevant events associated with the diagnosis of NMIBC. Tumour recurrences and new occurrences are observed in approximately two-thirds of patients during follow-up, depending on several prognostic factors such as stage, grade, number, and size of initial lesions. The presence of recurrence at the first cystoscopy at three months is a strong predictor of prognosis. Progression from NMIBC to MIBC varies depending on stage, grade, number, and size of initial lesion/s from approximately 4% for low-grade Ta tumours to 50% for high-grade T1 tumours. Associated Cis is known to substantially increase the risk of progression.

**Follow-Up**

Patients with pTa, pT1, and low-grade tumours should receive UC and cystoscopy three to four times per year for the first two years and at six-monthly intervals for the following three years.
Patients with high-grade lesions or Cis should be followed at three-monthly intervals for the first three years and at six-monthly intervals thereafter.

Nothing special has to be considered for senior adults, except for an in-depth discussion regarding the benefits and drawbacks of instillations, especially for BCG. This is particularly important when side effects occur.

Treatment of Non-Metastatic MIBC
Real life data show that MIBC are undertreated worldwide, and especially in senior adults. The 5 and 10 year survival rates after radical cystectomy (RC) for MIBC are around 80% and 60% for organ confined disease, around 50% and 35% for non-organ confined disease (≥ pT3) and 35% and 30% in node positive disease. Systemic relapses are frequent, close to 20% for organ confined, 35% for non-organ confined and 50% for node positive disease.

The optimal way to manage T2-4 N0 M0 MIBC is neoadjuvant polychemotherapy containing cisplatin followed by RC and extended nodal dissection. This dissection comprises the bilateral obturator, internal and external iliac nodal region up to the primary iliac at the level of the crossing ureter. This is a minimum, and more extended templates have been suggested but are still under discussion. In men, this procedure includes “en bloc” removal of the bladder, the prostate and the seminal vesicles. In women, usually part of the anterior vaginal wall is removed with the uterus and the ovaries. Every attempt must be made not to perforate the bladder during the procedure, and to obtain negative surgical margins, including at least frozen sections at the urethral level.

Following cystectomy, urinary diversion is necessary. It can be either through an ileal conduit, with a neobladder, or with a continent catheterisable reservoir implanted most frequently at the lower right abdomen. These latter procedures are more surgically demanding and are associated with more post-operative complications compared with the ileal conduit. Finally, the real quality of life improvement is still under debate, although they lead to a better self-image compared with the ileal conduit.

This treatment approach is associated with significant mortality and morbidity, especially the surgical part. Therefore, treating senior adults represents a major challenge and this is best done by a specialist team.

Neoadjuvant chemotherapy is a must, provided patients are fit enough to receive polychemotherapy including cisplatin before surgery. It is associated with a 5% absolute (19% relative) survival benefit. Carboplatin has no place in this situation. The toxicity of GC (gemcitabine-cisplatin), MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) or DD MVAC (dose dense MVAC) must lead to a detailed discussion but usually precludes their use in patients above 75 years of age, even if physiologically fit.
RC in the senior adult is a major procedure, associated with a 90-day mortality rate of around 7%. However, the key driver of mortality is not age, but mainly the initial nutritional status and comorbidities. There is a trend suggesting a decreased mortality with a higher case load. Significant morbidity is frequent, mainly medical (e.g. infection, cardiovascular, pulmonary infections, disorientation) or surgical (mainly ileus and wound problems). Increased age is associated with increased morbidity, but again the key drivers are the initial comorbidities and the impaired cardiopulmonary reserve. In senior adults, morbidities are characterised by a prolonged recovery period. To optimise the outcome, the key is to implement a team including a surgeon, an anaesthesiologist and also a paramedical team.

Ileal neobladder is feasible beyond 75 years and can be discussed in male patients. However, there is a clear decreased continence rate with increasing age, as well as an increased self-catheterisation need. Therefore, the ileal conduit is the standard in senior adults.

Initial comorbidity evaluation is mandatory. The Charlson score is not designed for everyday use in clinic. This evaluation is best done by a comprehensive geriatric assessment which will detect frail and vulnerable patients, allow the optimisation of the patient’s medical conditions, finally leading to optimised treatment decisions. It is time consuming, and limited by the availability of a geriatrician. An effective screening tool is available (the G8) that allows for an effective discrimination of those patients in need of the comprehensive geriatric assessment.

Alternative procedures to the standard RC have been developed. A very aggressive deep and extended TURB monotherapy is feasible for very selected patients. Similar results have been suggested with partial cystectomy, provided the lesion is located on the mobile part of the bladder. The most studied alternative however is the combination of pelvic and bladder radiotherapy associated with chemotherapy. Most studies have used cisplatin-based chemotherapy or the combination of mitomycin C and 5-fluorouracil (which allows renal function down to 25 ml/min). Radiotherapy is usually given at a dose of 65 Gy to the bladder and 45 Gy to the pelvis. The main results are a well-functioning bladder, improved local control, but a lack of survival benefit compared with radiotherapy monotherapy. A formal comparison with radical surgery is lacking, but this modality represents an acceptable alternative for unfit patients or those unwilling to undergo a cystectomy. In all of these conservative approaches, the best survival results have been obtained in patients with a single T2 lesion, less than 3 cm, without Cis and hydronephrosis. The combination of radiotherapy with concomitant chemotherapy is also effective in more advanced lesions. Patients must be aware that the remaining bladder carries a risk of relapse in up to approximately 50% of NMIBC, requiring a standard approach and close to 20% of MIBC, where radical cystectomy is the standard of care, provided it is feasible.

In the frailest patients, external beam radiotherapy is effective for palliation, and hypofractionation is an attractive modality.
Treatment of Metastatic MIBC

Metastatic BC is associated with an overall poor prognosis. It might be approached using the Bajorin classification based on performance status (PS), location of the metastases and haemoglobin level. The median survival is around 36 months (Karnofsky PS > 80, no visceral metastases, normal haemoglobin level) compared with 12 months if PS < 80, visceral metastases and anaemia are present.

The standard regimen is cisplatin-based polychemotherapy (either MVAC, DD MVAC or GC). The response rate is around 50%, the complete response rate around 20%, and the overall median survival around 14 months. The main prerequisite is an adequate renal function, either estimated using the MDR formula, or a real measured renal clearance.

There are limited data on senior adults as they are under-represented in clinical trials. Furthermore, they often have a decreased bone marrow reserve. At least 50% are unfit for cisplatin either due to poor renal function (creatinine clearance < 60 ml/min) and/or an ECOG PS < 2. In cases where one of these two criteria is met, the options are limited to carboplatin-based combination regimens (such as carboplatin –gemcitabine). When both criteria are met, based on the very poor outcome, a detailed discussion is mandatory as best supportive care/palliative care might often represent the best treatment option.

Relapse after first-line treatment is associated with a median survival between 5 to 12 months, depending on several risk factors. In theory if the relapse is more than 6-12 months after the first regimen, another platinum-based regimen is standard of care, if feasible. This will be the exception in senior adults. Provided the patient has a PS 0-1, a vinflunine-based regimen might be discussed. Otherwise best supportive/palliative care will be the standard.

Further Reading

Chapter 17 – Gynaecological Cancer in the Senior Patient

Introduction
About 20% of visceral cancers in women are of the genital tract. The top three genital tract malignancies are uterine, ovarian, and cervical cancers. The lifetime risk of developing these cancers in an industrialised country is respectively 1 in 38, 1 in 68, and 1 in 135. Unfortunately, many women are not treated according to the guidelines, which results in a poor survival. A lack of surgical skills, poor tolerance and fear of toxicity in older patients all contribute to this. When chemoradiation is indicated, cisplatin is indicated which is not appropriate for all older patients, therefore patient selection is critical. This chapter gives a basic overview of the different treatment strategies for local, locoregional, and metastatic genital tract cancers in senior women.

Cervical Cancer
The staging of cervical cancer is clinically based on the Fédération Internationale de Gynécologie Obstétrique (FIGO) staging system. The squamous carcinomas account for 80% of all cases and are declining due to the screening. Adenocarcinomas account for 15% of cases, but the incidence has almost doubled during the last 20 years despite screening.

The diagnosis is made by a (cone) biopsy. The average age of a women with cervical cancer is between 35 and 45. The 2008 FIGO staging system is used.

Among other rare types of cervical cancer are neuroendocrine small cell carcinomas of the cervix. The treatment of these carcinomas should conform to those of small cell lung cancer.

Stage 0 Cervical Cancer
This is carcinoma in situ. The five-year survival rate is 100%. Treatment could be conisation (preferable) or hysterectomy. One can opt for the latter if the patient has other gynaecological problems.

Stage I Cervical Cancer
This is cancer strictly confined to the cervix, and it can be divided into IA and IB. The five-year survival is about 80%. Surgery for these patients is the preferred approach. However, if the patient is unfit for surgery, one can opt for concomitant chemoradiation or radiotherapy alone.

Stage IA1
This stage includes tumours with stromal invasion of 3 mm in depth and horizontal extension of 7 mm. Adenocarcinomas and adenosquamous carcinomas should be treated in the same way as squamous carcinomas.
• If there is no lymphovascular space invasion (LVSI), the preferred treatment is conisation or type 1 hysterectomy if there are associated (benign) problems. There is no indication for node dissection (lymph node metastasis rate is <0.5%) or ovariectomy.

• If there is LVSI, the preferable treatment in elderly women is a type 1 or 2 hysterectomy with pelvic node dissection. A node dissection is indicated since the lymph node metastasis rate is up to 4.7%. There is no indication for an ovariectomy. An alternative to a hysterectomy could be a conisation or modified radical trachelectomy for younger patients who wish to preserve fertility.

Stage IA2
This stage includes tumours with a stromal invasion of >3 mm and 5 mm in depth and horizontal extension of 7 mm.

• If there is no LVSI, the rate of lymph node metastasis is up to 3.4%. The treatment could be conisation or a type 1 hysterectomy or, alternatively, a radical trachelectomy or a type 2 hysterectomy. All procedures should be combined with a pelvic (laparoscopy/laparotomy) lymph node dissection. There is no indication for an ovariectomy.

• If there is LVSI, the rate of lymph node metastasis is up to 11.1%. The treatment options are radical trachelectomy with pelvic lymph node dissection or a type 2 hysterectomy with pelvic node dissection. There is no indication for an ovariectomy.

Stage IB1
This is a clinically visible lesion up to 4.0 cm in greatest dimension.

• One should opt for a radical hysterectomy. The operation should always be combined with a bilateral pelvic lymphadenectomy. Alternatively, a radical trachelectomy, either vaginal or abdominal, can be performed. The radical trachelectomy should ideally be reserved for patients with a well-differentiated tumour of less than 2 cm in size and no evidence of LVSI. Depending on final pathology (presence of LVSI, depth of cervical invasion and tumour size) the patient may or may not require postoperative radiation therapy or chemoradiation therapy.

• Another approach is definitive concomitant chemoradiation therapy.

Stage IB2
This is a clinically visible lesion >4.0 cm. The treatment can be a type 2 or 3 radical hysterectomy with bilateral pelvic and para-aortic lymph node dissection or concomitant chemoradiation.

Primary concomitant chemoradiation [cisplatin 40 mg/m2/week intravenously during radiotherapy (six weeks)] is equally effective as primary radical surgery for disease-free
and overall survival. Treatment choice is based on the features of the tumour, the treatment-related morbidity, condition, and wishes of the patient. One should try to avoid the combination of chemoradiation and radical surgery to reduce therapy-related morbidity.

