Geriatric Oncology

for daily practice by

FROG

FRANCILIAN ONCOGERIATRIC GROUP

4th edition
May 2023

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Principles of Geriatric Oncology

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This book was produced in collaboration with health professionals. The authors' declarations of conflict of interest concerning the content of this work are available from the publisher.

Its content reflects only the point of view of the authors and in no way engages the responsibility of Kephren Publishing.

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The book is published under the auspices of the International Society of Geriatric Oncology (SIOG) and the Francophone Society of OncoGeriatrics (SoFOG).

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PREFACE

Laure de Decker, Etienne Brain, Djamel Ghebriou

As the population continues to age, the management of cancer in the older adult has become a major public and societal health issue. Today, nearly one in three cancers is diagnosed in patients older than 75, often in the context of multimorbidity. This proportion is expected to increase in the future. In France, by 2050, half of the new cancer diagnosis will occur in people over 75.

"Geriatric Oncology for Daily Practice" is an educational tool that can help us meet the challenges of Geriatric Oncology. Since its initial paper format released in 2015, it has been invaluable for multiple clinicians in their professional practices. This new and innovative digital edition will help medical professionals, once again, with their patient care.

Congratulations and thank you to the authors who contributed to this project, for their dynamism and for their willingness to share their knowledge and expertise with this new edition of "Geriatric Oncology for Daily Practice".

Professor Laure de DECKER,
President of SOFOG

A fourth edition, and this time in a double format, printed and digital! The FROG no longer must prove it knows how to bring together the expertise of so many professionals and create a very practical tool that fits in the pocket of your coat or can be found in a downloadable application. It includes multiple clear summaries, essential for the management of cancer in the older patient. We suspect that the readers of this new edition will not only be young practitioners in training, but also older, more experienced clinicians, who will find in it the important and didactic messages that they have long championed.

The decision to partner with the International Society of Geriatric Oncology (SIOG) and the distribution of this tool, very soon in English, beyond France, shows the strength and structure of the French OncoGeriatrics. We can be proud of our achievements, our models of care and our history.

When a certain population is at the forefront, it is no longer a "special" population. It is time to make it politically and "precisely" the most frequent population in order to reverse the inequalities of care and improve access to therapeutic progress. Through its work, the FROG helps us achieve this goal. Thank FROG for that.

Dr Etienne BRAIN,
former president of the DIALOG group and the SIOG

I would like to profusely thank our industry partners. Their support has allowed this tool to be distributed free of charge since its creation.

On January 10, 2012, Danièle Avenin, Nabil Baba Hamed, Djamel Ghebriou, Sidonie Hubert, Mehran Khatibi, Youlia Kirova, Karin Maley, Aurelien Minard, Olivier Mir and Florence Rollot Trad founded the FRancilian Oncogeriatric Group (FROG), bringing together a group of friends passionate about oncogeriatrics. Quickly, Hélène Boussion, Leïla Bengrine Lefèvre, Driss Chaoui, Elise Cotto, Tristan Cudennec, Virginie Fossey Diaz, Mathilde Gisselbrecht, Thierry Landré, Camille Lobey, Daniel Lopez Trabada Ataz, Caroline Marquis, Frédérique Péchinot-Guedj brought their dynamism to the group to organize numerous training meetings and work on the creation of the book "Geriatric Oncology for daily practice" by FROG. The fourth edition is published under the auspices of the SoFOG and the SIOG. This preface is an opportunity to express my gratitude and my friendship to my friends.

Thanks to Sébastien Rocca, talented designer (https://www.lamisseb.com/), who created the famous FROG frog as well as many original drawings to illustrate our ideas.

To extend my thanks, I want to express my gratitude to our publisher Kephren Publishing who has worked closely with us since the creation of FROG.

May this book, available in French and English, help optimize the practices of its readers and improve cancer care for our elders.