Patients with lymph node metastasis or positive tumour margins should receive adjuvant concomitant chemoradiation. Ideally, surgery should be performed on patients without lymph node involvement. Sentinel node biopsy may be ideal to tailor the treatment. The technique is feasible, but its sensitivity and specificity are unclear at the moment. Studies are ongoing to evaluate the value of sentinel node biopsy in patients with cervical cancer. Until the results are known, sentinel node biopsy cannot be considered as the standard approach for patients with cervical cancer.

**Stage II**

Tumour extends beyond the cervix but not to the pelvic sidewall nor to the lower third of the vagina. The five-year survival is 60%.

Stage II is subdivided into the following:

- IIA tumour: no parametrial involvement
- IIA1: clinical lesion ≤4.0 cm
- IIA2: clinical visible lesions >4.0 cm Treatment in the same way as stage IB
- IIB tumour: with obvious parametrial involvement

Treatment: concomitant chemoradiation is the preferred approach.

**Stage III**

The tumour extends to the pelvic sidewall and/or the lower one-third of the vagina and/or causes hydronephrosis or a nonfunctioning kidney. Overall survival is 30%.

Stage III is subdivided into the following:

- IIIA: Tumour involves lower third of the vagina, with no extension to the pelvic wall.
- IIIB: Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.

The preferred treatment is concomitant chemoradiation.

**Stage IV**

Tumour extends beyond the true pelvis or involves (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a patient to be allotted to stage IV. Overall survival is 5%.

It is subdivided into the following:
• IVA: spread of growth to adjacent organs. Standard treatment is concomitant chemoradiation. If there are fistula or if it is only localised disease with no signs of disease outside the pelvis, one can opt for pelvic exenteration. However, this leads to a high morbidity, and careful staging is of utmost importance.
• IVB: spread to distant organs. Treatment is palliative and consists of chemotherapy. Chemotherapy (e.g., cisplatin, carboplatin, paclitaxel, or topotecan) can give a response in up to 30% of patients. In a new study, bevacizumab has also been shown to be effective in combination with chemotherapy (paclitaxel and cisplatin).

Bevacizumab
Bevacizumab is approved by the European Medicines Agency (EMA) and the Food and Drug Administration of the United States (FDA). The EMA has approved the drug for first line treatment of patients with stages III and IV epithelial ovarian, fallopian-tube, or primary peritoneal cancer, in combination with carboplatin and gemcitabine in first recurrence of platinum-sensitive epithelial-ovarian, fallopian-tube or primary peritoneal cancer with no prior therapy with bevacizumab and in combination with paclitaxel and cisplatin, or paclitaxel and topotecan, in patients who cannot receive platinum therapy. In ovarian cancer, the FDA approval is for platinum resistant disease only. The approvals were based on progression free survival data with improvements of 2-4 months. This must be weighed versus the known increased toxicity of bevacizumab in older patients including arterial thromboembolic events, hypertension and perforation. It is also approved for the treatment of patients with persistent, recurrent, or metastatic carcinoma of the cervix.

BRCA
BRCA mutation is a mutation in either of the BRCA1 or BRCA2 genes. They are tumor suppressor genes in which harmful mutations can lead to an increase of ovarian cancer, primarily high grade serous carcinoma. Testing for these mutations has become an integral part of care of these patients. The detection of these genes is helpful in screening for other disorders, particularly breast cancer in the patient, siblings, children and other relatives. This can include decisions regarding risk-reducing surgery and chemoprevention.

Olaparib is a targeted therapy approved by both the FDA and EMA. The oral drug is an inhibitor of PARP (poly ADP ribose polymerase), which is involved in DNA repair. The FDA has approved it for germline BRCA-mutated advanced ovarian cancer after three or more lines of chemotherapy. The EMA approval in BRCA-mutated patients includes maintenance therapy of high grade serous ovarian cancer and patients who have recurrent disease after platinum based therapy where the response was ≥6 months.

Uterine Cancer
Uterine cancer is the most common malignancy of the female tract in the industrialised world. Its incidence in women < 65 years is 13.1/100,000 and in women >65 years
The incidence worldwide is 17.8/100,000. The 2008 FIGO staging system is used.

Stage I
In stage I the tumour is confined to the uterine corpus. The five-year survival is about 90%.

Stage I can be divided into the following:

• IA: None or less than half of the myometrium is invaded. Treatment consists of hysterectomy with bilateral salpingo-oophorectomy; lymph node dissection should be considered if the tumour is FIGO grade II/III. In patients with papillary serous or clear cell carcinoma histology, a lymph node dissection should also be performed.
• IB: Invasion to at least half of the myometrium. The preferred treatment is a hysterectomy with bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node dissection.

More recently the sentinel lymph node mapping algorithm is being performed in clinically early stage disease in lieu of a systematic lymph node dissection. Adjuvant radiotherapy is indicated in case of lymph node involvement. Other factors for adjuvant treatment include depth of myometrial invasion, the presence of LVSI, age, and grade. Adjuvant chemotherapy is probably as effective as radiotherapy in early stage endometrial cancers. In patients with high risk pathology such as papillary serous or clear cell carcinoma, the preferred treatment is carboplatin in combination with paclitaxel.

Stage II
In stage II the tumour invades the cervical stroma but does not extend beyond the uterus. The five-year survival is between 70% and 80%. Treatment is similar to that for stage IB. Adjuvant radiation therapy is usually recommended.

Stage III
In this stage there is local and/or regional spread of the tumour. Positive cytology has to be reported separately without changing the stage. The five-year survival is about 30% to 60%.

Stage III can be divided into the following:

• IIIA: Tumour invades the serosa of the corpus uteri and/or adnexae.
• IIIB: Vaginal and/or parametrial involvement.
• IIIC: Metastases to pelvic and/or para-aortic lymph nodes.
• IIIC1: Positive pelvic nodes.
• IIIC2: Positive para-aortic lymph nodes with or without positive pelvic lymph nodes.
Treatment is similar to stage IV disease.

**Stage IV**
In stage IV the tumour invades bladder and/or bowel mucosa, and/or distant metastases are present. The five-year survival is about 10%.

Stage IV can be divided into the following:

- IVA: tumour invasion of bladder and/or bowel mucosa
- IVB: distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Stages III and IV are best treated by optimal cytoreductive surgery followed by systemic chemotherapy and/or radiotherapy. Chemotherapy regimens should preferably include doxorubicin and cisplatin or carbo platin and paclitaxel. When there is widespread metastatic disease and the tumour is oestrogen receptor and/or progesterone receptor positive, hormonal therapy (progestins, tamoxifen, or aromatase inhibitors) should be considered. This can be alone or following chemotherapy.

Pelvic exenteration should be considered when the tumour is limited to the bladder or rectum.

**Special Types of Endometrial Malignancy**
About 3% of endometrial malignancies are sarcomas. Uterine sarcomas can be classified as leiomyosarcoma, endometrial stromal sarcoma, high-grade undifferentiated sarcoma (HGUD), or pure heterologous sarcoma. The 2008 FIGO staging system is used. The treatment of leiomyosarcomas, endometrial stromal sarcomas, and adenosarcomas consists of a hysterectomy without lymph node dissection (see details below). A bilateral salpingo-oophorectomy is recommended for postmenopausal women or those with stromal sarcomas. The clinical course of uterine sarcomas is difficult to predict and the staging systems are likely not adequate to predict outcomes. Until today there are no proven adjuvant strategies to improve survival in patients diagnosed with early stage uterine sarcomas. Therefore, generally no adjuvant treatment is recommended.

**Leiomyosarcomas and Endometrial Stromal Sarcomas**

**Stage I: Tumour limited to uterus**
- IA ≤5.0 cm
- IB >5.0 cm

**Stage II: Tumour extends beyond the uterus, within the pelvis**
- IIA Adnexal involvement
- IIB Involvement of other pelvic tissues
Stage III: **Tumour invades abdominal tissues (not just protruding into the abdomen)**
- IIIA 1 site
- IIIB >1 site
- IIIC Metastasis to pelvic and/or para-aortic lymph nodes

Stage IV
- IVA Tumour invades bladder and/or rectum
- IVB Distant metastasis

*aSimultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent tumours.*

Adenosarcomas

**Stage I: Tumour limited to uterus**
- IA Tumour limited to endometrium/endocervix with no myometrial invasion
- IB Myometrial invasion ≤50%
- IC Myometrial invasion >50%

**Stage II: Tumour extends beyond the uterus, within the pelvis**
- IIA Adnexal involvement
- IIB Involvement of other pelvic tissues

**Stage III: Tumour invades abdominal tissues (not just protruding into the abdomen)**
- IIIA 1 site
- IIIB >1 site
- IIIC Metastasis to pelvic and/or para-aortic lymph nodes

**Stage IV**
- IVA Tumour invades bladder and/or rectum
- IVB Distant metastasis

Carcinosarcomas should be staged and treated as carcinomas of the endometrium. The treatment includes hysterectomy and bilateral salpingo-oophorectomy and generally requires platinum based adjuvant chemotherapy with or without radiation therapy.

In advanced stages of leiomyosarcomas, chemotherapy and/or hormonal therapy should be used. The endometrial stromal sarcomas and adeno- sarcomas are preferably treated with hormonal therapy.

**Vaginal Cancer**
Primary vaginal cancers represent only 2% of female genital tract malignancies. It is mainly a disease of women > 60 years of age. Women treated for anogenital
precancerous lesions or cancer in the past are considered to be at high risk for vaginal cancer. The 2008 FIGO staging system is used.

**Stage 0**
Stage 0 represents a carcinoma in situ. The five-year survival is 100%. The preferred treatment is surgical excision of the lesion.

**Stage I**
In stage I the disease is limited to the vagina wall. The five-year survival in 70%.

The preferred treatment is an excision of the lesion (so-called partial or complete vaginectomy) and lymph node dissection.

- If the lesion is in the upper one-third of the vagina, pelvic lymphadenectomy should be performed.
- If the lesion is located in the lower one-third part, an inguinal lymphadectomy should be performed.
- If the lesions are located in the middle, both inguinal and pelvic lymphadnectomy should be performed.

Sentinel node biopsy will be helpful in determining which nodes should be removed, but at present there are no data supporting the use of this procedure and, because of the rareness of the disease, it is unlikely that there will be any data to support the use of sentinel node biopsy in vaginal cancer.

Concomitant chemoradiation can be used as an alternative to surgery.

**Stage II**
In stage II the carcinoma involves the subvaginal tissue but has not extended to the pelvic wall. The five-year survival is 50%. The treatment is similar to that for stage I disease.

**Stage III**
In stage III the carcinoma has extended to the pelvic wall. The five-year survival is 20%. If possible, surgery can be considered; however, the preferable treatment in this stage is concomitant chemoradiation.

**Stage IV**
In stage IV the carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous oedema, as such, does not permit a patient to be allotted to stage IV.

Stage IV can be divided into the following:
• IVA: Tumour invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis. Treatment: In localised disease, a pelvic exenteration is a surgical option with a cure rate of about 50%.
• IVB: Spread to distant organs. Treatment: Palliative chemotherapy can be considered.

The prognosis of stage IV disease is poor, with a five-year survival of <10%. However, in case of a rectovaginal or vesicovaginal fistula with distant disease, one should also consider exenteration or derivation surgery to improve quality of life.

Adjuvant concomitant chemoradiation is recommended in case of lymph nodes or surgical margin involvement.

**Vulvar Cancer**
Primary vulvar cancers represent about 4% of female genital tract malignancies. It is mainly a disease for women older than 60 years. The 2008 FIGO staging system is used.

**Stage 0**
Stage 0 represents a carcinoma in situ. The five-year survival is 100%. The preferred treatment is surgical excision of the lesion. Alternatively, after invasive disease has been ruled out, topical administration of 5-fluorouracil or imiquimod can be used.

**Stage I**
In stage I the tumour is confined to the vulva. Stage I can be divided into the following:

- IA: The lesions are ≤2.0 cm in size, confined to the vulva or perineum and with stromal invasion <1.0 mm and no nodal metastasis(es). Treatment consists of wide local excision (tumour-free margin ≤1.0 cm) without lymph node dissection.
- IB: The lesions are >2.0 cm in size or with stromal invasion ≤1.0 mm, confined to the vulva or perineum with negative nodes. Treatment consists of wide local excision or (hemi)vulvectomy (tumour-free margin ≤1.0 cm) with lymph node dissection.
  - The use of sentinel node biopsy is recommended for evaluation of the lymph nodes.
    - If the lymph node is involved, an inguinofemoral lymphadenectomy should be performed.
    - For centralised lesions, a bilateral inguinofemoral lymphadenectomy is indicated.
    - For lateralised lesion, an ipsilateral inguinofemoral lymphadenectomy is performed.
  - Adjuvant chemoradiation is indicated in patients with involved lymph nodes or margins, which cannot be re-resected. Cisplatin is preferably used as a radiation sensitiser.
Stage II
Stage II consists of a tumour of any size with extension to adjacent perineal structures (one-third of lower urethra, one-third of lower vagina, anus) without lymph node involvement.

Treatment is similar to that for stage IB.

Stage III
Stage III encompasses a tumour of any size with or without extension to adjacent perineal structures (one-third of lower urethra, one-third of lower vagina, anus) with involvement of inguinofemoral lymph nodes.

Stage III can be divided into the following:

- IIIA: (i) one or two lymph node metastasis(es) (<5.0 mm) or (ii) one lymph node metastasis (≥5.0 mm)
- IIIB: (i) three or more lymph node metastases (<5.0 mm) or (ii) two or more lymph node metastases (≥5.0 mm)
- IIIC: positive lymph nodes with extracapsular spread

The treatment should be individualised. In selected patients, radical vulvectomy with bilateral inguinofemoral lymphadenectomy is indicated, which is sometimes preceded by neoadjuvant chemotherapy and postoperative radiotherapy. All other patients should be treated by definitive chemoradiation.

Stage IV
In stage IV the tumour invades other regional (two-thirds of upper urethra, two-thirds of upper vagina) or distant structures.

It can be divided into the following:

- IVA: Tumour invades any of the following: (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone or (ii) fixed or ulcerated inguinofemoral lymph nodes. Treatment: See stage III. In cases of fistulisation or centralised local disease, an exenteration can be considered.
- IVB: Any distant metastasis(es) including pelvic lymph nodes. Treatment consists of palliative chemotherapy (e.g. cisplatin, carboplatin, paclitaxel, or topotecan) and can result in a response in up to 20% of patients.

Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer
For staging of ovarian and primary peritoneal cancer, the FIGO 1988 staging system is used, while for fallopian tube cancer, the 1991 system is used. The majority of women
(70%) are diagnosed in an advanced stage (III/IV). The five-year survival for these stages is <50%.

Staging of Ovarian Cancer

**Stage I: Growth limited to the ovaries**
- IA Growth limited to one ovary; no ascites present containing malignant cells. No tumour on the external surface; capsule intact.
- IB Growth limited to both ovaries; no ascites present containing malignant cells. No tumour on the external surfaces; capsules intact.
- IC Tumour either stage IA or IB, but with tumour on the surface of one or both ovaries or with capsule ruptured or with ascites present containing malignant cells or with positive peritoneal washings.

**Stage II: Growth involving one or both ovaries with pelvic extension.**
- IIA Extension and/or metastases to the uterus and/or tubes.
- IIB Extension to other pelvic tissues.
- IIC Tumour either stage IIA or IIB, but with tumour on the surface of one or both ovaries or with capsule(s) ruptured or with ascites present containing malignant cells or with positive peritoneal washings.

**Stage III: Tumour involving one or both ovaries with histologically confirmed peritoneal implants outside implants outside the pelvis and/or positive regional lymph nodes. Superficial liver metastases equals stage III disease. Tumour is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum.**
- IIIA Tumour grossly limited to the true pelvis, with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces or histologically proven extension to the small bowel or mesentery.
- IIIB Tumour of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, not exceeding 2.0 cm in diameter; nodes are negative.
- IIIC Peritoneal metastasis beyond the pelvis >2.0 cm in diameter and/or positive regional lymph nodes.
Stage IV: Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastasis equals stage IV disease.

Staging of the Cancer of the Fallopian Tube

Stage 0: Carcinoma in situ (limited to tubal mucosa).

Stage I: Growth limited to the fallopian tubes.

- IA Growth is limited to one tube, with extension into the submucosa and/or and/or muscularis but not penetrating the serosal surface; no ascites.
- IB Growth is limited to both tubes, with extension into the submucosa and/or muscularis but not penetrating the serosal surface; no ascites.
- IC Tumour either stage IA of IB, but with tumour extension through or into the tubal serosa or with ascites present containing malignant cells or without positive peritoneal washings.

Stage II: Growth involving one or both fallopian tubes with pelvic extension.

- IIA Extension and/or metastasis to the uterus and/or ovaries.
- IIB Extension to other pelvic tissues.
- IIC Tumour either stage IIA of IIB and with ascites present containing malignant cells or with positive peritoneal washings.

Stage III: Tumour involves one or both fallopian tubes, with peritoneal implants outside the pelvis and/or positive regional lymph nodes. Superficial liver metastasis equals stage III disease. Tumour appears limited to the true pelvis, but with histologically proven malignant extension to the small bowel or omentum.

- IIIA Tumour is grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
- IIIB Tumour involving one or both tubes, with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2.0 cm in diameter. Lymph nodes are negative.
- IIIC Abdominal implants >2.0 cm in diameter and/or positive retroperitoneal or inguinal nodes.

Stage IV: Growth involving one or both fallopian tubes with distant metastases. If pleural effusion is present, there must be positive cytology to categorised as stage IV disease. Parenchymal liver metastases equals stage IV disease.

Treatment

Borderline Tumours

The treatment should only consist of a surgical resection of the tumour and implants. There is no role for lymphadenectomy or adjuvant chemo- or radiotherapy.
**Invasive Ovarian and Peritoneal Cancers**

Patients with invasive cancers should have a meticulous surgical staging. The staging includes an en bloc resection of the ovarian tumour and the other ovary, hysterectomy, pelvic and para-aortic lymphadenectomy, omentectomy, aspiration of free fluid or peritoneal washings, and systematic exploration of the lower and upper abdomen with removal of all adhesions or suspicious lesions. In mucinous tumours, an appendectomy should also be performed.

The goal of surgery is the removal of all visible lesions (optimal debulking or cytoreductive surgery to obtain no visible residual disease). If this cannot be achieved, the value of surgery is minimal. When the preoperative evaluation indicates that the patient cannot be optimally debulked because of extensive disease or when the patient is in a poor surgical condition, one should opt for neo-adjuvant chemotherapy. In case of a response allowing optimal surgery, interval debulking surgery should be performed. Sometimes palliative surgery is performed to improve the quality of life.

Adjuvant chemotherapy should be given to all patients with stage IA (grades II and III), IB (grade II and III), IC, II, III, and IV. The combination of carboplatin with paclitaxel is the first choice. It can be administrated intravenously or, in selected patients, intraperitoneally (paclitaxel and cisplatin).

**Relapse of Ovarian and Peritoneal Cancers**

The majority of patients will relapse. The time to relapse is important for determining treatment. If the disease relapses six months or more after completion of first-line therapy, the disease is considered to be platinum-sensitive and platinum-based chemotherapy can be used again. If the disease relapses within six months, other drugs should be used. These other drugs include single-agent or combination therapy of liposomal doxorubicin, gemcitabine and topotecan. Alternatively, one can opt for tamoxifen (hormonal therapy) or bevacizumab (monoclonal antibody therapy). Secondary cytoreductive surgery should only be performed in select cases with resectable disease before initiating chemotherapy.

**Conclusion**

Selected gynaecological cancers are mainly observed in senior patients, and for many, cancer surgery is the main treatment option. Senior patients should receive the same treatment as younger women if their surgical condition allows optimal surgery. The multimodality treatment of gynaecological malignancies should be considered in fit senior patients, but interdisciplinary cooperation is of utmost importance to select the appropriate treatment for the individual senior patient.

**Further Reading**

Chapter 18 – Head and Neck Cancer in the Elderly

Introduction
Malignancies of the head and neck region represent the seventh most common cancer type with 650,000 new cases and 350,000 deaths each year worldwide. The majority of head and neck malignancies occur between the fifth and sixth decades of life. In addition, approximately 40% of all patients diagnosed with tumours of the head and neck region are over the age of 65 years. It is estimated, that the incidence will increase to 60% by the year 2030. Squamous cell carcinoma is the most frequent histological type of head and neck cancer and accounts for 95% of all cases.

There is a different clinical profile of squamous cell carcinoma of the head and neck (SCCHN) in senior patients. The main sites of SCCHN in elderly patients are the oral cavity and the larynx. Carcinomas of the oropharynx are not as common as they are in younger patients. In addition, compared to younger patients, the involvement of regional lymph nodes is less frequent, while T stage distribution appears to be similar. The sex ratio is slightly higher in women. SCCHN in elderly patients is less frequently associated with tobacco use and positive human papillomavirus (HPV) status.

Retrospective studies support elderly fit patients, with early stage disease, being treated with surgery or radiotherapy (RT) with curative intent, similar to younger patients. Locally advanced disease often represents a therapeutic dilemma. Curative intent from multimodality therapy utilising surgery, RT, chemotherapy and targeted therapy in various combinations should be balanced against potential toxicity and co-morbidities in order to provide optimal therapeutic plans for elderly patients. Impaired organ function, co-morbidities, poly-pharmacy, distinct metabolism and life expectancy, should all be taken into account in decision making.

Surgery
Surgery alone can be a reasonable option for early stage disease in senior patients according to data from retrospective series. The efficacy of surgical excision and operative morbidity rates in elderly patients are comparable to those of younger patients who are treated in a similar way. Favourable clinical outcomes of aggressive surgical management, for locally advanced disease in elderly patients, is shown within the majority of retrospective studies. Surgical mortality, complications and resectability rates in elderly patients were similar to those of young patients, even in the case of major surgical procedures. Age itself should not be considered a limiting factor in the surgical management of an otherwise fit elderly patient. Patients with comorbidities on the other hand can experience significant post-operative complications and might not be ideal surgical candidates. Preoperative frailty assessments of these patients is required before initiation of aggressive surgical procedures.
Improved survival in elderly patients, who are treated aggressively for SCCHN, underscores the necessity for integration of reconstructive surgery in the surgical plan. Retrospective data indicate that free flaps can be used safely and efficiently in senior patients. Post-operative complications are associated with the presence of comorbidities, rather than with the presence of advanced chronological age.