Dr. Djamel GHEBRIOU,
President of FROG

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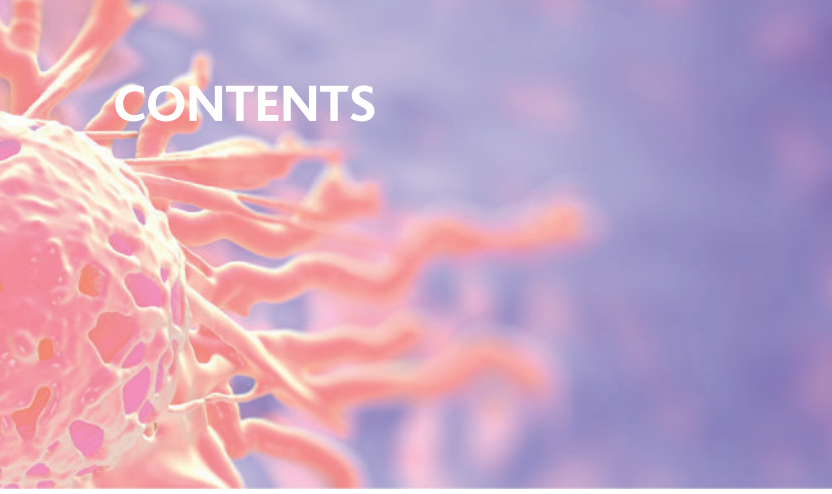

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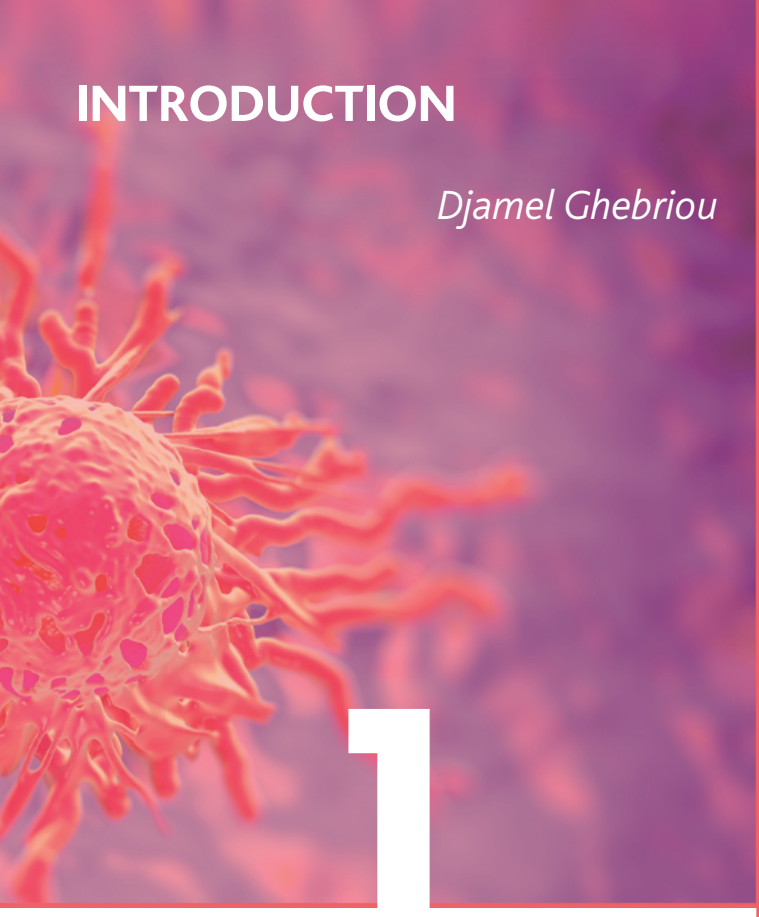
INTRODUCTION

Djamel Ghebriou



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The Francilian Oncogeriatric Group (FROG) is happy and proud to present the 4th edition of the book "Geriatric Oncology for Daily Practice" published under the auspices of the French speaking Society of Geriatric Oncology (SoFOG) and the International Society of Geriatric Oncology (SIOG). Its goal is to enhance the clinician's knowledge in the fields of oncology and geriatrics. We hope it will be helpful for the optimization of your practices based on the latest evidence-based knowledge and techniques. This book, available in French and English languages, is also available in digital form on the free application "FROG ONCOGERIATRICS". The first volume highlights the frailty of the older cancer patient, the course of oncological care and the optimization of cancer treatment in this population.

The second volume summarizes existing recommendations and formulates specific management proposals for the older cancer patient with a solid tumor or hematologic malignancy.