In conclusion, surgical management of advanced disease, in medically fit elderly patients, should be considered if radical resection of the tumour with acceptable functional outcome is feasible.

**Radiotherapy**

RT represents both a potential option for radical treatment of SCCHN and an effective palliative procedure for symptomatic relief. In early stage glottic and oropharyngeal cancer, radical RT alone achieves high rates of loco-regional control which are equivalent to surgical approaches, while allowing for organ preservation and better quality of life. In addition, RT can be an alternative option for surgically unfit patients and for patients to whom major functional impairment is to be expected after surgery. Despite the wealth of prospective data on the management of SCCHN with RT, trials dealing with the subgroup of elderly patients with SCCHN treated with RT are lacking.

According to the majority of retrospective studies, RT alone, in elderly SCCHN patients, is well tolerated and provides high rates of local control and overall survival. A secondary analysis of five prospective studies, with 1598 patients with SCCHN who received RT, revealed similar loco-regional control and survival rates among young and elderly patients. Importantly, acute and late toxicity rates were not influenced by age.

The meta-analysis (MARCH) evaluating hyperfractionated or accelerated RT versus conventional RT in SCCHN patients, found altered RT is more beneficial to loco regional tumour control and overall survival. Nevertheless, the positive effect on the overall survival of altered RT decreased with increasing age. The delivery of altered RT in elderly patients was associated with a decrease in patient tolerance and patient compliance when compared to both younger patients or to patients who were treated with conventional RT. Interestingly, a recent update of this meta-analysis revealed the proportion of non-cancer related deaths increased as age increased (18% at the age of 50 years and 41% at the age over 71 years). Given recent data about the effect of altered RT on overall survival in senior patients, it is not clear whether these patients benefit from this approach. In summary, existing data on senior patients indicate that conventional RT (1.8-2 Gy / fraction for 5-7 weeks) is the gold standard for these patients.

**Chemoradiation**

Concomitant chemoradiation represents a combined treatment modality which is applied with curative intent for advanced locoregional SCCHN. Postoperative chemoradiation is indicated for some patients with specific risk factors (positive margins, residual disease,
extra-capsular lymph node invasion), since it improves loco-regional control rates. Data supporting the positive effect of combination treatment for elderly patients with advanced stages are scarce.

Results from retrospective studies addressing the role of concomitant chemoradiation for elderly patients with SCCHN show mixed results. Some, elderly and younger patients have similar survival and side effects rates from multi-modality treatment. Whereas in others, advanced age is associated with inferior outcomes. Controversy in the results of these studies largely reflects the diverse populations, as well as the bias related to the retrospective nature of the relevant data. In contrast to the group of studies which compare older to younger patients, a recent single institution retrospective study included a comparison between elderly patients with advanced disease, who receive single modality treatment, and those treated with multi-modality therapy. While elderly patients on multimodality therapy had similar survival to younger patients, elderly patients on single modality therapy had strikingly inferior outcomes. Although these results should be interpreted with caution and under the prism of the retrospective design, they indicate that there is a subgroup of elderly patients who benefit from aggressive therapy. Therefore, elderly patients should be offered multi-modality therapy, if they are otherwise medically fit to be treated aggressively. The effect of adding chemotherapy to loco-regional treatment was the subject of a meta-analysis (MACH-NC). A total number of 87 trials were included and data from approximately 16,500 patients were analysed. The addition of chemotherapy improved survival, however this was less clear with increasing age. An increased number of non-cancer related deaths with increasing age (15% at the age of 50 years, 39% at the age of more than 70 years) might account for no overall survival benefit being demonstrated in this age group.

In interpreting the data, we need to take into account that elderly patients are a heterogeneous group: at the end of the spectrum, frail patients will not benefit from aggressive approaches whereas at the other end, patients with favourable biologic age could be treated aggressively, despite their advanced chronologic age. In conclusion, existing evidence indicates that multi-modality therapy offers a survival benefit in appropriately selected elderly patients.

**Chemotherapy and Targeted Therapies**

**Chemotherapy**

Chemotherapy represents the gold standard for recurrent and metastatic SCCHN. The benefit of chemotherapy for senior patients was reported in a landmark study combining data from two phase III trials (ECOG 1393 & ECOG 1395). Both studies used cisplatin-based regimens and showed similar overall survival and loco regional control rates, for both elderly and younger patients. Elderly patients had higher rates of nephrotoxicity, diarrhoea and thrombocytopenia. Toxicity-related death rates were higher for elderly patients than they were for younger patients. However, these differences were not statistically significant.
Targeted Therapies
Cetuximab (monoclonal antibody against epidermal growth factor receptor [EGFR]), can be a significant component of front line and salvage treatment in recurrent and metastatic SCCHN, as well as part of multimodality treatment in regionally advanced disease. It is perceived to be better tolerated compared to chemotherapy and as such its use is increasing in the elderly population. Despite trends in clinical practise, evidence for cetuximab favourable safety profile over chemotherapy, in older patients, is limited. While it remains an option, one should not assume that its use is always safe, especially when combined with RT in frail patients.

Geriatric Assessment
Factors which influence diagnosis and treatment of the patient, like comorbidity, decline of physical activity, polypharmacy, geriatric syndromes, malnutrition and socioeconomic issues are often associated with ageing. According to a large retrospective study by Peters et al, comorbidity represents a prognostic factor for senior patients with SCCHN. The most frequently applied diagnostic tools for frailty assessment are Vulnerable Elders Survey-13 (VES-13), G8 and the Combined Screening Tool 'VES-13 + (17-G8)' or CST. Comprehensive geriatric assessment (CGA) is mandatory, if screening tools are positive. A multidisciplinary approach, combined with the utilisation of CGA, may facilitate appropriate therapeutic decision making for senior patients with advanced stage disease. Finally, an ongoing phase III trial is studying the impact of CGA on overall survival, function and nutrition in elderly patients with SCCHN.

Conclusions
With an ageing population, caring for the geriatric patient with cancer is becoming an increasingly common clinical scenario. SCCHN is particularly challenging in this regard, both the cancer and its treatment can have a tremendous burden on the patient’s quality of life. The disease and its treatment, affect an anatomic site which is vital for food intake, breathing, speech and one’s sense of identity and well-being. Existing evidence predominately comes from retrospective data and indicates that biological age better determines treatment benefits, compared to chronological age. Oncologists should not withhold treatment merely on the basis of age, nevertheless they should be cautious with aggressive treatment in frail geriatric patients with SCCHN.

Further Reading
• Moye VA, Chandramouleeswaran S, Zhao N et al. Elderly patients with squamous cell carcinoma of the head and neck and the benefit of multimodality therapy. Oncologist 2015; 20: 159-165.
• Peters TT, Post SF, van Dijk BA et al. Free flap reconstruction for head and neck cancer can be safely performed in both young and elderly patients after careful patient selection. Eur Arch Otorhinolaryngol 2014.
Chapter 19 - Renal Cell Cancer

Introduction
Renal cell carcinoma (RCC) primarily affects older individuals, with approximately half of all new RCC diagnoses being made in people aged 65 or older. An incidence of more than 60,000 cases is expected in 2016. Epidemiological studies have shown that up to two-thirds of 75-year old renal cancer patients also suffer from conditions such as hypertension, cardiovascular disease, or diabetes.

Several of the novel targeted agents are associated with toxicities such as hypertension or diarrhoea, which have special relevance to an elderly population. Drugs used to manage comorbid conditions (such as antihypertensives and oral anticoagulants) may interact with agents given to treat renal cancer, altering pharmacokinetics and potentially increasing toxicity, reducing efficacy, or both. Furthermore, some side effects of targeted agents (e.g. fatigue, diarrhoea, and dehydration) are exacerbated in older patients with cognitive impairment and may result in delirium. Fatigue and asthenia are also frequently observed and clinically significant side effects of targeted agents in elderly patients. Physical therapy may be a suitable preventive intervention in patients who experience these symptoms.

It should be emphasised that although toxicity is not always more frequent in the elderly population its impact may be greater than in younger patients. Therefore, targeted agents commonly associated with these side effects should be carefully monitored and attention should be given to the dose used and potential pharmacological interactions, with additional supportive measures, such as hydration, being provided by caregivers.

Surgery in the Senior Cancer Patient
The potential risks and benefits of cytoreductive nephrectomy in elderly renal cancer patients have been compared with those in a younger age group. In this study, 79% of patients in both groups had distant metastases. The results confirmed the additional surgical risk in patients aged over 75 years: perioperative mortality (i.e. within a month of surgery) was 21% (5 deaths in 24 patients), compared with 1% in a large cohort of younger patients with similar disease characteristics and performance status. Early mortality in the elderly was associated with longer surgical time and greater blood loss, which the investigators suggest puts unsustainable strain on diminished physiological reserves. However, even when these early deaths were included, the median overall survival (OS) among patients aged over 75 was not significantly different than in younger patients (16.6 months versus 13.7 months, respectively), although it should be noted that the number of patients involved in this study was small.

A recent retrospective analysis including a large cohort of patients from the International Metastatic RCC Database Consortium (IMDC) showed that cytoreductive nephrectomy has a defined role in the targeted-therapy era. However, a clinical benefit was only found
in patients with a smaller number of high-risk features. Given the still limited amount of information in elderly patients, it would be appropriate to remember that patients aged over 65 years are more likely to encounter postoperative complications. Therefore, although selected patients undoubtedly do well, the decision to undertake cytoreductive nephrectomy should be approached with caution.

**Systemic Therapy of Metastatic Renal Cell Carcinoma in the Senior Cancer Patient**

**Targeted Agents**

Until recently, treatment options were limited for patients with RCC. Options for the medical management of metastatic RCC (mRCC) have been radically improved through the introduction of agents targeting tumour angiogenesis or intracellular pathways mediating cell growth and proliferation. Recommendations are needed on how to integrate specific management strategies into clinical practice to optimise the use of these targeted agents in the elderly. The goal is to maximise the clinical benefit through strategies focused on patient selection, assessment of quality of life, management of adverse events, and appropriate dose modification.

The main targeted agents used to manage mRCC are the small-molecule inhibitors sorafenib, sunitinib, pazopanib, axitinib, everolimus, temsirolimus, and the monoclonal antibody bevacizumab.

- Sorafenib, sunitinib, pazopanib and axitinib are orally bioavailable, small-molecule tyrosine kinase inhibitors (TKIs). They have a broad range of targets, among which they both inhibit vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinases. Similarly, cabozantinib, an agent targeting VEGF, AXL, and MET, has shown improved clinical outcomes in patients with mRCC (METEOR trial).

- Temsirolimus and everolimus differ from these agents in targeting the mammalian target of rapamycin (mTOR), a kinase that is active in a cell growth and proliferation pathway frequently activated in advanced RCC.

- The monoclonal antibody bevacizumab has antiangiogenic activity by targeting different isoforms of VEGF.

All of these targeted agents have been shown to add significant clinical benefit when compared with placebo or interferon (IFN) therapy in the treatment of mRCC (Table 1). Although at the present time it does not seem that targeted agents will offer a complete cure for mRCC, with careful management, they may offer the potential to transform it into a chronically treatable disease. Indeed, the median OS for patients with mRCC has increased from around 13 months in the IFN immunotherapy era to around 24 to 30 months in recent years and it is expected to improve further with the incorporation of new immunotherapies that target immune checkpoints.
Randomised controlled trials (RCTs) have shown that six targeted agents - sorafenib, sunitinib, pazopanib, temsirolimus, bevacizumab, and everolimus - improve outcome in advanced RCC.

Clinical experience suggests sorafenib, sunitinib, pazopanib, and bevacizumab-INF are all associated with different toxicities, and it may be helpful to take this into account in the case of individual patients (such as those who have cardiac risk factors or are elderly). Given the data available from randomised trials, sunitinib and pazopanib (along with bevacizumab plus INF) should be considered the preferred first-line therapy in patients in favourable and intermediate-risk categories, although sorafenib (despite the lack of supporting data from randomized trials) might be indicated in selected populations at risk, such as elderly patients. The COMPARZ trial was the first trial which aimed to show non-inferiority of sunitinib versus pazopanib with respect to progression-free survival (PFS) in patients with mRCC. Both drugs demonstrated similar efficacy in this trial, however, pazopanib had a more favourable toxicity profile than sunitinib. These findings may be helpful when choosing treatments for elderly patients, although no trial has specifically tested pazopanib in the elderly population.

Everolimus is approved in the European Union and in the United States for the treatment of advanced RCC that has progressed on or after treatment with VEGF-targeted therapy.

Table 1. Summary of Phase III Clinical Trials with Approved Targeted Agents

<table>
<thead>
<tr>
<th>Trial designs</th>
<th>Line of treatment/patient characteristic</th>
<th>Benefit from novel agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib vs. placebo</td>
<td>Second line/ECOG PS 0-1</td>
<td>Median PFS 5.5 vs. 2.8 mo Better OS (censoring data for crossover)</td>
</tr>
<tr>
<td>Sunitinib vs. IFN</td>
<td>First line/ECOG PS 0-1</td>
<td>Median PFS 11 vs. 5mo Median OS 26 vs. 22 moa</td>
</tr>
<tr>
<td>Pazopanib vs placebo</td>
<td>First-line</td>
<td>Median PFS 9.2 vs. 4.2 mo Median OS 22.9 mo vs.20.5 mo</td>
</tr>
<tr>
<td>Bevacizumab plus IFN vs. placebo plus IFN</td>
<td>First line</td>
<td>Median PFS 10.2 vs. 5.4 mo</td>
</tr>
<tr>
<td>Bevacizumab plus IFN</td>
<td>First line</td>
<td>Median PFS 8.5 vs. 5.2 mo</td>
</tr>
<tr>
<td>Treatment</td>
<td>Line of Treatment</td>
<td>Median OS/Mo (Comparison)</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Temsirolimus vs. IFN</td>
<td>First line (poor risk)</td>
<td>11 vs. 7 mo^b</td>
</tr>
<tr>
<td>Everolimus vs. placebo</td>
<td>Second line post TKI</td>
<td>4.0 vs. 1.9 mo</td>
</tr>
<tr>
<td>Sunitinib vs. Pazopanib^c</td>
<td>First Line</td>
<td>26.9 vs. 26.1 mo</td>
</tr>
<tr>
<td>Axitinib vs. Sorafenib</td>
<td>Second Line</td>
<td>8.3 vs. 5.7 mo</td>
</tr>
</tbody>
</table>

^aSignificant when patients crossing over from IFN to sunitinib are excluded.
^bComparison is temsirolimus versus IFN; median OS in the temsirolimus plus IFN arm was eight months.
^cNon-Inferiority trial

Abbreviations: IFN, interferon; PFS, progression-free survival; PS, performance status; TKI, tyrosine kinase inhibitor; OS, overall survival; mo, months; ECOG, Eastern Cooperative Oncology Group.


None of the phase III trials listed in Table 1 had an upper age limit to recruitment. This itself is of interest since a maximum age would generally have been stipulated in similar studies carried out a decade ago. The average age of patients across these studies and their treatment arms was remarkably similar (the lowest median being 58 years in the sorafenib arm of the placebo-controlled phase III trial, and the highest a median of 62 years in the sunitinib arm of the study versus IFN). These trials were also very consistent in the range of ages included (typically, the youngest patients entered were 25–35 years old, and the oldest were 80–86 years old). Along the same lines, recent pivotal trials in mRCC are notable for the fact that they have not restricted eligibility by age. All included some patients over the age of 80 years, and around a third of those accrued were aged over 65.

This offers the opportunity for subgroup analyses to assess the relationship between age and treatment benefit. Since such analyses have been undertaken retrospectively they should be regarded as hypothesis-generating and certainly not as definitive. Nevertheless, they provide grounds for further investigation. All the recent randomised phase III trials report the proportion of patients aged 65 years or over: 36% in the sunitinib study, 30% in the sorafenib study, 30% in the study involving temsirolimus, and 37% in the bevacizumab trial. This proportion (roughly one-third) certainly under-represents the proportion of patients aged 65 years or over in the general population of patients with mRCC. However, due to the large size of these trials there was a sufficiently high number
of elderly patients involved to allow at least some assessment of the relationship between age and the efficacy and tolerability of treatment.

While these trials were similar in age characteristics, they differ somewhat in the apparent effect of age on the benefits of treatment.

- The sunitinib and bevacizumab studies suggest that there is little (if any) influence of age on the effect of these targeted agents.
- However, in the sorafenib study, it seems that the benefit of this TKI relative to placebo is greater in more elderly patients than in younger patients.

In the COMPARZ study there is a non-statistically significant trend favouring sunitinib in patients ≥ 65 years.

- Hazard ratios from the subset analysis of the temsirolimus study suggest a trend toward the reverse effect, but confidence intervals around these estimates are wide and no definite conclusion can be drawn on this point without a prospective study (Fig. 1).
- Recently, a randomised phase III clinical trial showed a significant improvement in PFS with cabozantinib compared to everolimus in patients with mRCC previously treated with VEGF targeted therapy (7.4 vs. 3.8 months, respectively). However, further analyses are needed to define the impact of this agent in the older population.

Figure 1. Progression-free survival benefit of targeted therapies in elderly and younger patients enrolled in phase III clinical trials.

Abbreviations: IFN, interferon; PFS, progression-free survival.

**Immunotherapy**

The concept that the immune system has an important role in the development and progression of malignancies has been postulated for over a century. For decades
immunotherapeutic strategies, such as IFN and high dose interleukin 2 (IL-2), were the only treatment for advanced RCC, with their use limited in elderly patients due to toxicity and modest clinical benefit.

Recently, immune checkpoints have been described as key regulators of the T cell immune response that are able to inactivate or activate the immune system. This knowledge has led to the development of monoclonal antibodies that block the interaction between immune checkpoint proteins and their receptors, leading to promising and durable responses in patients with advanced RCC.

A phase II study of nivolumab, an inhibitor of programmed cell death protein 1 (PD-1), in previously treated patients with mRCC showed an overall response rate of 20% and median OS ranging from 18.2 to 25.5 months, depending on the dose received. An acceptable toxicity profile, and one which differs from that observed with VEGF-targeted therapies, was reported. Positive results from a pivotal phase III trial comparing nivolumab with everolimus in previously treated patients with metastatic clear cell RCC, have been recently reported. The final analysis showed an improvement in OS (25 vs. 19.5 months, respectively), including an elderly population. Similarly, early phase studies evaluating the role of the combination of immune checkpoint inhibitors have reported encouraging preliminary results (NCT01472081). However, the toxicity profile of the combination may limit their use in the elderly population.

**Patient-Focused Approach**

The populations enrolled in the pivotal RCTs differ, which renders comparisons regarding efficacy and tolerability difficult. Patients with mRCC represent a heterogeneous group and no single agent will provide optimal benefit to all patients. In addition, populations recruited to RCTs under-represent certain patient subtypes, notably the elderly and those with comorbidities. Consequently, the suitability of a specific targeted agent for a given patient group, such as the elderly, will depend on a number of factors, including disease-, patient- and treatment-related characteristics. Data from expanded access studies and clinical experience may be as relevant as the results of RCTs when making the difficult decision regarding which agent is best for a specific patient.

A schema has been proposed to show how different sources of data can be integrated when selecting treatments. This takes into account nine factors relevant to clinical decision making and provides an easily understandable visual indication when assigning the strength with which a particular agent can be recommended for use in specific patient subgroups (Fig. 2). In this “patient-focused schema,” an individualised approach to treatment selection is proposed. Treatment should be tailored according to the available agent (sunitinib, axitinib, pazopanib, sorafenib, bevacizumab, temsirolimus, or everolimus) to meet individual circumstances and needs. For a given case, patient-, disease-, and treatment-related characteristics should be evaluated individually. These should be taken into consideration together with the efficacy and toxicity/tolerability profile of each targeted agent to allow a tailored treatment.
We recommend the integration of this approach into everyday clinical practice, even though achieving this is a considerable clinical challenge. Notably, recently published international guidelines for the treatment of RCC, such as the kidney cancer guidelines from the National Comprehensive Cancer Network (NCCN), recognise the importance of an individualised approach to therapy and base their recommendations on broader criteria, emphasising the value of clinical judgement and experience to support treatment decisions for individual patients.

In the absence of controlled comparisons between the agents discussed in an elderly population, it is not possible to say that any one of these agents is more or less suited for use in elderly patients.

Even an indirect comparison of the relative frequency or severity of a specific toxicity is inappropriate since the phase III studies, which provide the most robust toxicity data, were conducted in different populations and the side effects of treatment were assessed by different groups of investigators.

Table 2. Most Common Adverse Events (All Grades) in Descending Order of Frequency, as Reported in the Pivotal Studies with Single-Agent Targeted Therapy.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Non-haematological adverse event</th>
<th>Haematological adverse events</th>
<th>Other laboratory abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>Hypertension</td>
<td>None listed</td>
<td>None listed</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Side Effects</td>
<td>Laboratory Changes</td>
<td>Additional Changes</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Fatigue, Changes in hair colour, Hand-Foot Skin reaction, Dysgeusia, Rash, Constipation, Weight loss</td>
<td>Leukopaenia, Thrombocytopenia</td>
<td>Increased AST, Increased ALT</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Diarrhoea, Rash or desquamation, Fatigue, Hand-foot skin reaction, Alopecia, Nausea, Pruritis, Hypertension, Anorexia, Vomiting</td>
<td>Decreased haemoglobin</td>
<td>None listed</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Diarrhoea, Fatigue, Nausea, Stomatitis, Vomiting, Hypertension, Hand-foot syndrome, Mucosal inflammation, Rash, Asthenia</td>
<td>Leukopaenia, Neutropaenia</td>
<td>Increased creatinine, Increased lipase</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Asthenia, Rash, Nausea, Anorexia, Pain, Dyspnoea, Infection, Diarrhoea</td>
<td>Anaemia, Thrombocytopenia</td>
<td>Hyperlipidaemia, Hyperglycaemia</td>
</tr>
</tbody>
</table>
Peripheral oedema  
Cough

AST, aspartate transaminase; ALT, alanine transaminase.


However, considering the ranking of toxicities as they appeared for each agent in the pivotal phase III studies (Table 2) might be reasonable for a personalised approach when assessing treatment options in an individual patient with comorbidities, especially when taken together with the “patient-focused schema.” A definitive answer to the question of whether drugs should be selected according to specific comorbidities will require prospectively designed trials.

Conclusion

Many elderly patients require special considerations when devising a treatment plan. Age-related physiological, cognitive, and social factors seen in this patient population may influence treatment selection, goals of treatment, response to therapy, and the management of adverse effects. However, none of these factors should necessarily preclude an elderly patient from receiving treatment with targeted therapies. With a proper understanding of these particular considerations and the biology underlying RCC, appropriate preparation, patient education, and regular monitoring for and management of adverse effects can allow elderly patients with RCC to benefit from such therapies. The new immunotherapeutic approaches (mainly the anti PD-1/PD-L1 compounds) bring new and promising treatment opportunities in the elderly patient population due to their tolerability profile and merit further exploration in the subgroup of elderly patients with mRCC.

Further Reading

Chapter 20 - Psychological Problems in Older Cancer Patients

Introduction
Depression and anxiety are two of the most prevalent psychological disorders in older cancer patients. Given the severity of a cancer diagnosis, it is understandable for patients to experience symptoms of general distress, worry, and anxiety. However, distress is often experienced on a continuum from minor situational anxiety and transient depressive symptoms to more severe disorders that require intervention and treatment. Throughout the cancer experience, patients may have brief periods of denial or despair followed by distress, with a mixture of depressed mood and anxiety, insomnia, and irritability. These symptoms may last for days to several weeks, after which usual patterns of adaptation return. This response is highly variable. However, it is important to remember that consistent symptoms of severe depression or anxiety are not part of a normal adjustment process for older patients with cancer.

Depression
Despite the high prevalence rates and deleterious effects of depression, elderly patients are far less likely to be diagnosed with major depression or dysthymia than any other age group. Moreover, when depression is present, it is frequently undertreated.

Depressive symptoms manifest themselves differently in both later adulthood and in patients with cancer. For example, the symptoms of cancer and the side effects of treatment such as pain, fatigue, insomnia, changes in appetite, anxiety, or adjustment to the cancer diagnosis often overlap with many symptoms of depression. Older depressed adults often present with more somatic complaints (such as body aches and malaise) as opposed to affective complaints (i.e., sadness, guilt, and self-criticism). The prevalence of depression in patients with cancer ranges from 6% to 25%.

Many cancer centres now screen patients for general psychological distress using the distress thermometer, a brief self-administered visual analogue scale that has been used extensively and well validated in patients with cancer. This tool may be a good gateway for more elaborate screening for anxiety and depression.

Depression in Geriatric Patients with Cancer
Exploration of the two gateway symptoms of depression is important (i.e., depressed mood and loss of interest). It is important to elicit information about other potential symptoms of depression in older patients. These would include “general malaise” as opposed to being depressed or having loss of interest due to pain or fatigue, or “general” aches and pains or stomach aches as opposed to specific tumour site pain or specific side effect of cancer treatment. Hopelessness is also an important aspect to investigate; many patients with cancer express some hope for a meaningful future regardless of prognosis, or a cure of their cancer; thus reporting little or no hope for either may be a
Sign of depression. Sleep may be problematic for both patients with cancer and older patients; however, it is important to ask if the patient wakes up in the middle of the night (middle insomnia) and has difficulty getting back to sleep because they worry or feel anxious or wake up too early in the morning. An older depressed patient may also report mood variation during the day.

**Treatment for Depressed Patients with Cancer**
While there is evidence about the efficacy of treatments for geriatric depression, there is minimal evidence specifically demonstrating the effectiveness of psychological and pharmacological treatments in depressed patients with cancer. The level and duration of distress, the inability to carry out daily activities, and the response to psychotherapeutic interventions are the signs used to determine when a psychotropic medication is needed.

- Medications that are typically used to treat depression in patients with cancer are those that are used in treating depression in general. Most commonly, serotonin-specific reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are prescribed for older patients with cancer. All antidepressants now carry a ‘Black Box’ warning for possibly causing suicidal ideation.
  - The SSRIs do not have the same risks of cardiac arrhythmias, hypotension, and troublesome anticholinergic effects such as urinary retention, memory impairment, sedation, and reduced awareness as older antidepressants, such as the tricyclic antidepressants (TCAs) do. The most common side effects of the SSRIs include gastric distress, nausea, brief periods of increased headache, and insomnia (and sometimes hypersomnia). Some patients may experience anxiety, tremour, restlessness, and akathisia, while others may feel sluggish. SSRIs can cause sexual dysfunction in men and women, a side effect that often leads to cessation of the medication even in older adults. Consideration must be given to interactions with other medications such as coumadin, digoxin, and cisplatin.

  All the SSRIs have the ability to inhibit the hepatic isoenzyme P450 2D6. It is important to consider additional drug-drug interactions especially in the elderly who may be on multiple medication regimens and have various physicians. This has been elucidated as many anti-depressants decrease effective levels of tamoxifen, a hormonal agent used in breast cancer. It appears that venlafaxine and mirtazapine are least interactive with tamoxifen, though further research is needed. SSRIs should be avoided with the chemotherapeutic agent procarbazine, which has monoamine oxidase inhibitor (MAOI)-like properties.

- SNRIs are potent inhibitors of neuronal serotonin and nor-epinephrine reuptake. They are similar to TCAs in terms of efficacy, without the same problematic side effects. These antidepressants should also not be used in patients receiving MAOIs. Mirtazapine is a sedating antidepressant, useful in
depressed patients with associated anxiety and insomnia. It has few gastrointestinal and sexual side effects and may induce weight gain. It is usually dosed at bedtime because it can be sedating.

- Bupropion has an activating side effect profile that makes it useful in lethargic medically ill patients, yet it should be avoided in patients with a history of seizure disorders and in those who are malnourished; it may cause anxiety or restlessness in some patients.

- TCAs may be used when patients have severe, treatment-resistant depression or have concomitant neuropathic pain syndromes; however, they are difficult for the elderly to tolerate at therapeutic doses. The anticholinergic actions of TCAs can cause confusion as well as serious tachycardia, and the quinidine-like effects of TCAs can lead to arrhythmias. Postural hypotension and dizziness may also occur; these are of particular concern for the frail, volume-depleted patient who is at risk for falls and possible osteoporosis-related fractures. Urinary retention and constipation are also problematic side effects for the elderly.

- Psychostimulants may be used when there is coexisting fatigue or malaise. There is growing experience for supporting the use of these medications to treat depressive symptoms in patients with cancer, on the basis of their quick response time and its alleviation of concomitant symptoms of fatigue, sedation, and poor concentration. They may be useful early in the treatment of depression until an antidepressant has a chance to become therapeutic.

Choosing an antidepressant in the elderly cancer population may be based on whether a patient or a family member has responded well to an antidepressant in the past. Other factors that should be considered include the patient’s overall health and cognitive abilities; the social and financial resources, which are often limited in this patient population; and any other existing psychiatric conditions (i.e. substance abuse, psychosis, or anxiety disorders). Additionally, it is useful to note if there is a need for physical symptom control (i.e. neuropathic pain, fatigue, and insomnia) as well as management of the psychiatric symptoms. It is helpful to consider the side effect profiles of different antidepressants that may be useful as well as those that should be avoided. For example, if a patient presents with fatigue or sedation, the most appropriate agent may be an energising antidepressant or a psychostimulant. Consider mirtazapine in a patient who is experiencing anxiety or insomnia, gastric upset, or loss of appetite.

Patients who are unable to swallow pills may be able to take an antidepressant in an elixir or mirtazapine, which comes in a soluble tablet preparation. Patients with stomatitis secondary to chemotherapy or radiotherapy or those who have slow intestinal motility or urinary retention should receive an antidepressant with the least anticholinergic side effects such as sertraline.
Psychotherapy, including supportive therapy, psychoeducational interventions, cognitive behavioural therapy (CBT), interpersonal therapy (IPT), and problem-solving therapy also appear to help older depressed patients with cancer. Supportive techniques such as active listening with supportive comments can be readily applied by oncologists and oncology nurses. Cognitive therapy, which focuses on how an individual’s inaccurate thoughts or assessments of his/her situation lead to anxious and depressed feelings, can be used to help a patient develop an adaptive perspective on his/her circumstances.

- CBT has been found to help depressed patients with cancer, in particular by combining behavioural activation with cognitive techniques.
- Group therapy for patients with cancer, caregivers, and families may be advantageous, allowing individuals to receive support from others facing similar problems.

**Anxiety**

Anxiety disorders in older cancer patients are common. As with depression, there needs to be greater attention on understanding and recognising anxiety disorders in older adults with cancer.

**Anxiety in Geriatric Patients with Cancer**

Prevalence rates of anxiety vary between 1% and 23% in studies of patients with cancer. In patients with advanced cancer, rates of anxiety have been found to be close to 30%. Older adults with cancer often have multiple medical conditions and complex polypharmacy issues that may blur the clinical presentation of anxiety. The diagnosis of anxiety in older patients with cancer is usually determined by questions about ongoing worry, restlessness, pacing, apprehension, and hypervigilance. Several factors that can complicate the diagnosis of anxiety in older patients with cancer include pain, respiratory distress, sepsis, endocrine abnormalities, hypoglycaemia, hypocalcaemia, hormone-secreting tumours, and pancreatic cancer. A change in metabolic state or an impending medical catastrophe may be heralded by symptoms of anxiety. Suddenly occurring symptoms of anxiety with chest pain, respiratory distress, restlessness, and a feeling of “jumping out of my skin” may indicate a pulmonary embolus. Patients who are hypoxic often appear anxious and fear that they are suffocating or dying.

The use of steroids, anti-emetics, and withdrawal from narcotics, benzodiazepines, and alcohol can all cause anxiety. Akathisia, a common side effect of neuroleptic drugs used to control nausea, may often manifest as anxiety and restlessness. These symptoms can be controlled by the addition of a benzodiazepine or a beta-blocker.

Withdrawal states from alcohol, opioids, and benzodiazepines are often overlooked as causes of anxiety and agitation even in older patients. Patients in the palliative care setting may have been prescribed shorter-acting benzodiazepines (e.g., lorazepam, alprazolam, and oxazepam) to control both anxiety and nausea. With inadequate dosing
or tapering regimens, these patients often have rebound anxiety or withdrawal between doses.

Panic disorder often presents as a sudden, unpredictable episode of intense discomfort and fear with thoughts of impending doom. Patients who have already compromised respiratory function may have cyclical exacerbations of their anxiety and breathing problems. Symptoms of a pre-existing panic disorder may intensify during the palliative care phase when patients are confronting increasing physical symptoms and disability and their own mortality.

Treatment for Anxious Older Patients with Cancer
Psychotherapeutic and pharmacological approaches have been shown to successfully treat anxiety disorders in older adults. Individual and group cognitive-behavioural interventions and supportive therapy, IPT, problem-solving therapy, and insight-oriented therapy have been used successfully with older patients to relieve anxiety.

- For patients with mild to moderate anxiety, the use of psychological techniques alone may be sufficient to assist them in managing anxiety. Psychoeducational interventions are particularly useful for anxious patients who have difficulty understanding medical information about their prognoses and symptoms. Explaining the predictable emotional phases through which patients pass as they face new and frightening information may also alleviate their anxiety. Providing information to patients’ families enables them to cope more effectively, which in turn enhances patients’ sense of support. Cognitive-behavioural interventions include reframing negative, irrational thought processes, progressive relaxation, distraction, guided imagery, meditation, biofeedback, and hypnosis. Other psychotherapeutic techniques such as supportive and insight-oriented therapy may be helpful to reduce anxiety symptoms and allow for better coping with the cancer. When working with older cancer patients, having the flexibility to adjust the length of sessions, intervals between sessions, and use of the telephone for those who have difficulty coming into your office is imperative.

- One quarter to one-third of patients with advanced cancer receive antianxiety medication during their hospitalisations. In deciding whether a pharmacological approach may be useful, the severity of the patient's anxiety symptoms and the degree to which they interfere with overall well-being are the most reliable guides. Given the possibility of compromised hepatic and renal functioning, as well as increased sensitivity to pharmacological interventions, drugs are to be used with caution in older patients. Starting with lower doses than would be used with younger, physically healthy patients, and increasing these doses more cautiously will lead to more successful outcomes.
  - The first-line antianxiety drugs are benzodiazepines. In older patients however, these medications may result in mental status changes such as confusion or
impaired concentration or memory. These changes are more often seen in those with advanced disease and those with impaired hepatic or brain function. Dose-dependent side effects such as drowsiness, confusion, and decreased motor coordination must be monitored carefully in elderly patients. Benzodiazepine use represents an important iatrogenic risk factor for falls in older adults. One must keep in mind the synergistic effects of the benzodiazepines with other medications that have central nervous system (CNS) depressant properties such as narcotics and some antidepressants. Elderly patients with dementia or brain injury who are administered benzodiazepines may experience paradoxical behavioural disturbances such as aggressiveness, irritability, and agitation.

- For insomnia, the benzodiazepine temazepam as well as the non-benzodiazepine hypnotics zolpidem, zaleplon, eszopiclone, or ramelteon may be effective. In addition, sedating antidepressants such as trazodone or mirtazapine may also help patients with persistent anxiety and insomnia. A sedating atypical neuroleptic such as olanzapine or quetiapine may be effective for the patient who is anxious or has trouble sleeping and is confused or has respiratory compromise. Neuroleptics may also be useful for the patient whose anxiety is substance induced (e.g. steroids) or in anxious patients with severely compromised pulmonary function. Buspirone is useful for patients with generalised anxiety disorder and for those in whom there is the potential for abuse. Buspirone is not effective on an as-needed basis, and its effects are not apparent for one to two weeks.

- In the oncology setting, the SSRIs are effective in the management of generalised anxiety and panic disorder.

**Conclusions**

Anxiety and depression are highly prevalent in older patients with cancer. This chapter has provided a summary of the issues that need to be considered when diagnosing and treating older cancer patients with anxiety and depression. Diagnosing depression and anxiety in older patients with cancer is difficult. Therefore, clinicians need to be familiar with the unusual presentation of these symptoms in this population.

Psychotherapeutic and psychopharmacological interventions are optimal in treating anxiety and depression in older patients with cancer. Oncologists should be aware of the indications for psychotrophic medications, the possible side effects and drug interactions of psychiatric medications, and how to obtain psychiatric consultation when needed.

**Further Reading**

Chapter 21 - Social and Ethical Aspects

Introduction

In western societies, about three-quarters of citizens will eventually become senior adults, meaning they will reach at least 70 years of age. They will have raised their family, many will have become grandparents, the vast majority will have retired from work, and almost all will be planning to enjoy their remaining lifetime in as good a general condition as possible.

However, when cancer knocks on the door of the elderly, it comes as a truly catastrophic event, exactly the same as when it happens to younger people; such bad news brings with it enough weight to put the life of the person in question in jeopardy, while the prospect of dying is quite logically closer and closer.

Many cancers though become chronic conditions, and their management may require serious additional resources. These may be limited by personal or societal realities because the cost of treatment will also have to be taken into account. Ageism may intervene to hinder appropriate management since it is an attitude frequently observed in both lay people and health professionals alike. It has been well demonstrated by multiple studies that cancers have a worse prognosis in senior adults than in younger patients.

Very soon, the third and fourth ages (65-80 and 80+) will represent about 20% of the entire population in low-income countries, and up to 30% in high-income countries. This calls for a rapid reworking of our respective social and health systems to preserve intergenerational solidarity, thus raising questions such as the following:

- What space does society intend to leave to its most senior citizens?
- How should the elderly behave to keep their current status safe?
- Or, which roles do senior adults want to play in their future?
- When death approaches, is there a right time to die?

Medical oncologists are faced with the complexity of treating senior adults (elderly, older people) with cancer. If not lead and inspired by “The Hippocratic Oath”, which appears nowadays sometimes not in keeping with modern reality, they should at least be lead and inspired by the concept of dignity that is attached to every human being on earth regardless of the subject’s personal condition.

From the professional point of view, senior adults with cancer deserve the following (Figure 1).

Figure 1. The Ten Commandments of senior adult care “TRAFICCPAD”
Respect
Over the years, senior adults have gained experience in life. In every society, they are most of the time recognised as wisdom holders. In addition, many continue to take community responsibilities despite being retired.

The question of life expectancy slowly surges and becomes evident to them since most of their time has already been lived. However, remaining lifetime is an individual matter that is influenced by the personal genetic background and the environmental hazards.

"Healthy octogenarians have more time to live than sick septuagenarians, and nonagenarians can enjoy an additional four-year life expectancy that will still be over one year at the age of 100."

Admiration
Besides the ability to reach a respectable age, senior adults actually want to avoid a premature end to life. Lifestyle and nutritional aspects of daily living thus match epidemiological projections showing that the annual probability of dying is kept below 10% until the age of 70 years. In other words, the risk of dying rises from 1 in 10,000 at the age of 10 years to 1 in 10 at the age of 70 years and almost 1 in 1 at the age of 100 years.

"Similar trends are observed throughout the world, suggesting a welcome global improvement of living conditions for the general population."
Attention
The prevalence of chronic conditions at an advanced age will continue to increase. In cancer patients, concomitant cardiovascular diseases will be present in up to half of the cases and more metabolic conditions such as diabetes mellitus are seen. Cognitive deficits are present in more than a quarter of senior adults after the age of 80 years, thus raising questions about comprehension and informed consent. Senior adults also accumulate general risk factors for mortality such as functional decline, delirium, falls, incontinence, and neglect.

"An interdisciplinary approach is an attractive and efficient way to tackle the multiple problems routinely encountered in senior adults."

Information
Senior adults were educated several decades ago when DNA had not been described and wireless communications had not even been imagined. Today, they listen, although what is said does not always correspond to what is understood. This may sometimes lead to misunderstandings and unrealistic expectations. They read and surf the internet to learn that 5-year breast cancer survival probability is over 80% regardless of age at diagnosis, provided standard adequate treatment is offered. Interestingly, published surveys have shown that quality of life (QoL), though being an ill-defined concept in senior adults, is more important for them than survival length.

“Additional efforts to properly communicate good news as well as bad news may help to share an active partnership with senior adults."

Protection
In a democracy, senior adults are voting citizens, and their influence on critical decisions is by no way to be minimised. “The grey power” is, therefore, a growing reality garnering more attention from politicians and from society itself. About half of the senior adults live on their own in the urban community, and the proportion decreases with age. In parallel, there is a feminisation of the oldest old because women have a definitive life expectancy advantage on men. And in many communities, only half or less of those with biological descendants can rely on help and assistance of a nearby living child.

Thus, advanced directives should be actively promoted by health professionals who must then obey their content and listen carefully to the therapeutic representative.

“Needs of senior adults are therefore becoming more and more specific to the societal transformation of their daily environment.”

Diagnosis
Senior adults are prone to cancer, with over 2,000 new cases per 100,000 inhabitants per year. This is a ten times higher incidence in comparison with the population below the
age of 65 years. Accurate diagnosis leading to further appropriate tests aiming at the best-designed treatment is the single way to maintain or improve the quality of the remaining time to live.

"Professional geriatric evaluation, together with scientific assessment of cancer cells by the pathologist and precise medical oncological clinical staging, is mandatory."

**Care**

Too many different drugs are prescribed to senior adults because of their comorbidities. The risk of interactions and detrimental side effects that can occur during the management of cancers and other diseases are well known. Poor outcomes have been reported, including fatal events caused by standard drugs. In addition, unlicensed substances, sometimes of a very poor quality, are used by as much as 50% of cancer patients. Optimal care should therefore encompass the traditional aspect of “bona fama” and complementary medicines.

“Four fundamental ethical principles must govern medical action with the aim of finding a valid balance between each of them, which are the following (Figure 2).”

Figure 2. The balance to be found between the four fundamental ethic principles.

- **Autonomy** means the capacity to decide what is good or not good for oneself; senior adults should fully understand the problem before giving consent to further tests or therapeutic measures.
- **Justice** (equity) is the capacity for a group to distribute wealth on an equal basis and above all for the most in need; senior adults should benefit from the resources generated within a community to maintain and/or improve health conditions.
• **Beneficency** is the capacity to do what is good for the other and of sanitary benefit; health professionals should use their skills to maintain and/or improve health conditions of senior adults.

• **Non-maleficiency** is the capacity to not harm the other; health professionals should take every precaution to make sure that health conditions of senior adults are not at risk to be damaged by diagnostic or therapeutic measures.

**Time**
As is the case with children in paediatrics, senior adults are most of the time accompanied by loved ones. But these may not be members of their family. The traditional composition of families has indeed undergone many changes during the past century in relation with the observed increased life expectancy. In many countries, a high incidence of divorce has profoundly modified intra-familial communication and composition. Senior adults and proxies may thus require more time for explanations and understanding of their personal situation. Distance to and from health centres may hamper access to care, requiring transport facilitation to be organised and social intervention to be implemented.

"Family and/or the most significant proxy should not be left without help and assistance to minimise the risk of burnout."

**Caution**
Senior adults use vulnerable and frail organs with a progressive reduction of the tolerance to stress and a loss of functional reserves. Striated muscles are replaced by increased fat, kidney function loses as much as 1 mL/min/year from the age of 40 years, and liver function is not as efficient at 80 years as it was at 50. But the worrying limitation is the incidence of cognitive troubles and the occurrence of dementia, which markedly increase with age to reach unexpected levels.

"Short assessment will provide useful information but will not preclude a more thorough neuropsychological evaluation to ascertain harmlessness."

**Freedom**
Thoughts and beliefs are daily life companions allowing the development of a personal spirituality. In many senior adults, the persistence or the resurgence of religious feelings must receive an appropriate answer. To cope with cancer, senior adults tend indeed to use prayers first before music, exercise, or meditation. On the other hand, in a few countries around the world, assisted suicide and/or euthanasia are now integrated in medical practice and are supported by the population. Beside palliative care, this is the end chosen by a minority of senior adults when facing physical or psychological suffering brought on by cancer. None of this should be ignored.

Please remember that historians judge the level of progress achieved by successful civilisations through the way they care for the weakest, the poorest, and the oldest.
Further Reading

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Chapter 22 - The Role of the Multidisciplinary Team

Introduction
The management of cancer is a complex rather than a complicated task. A complex situation may be comparable to a carpet, where each thread is essential to the picture (indeed, the word “complex” is derived from *cum plexere*, meaning to weave together). A complex situation implies a team approach, and in the case of the older-aged person, the scope of the multidisciplinary team encompasses areas outside cancer and even outside the medical domains.

As comorbidity is a hallmark of age, the team includes professionals experienced in the management of diseases other than cancer. The intervention of other professionals such as pharmacists, social workers, and dieticians is also required to make treatment accessible, safe, and effective. Last but not least, the role of the nurse is pivotal in the management of older cancer patients. By training, the nurse—who in German is called “Krankenschwester,” sister of the sick—is focused on the welfare of the whole person. Striking the ideal balance of medical and personal needs in each individual situation is the nurse’s unique expertise. In addition, the nurse is attuned to vocalise the patient’s unspoken needs and to identify early signs of discomfort and deconditioning and to bring them to the attention of the proper professional.

Ageing involves a progressive reduction in the functional reserve of multiple organs and systems and increased prevalence of comorbidity. This results in a reduction of a person’s life expectancy and stress tolerance and increases the risk of disability and functional dependence. In the meantime, cognitive restrictions and socioeconomic limitations may lessen the ability of the older person to compensate for his or her functional losses. Depression, malnutrition, and polypharmacy may further enhance the vulnerability and the disability of the aged.

The goals of cancer treatment in the older-aged person include prolongation of active life expectancy (that may also be referred to as compression of morbidity), in addition to the traditional goals of cure, prolongation of survival, maintenance of quality of life, and symptom management.

The management of the older person, with or without cancer, has to address multiple and different needs that imply a return to a brand of holistic medicine all but forgotten in times of specialised fast food–inspired medicine. This is the medicine practised in highly specialised centres, such as anticancer, cardiologic, or orthopaedic centres that offer only services limited to that specialty. The “we do this one food right” type of medicine is rarely beneficial to the older-aged person, who may die of a heart attack or become disabled while receiving “state-of-the-art” treatment for prostate or breast cancer. The team approach to the older cancer patients thus involves more than the welfare of the individual patient. It is a proposition and a demonstration of a medicine attuned to the ageing of the population.
In this chapter, we will provide three examples of the multidisciplinary approach to the older cancer patient in three critical areas: geriatric assessment, management of polypharmacy, and caregiver support. We will conclude with an overview of the team function and a brief discussion of future perspectives.

**The Assessment of Age**

The basic questions of geriatric oncology include the patient’s life expectancy and treatment tolerance, which can be determined by assessing the physiologic age of a patient.

As ageing is complex, it is unlikely that it can be measured by a single test measuring a single marker. The so called “inflammatory index”, reactive oxygen metabolites and total thiol levels and DNA methylation have been shown to be related to overall mortality and risk of disability in cohort studies, confirming that chronic and progressive inflammation contributes to ageing along with an accumulation of oxidative damage and epigenetic alterations. These markers have not yet been proven to predict benefits and risks of a specific treatment in individual patients.

- So far, the best-validated estimate of life expectancy has been obtained by integrating comorbidity and function (Fig. 1). Yourman et. al. have summarised the results of several studies to estimate the mortality risk of patients with different ages in a free website (ePrognosis.com), giving specific scores to age, specific functions and comorbidity in older individuals studied in different settings, such as home-based, assisted living and after hospital discharge (2012). This tool represents the most complete reference for the estimation of life expectancy in older individuals.

- The comprehensive geriatric assessment (CGA) also provides an estimate of the risk of chemotherapy-related haematological and non-haematological toxicity. In two prospective cohort studies, dependence in Instrumental Activities of Daily Living (IADL) and alterations in mental and nutritional status were independent variables predicting therapeutic toxicities.

- A novel and promising approach to estimate life expectancy and functional reserve uses “Principal Component Analysis” (PCA). This approach may best reflect the complexity of ageing by weaving together the CGA and other medical, functional, and social parameters.

Figure 1 Estimate of four-year mortality for patients aged 70 and older on the basis of function and comorbidity. Abbreviation: AUC: area under the curve. Source: From Lee et al.
Other benefits of the CGA involve recognition of conditions that may interfere with cancer treatment, such as cognitive disorders, depression (especially subclinical depression), nutritional risk, polypharmacy, and absence of an adequate caregiver. Some of these conditions may be reversible, and others may be compensated for with proper intervention. For example, a patient with memory disorders may require the assignment of a caregiver prior to the start of chemotherapy; a patient unable to use transportation may need the designation of a driver.

While there is general agreement that a CGA is essential to the management of older cancer patients, controversy lingers over its execution. Several practices have adopted some form of screening test to identify patients who need a more “in-depth” assessment. In any case, the CGA involves a multidisciplinary team. While the initial evaluation of the patient, including functional assessment, is best performed by a nurse, a social worker is needed for assessing cognition, living conditions, and availability of a caregiver, a pharmacist for the assessment of polypharmacy, and a nutritionist for the assessment of nutrition and nutritional risk. Ideally, the team should also have access to other medical specialists including cardiologists, neurologists, endocrinologists, and nephrologists; to a minister of the appropriate faith trained for the recognition and management of spiritual and existential distress; and to a physical therapist.

The role of the team in the CGA is not limited to the estimate of functional age. It also involves the management of conditions that may compromise cancer treatment and may lead to functional dependence. This task will be described in the team function.

**Polypharmacy**

The prevalence of polypharmacy increases with age because, in part, of increased prevalence of comorbidity and, in part, the increased utilisation of over-the-counter medications and alternative medicine products by older individuals.

A definition of polypharmacy is wanted, but a number of issues are clear.
• Cancer patients 70 years and older take an average of 11 non-cancer-related medications per patient.
• The risk of drug interactions increases geometrically for patients taking more than five medications on a single day.
• For patients taking eight medications each day, the risk of drug interaction is almost certain.
• Polypharmacy is a major cause of iatrogenic morbidity and mortality.

In a study performed at our institution, the interaction between cancer-unrelated drugs was associated with an 80% increase in the risk of chemotherapy complications.

Several studies in elderly patients with and without cancer have shown that polypharmacy is best managed when a pharmacist is part of the treatment team. In this the pharmacist may be helped by a computer programme capable of identifying all potential drug interactions and by a number of criteria describing inappropriate prescriptions in the elderly. In addition to medication interactions, these include utilisation of medications that are partially contraindicated in older age such as benzodiazepines or nonsteroidal anti-inflammatory agents.

To estimate both risks and benefits of polypharmacy, it would be very helpful to have a physician with geriatric experience on the team. This is the case in some countries such as France where an ongoing cooperation of geriatricians and oncologists assures the safest and most effective treatment of older cancer patients. Alternatively, one should make sure that the older cancer patient may rely on a primary care physician to whom the team pharmacist should communicate all planned treatment changes. These alternative approaches are illustrated in Figure 2.

Figure 2 The pharmacist is central to identify inappropriate prescriptions. This information may be conveyed to the geriatrician or the oncologist on the team or to the patient’s primary physician.
Management of the Caregiver

The home caregiver is essential to the management of older cancer patients, not only for those suffering from disability or memory disorders. The most basic requirement of the caregiver is to be readily available in case of emergency and to be capable of providing timely transportation of the patient to a care centre. Ideally, the caregiver should be able to provide emotional support to the patient to enhance the adhesion to the treatment programme; to ensure that the patient receives adequate nutrition and exercise; and to identify signs of distress or deconditioning. The caregiver may function as the spokesperson of the family when many different family members are involved in the care of the patient and be required to mediate conflicts among different relatives with different agendas. Even healthy elderly patients may develop chronic complications of cancer treatment, including fatigue and deconditioning, that are harbingers of disability and death. The caregiver may be pivotal in the prevention of these complications by encouraging the patient to exercise and to maintain a healthy lifestyle during treatment.

As the caregiver has this central role in the management of the older cancer patient, the physician, with the help of the team, should be able to identify and support the caregiver.

The evaluation of the caregiver includes the identification of this person, who is generally designated by the patient, and the recognition of potential shortcomings of the caregiver. Common problems include the following:

- The caregiver is an older spouse with health problems of his/her own. This person may not be able to undergo the heavy caregiving task and needs to be aided by a younger and healthier person. In extreme circumstances, when a more able caregiver is not found, the patient may need institutionalisation (at least for the treatment duration).
- The caregiver is an adult child, most commonly a daughter, with a profession and a family of his/her own. The main difficulty for this person is how to accommodate in a busy schedule the demands of caregiving along with those of their profession and of a younger family. This syndrome is referred to as the “Aeneas syndrome” from Raffaello’s depiction of Aeneas in the Vatican’s Stanze di Raffaello. There the Trojan hero is represented as carrying his older father on his shoulder and holding his young son with his left hand. In this case, it is important to know if the caregiver can get adequate respite from other family members and can conciliate family and work.

Caregiving is associated with a number of health problems, at least in the case of caregiving for Alzheimer patients. These include increased mortality, increased incidence of depression, increased risk of repeated infections, and delayed wound healings.

The management of the caregiver is a responsibility of the whole team and includes the following:
• Provision of adequate information related to the patient’s health status and the
caregiver’s own health risks, as well as health maintenance recommendations
• Instruction on how to address common problems related to cancer treatment, such
as nausea and vomiting, fever, delirium as well as depression and anger
• Instruction on the management of family conflicts
• Help in dealing with work-related and economic issues

The identification of the caregiver is generally a combined task for the nurse and the social
worker. Being on the forefront of the patient’s assessment, the nurse is in the best position
to recognise the person on whom the patient can rely most for support. In parallel, the
social worker has the competence to recognise the assets and liabilities of the designed
caregiver and to negotiate adequate solutions for the patient’s needs.

Correction of the caregiver’s shortcomings (e.g., finding a younger and independent
person to aid an elderly and disabled caregiver) is the responsibility of the social workers.

The training of the caregiver is a combined task of the team. The physician and nurse are
responsible for instructing the caregiver on how to manage common problems that may
occur during cancer treatment; the social worker has the central task to guide the
caregiver in the maintenance of his/her own health and to work out social issues such as
leave from work and help with childcare; the dietitian illustrates the most effective
techniques to maintain the patient’s nutritional status; while the pharmacist is of
assistance in assuring adherence to the treatment regimen and in minimising the potential
complications of drugs.

All team members are responsible for praising the caregiver and highlighting the
importance of caregiving. If the caregiver relies on faith for strength, the intervention of a
member of the clergy may also be desirable.

**Function of the Team**

The organisation of the team is not codified. In our institution, the H. Lee Moffitt Cancer
Center, a geriatric team has been operating for 21 years. Though it has undergone some
evolution, the basic organisation has remained the same (Fig. 3). All cancer patients aged
70 years and older are screened by a nurse for age-related problems. Patients who
screen positive undergo a consultation by the whole team that reports the findings to the
physician who is responsible for the initial treatment plans.

Figure 3 Organisation of the team at the H. Lee Moffitt Cancer Center and Research
Institute in Tampa.
All patients are discussed at the weekly multidisciplinary conference attended by the full team that issues final recommendations and a letter to the patient and the referring physician. During this informal discussion, new consultations are generated that might have been originally overlooked and all team members become aware of their own specific role in the management of the individual patient.

Of course, the functioning of the team is predicated on its cohesiveness and mutual trust of its members. Team building and team maintenance involve friendship, confidence, and open communication that are promoted by the team leader. This is not necessarily a physician; rather, the team member who is the most experienced in team building. The nurse practitioner and social worker have, at times, assumed such a role at our centre.

**Conclusions and Perspectives**
The management of the older person with or without cancer implies a return to a patient-centred practise. This is best conducted by a multi-disciplinary team, as a single person can no longer manage the available wealth of information.

The delivery of care by a multidisciplinary team is one of the most important future research issues.

**Further Reading**
• Balducci L, Aapro M. Complicated and complex: Helping the older cancer patient to exit the labyrinth. J Geriatr Oncol 2014; 5:116-118.
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