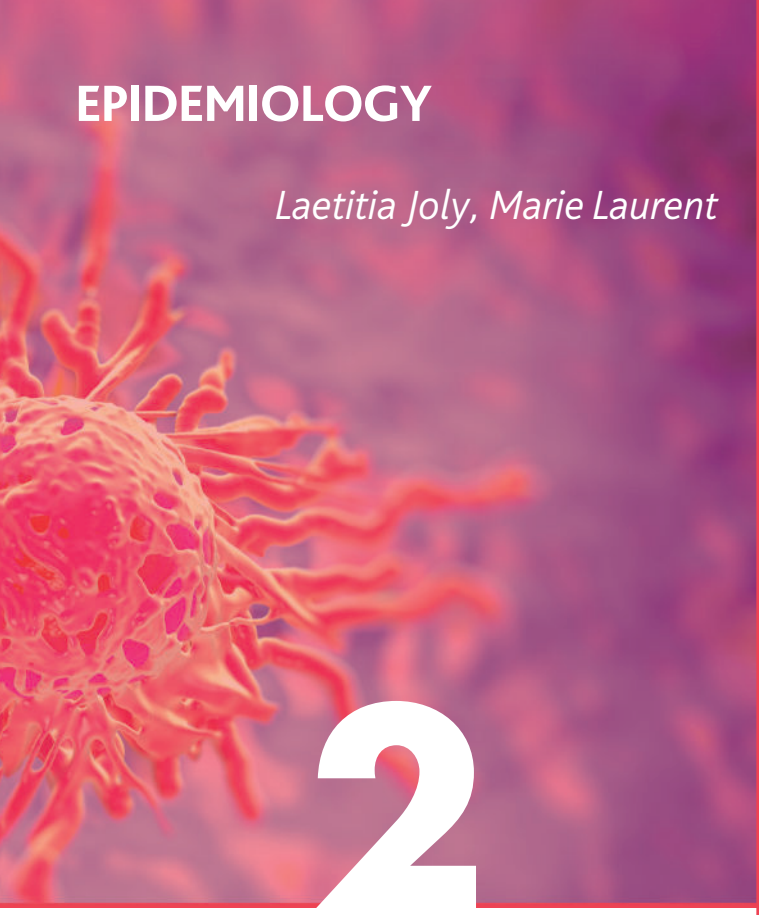
Patient functional age is a primary determination when considering appropriate therapy for an older patient with cancer. The Geriatric Assessment is used to determine the "right level" of cancer treatment ensuring the

highest level of agreement among the theoretical indication for oncological treatment for which a benefit is expected, the prognosis and therapeutic alternatives for cancer treatment, and the geriatric syndromes. The Geriatric Assessment's goal is to guide therapeutic interventions and devise strategies to make sure that the patient will have the functional reserves needed to tolerate potential complications. The therapeutic index is narrower in the older patient. The preservation of quality of life and functional independence are priorities.

The oncogeriatric literature shows that Geriatric Assessment and the identification of frailty influence initial cancer treatment decisions in 20-30% of the patients. Geriatric syndromes are frequent, and their recognition is essential. The over or under treatment of the older adult with cancer will continue to be very frequent if the patient presentation in a multidisciplinary consultation meeting is reduced to be tumor centered.

EPIDEMIOLOGY

Laetitia Joly, Marie Laurent



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Unlike previous editions, the cancer incidence and prevalence figures in France have not been updated since the last version in 2020: the cancer figures published in France are still those for 2018.

As this document is circulated beyond our borders, we have inserted data on cancer in Europe and worldwide.

Hence, in 2020 globally, according to the World Health Organization, cancer was the leading cause of death worldwide with an incidence of 19,292,789 new cases per year, and a mortality rate of 9,958,133 deaths per year[1].

At European level, in 2018, its incidence was 3.9 million new cancers and it was responsible for 1.9 million deaths[2].

Even though Europeans only represent one-tenth of the world population, they account for 25% of all annual cancer cases[3].

In mainland France, according to national incidence estimates for 2018, 382,000 new cancer cases were recorded, regardless of the cancer site; 204,600 were in men and 177,400 in women[4].

In France too, it was the leading cause of death, ahead of disorders of the circulatory system[5], with 157,400 deaths; 89,600 were in men and 67,800 in women[4].

In men, the cancer incidence rate (SMR) (SMR: number of cases for 100,000 people per year standardised for the age structure of the global population) between 1990 and 2018 has remained relatively stable, with an average annual variation of + 0.1%, whereas the number of new cancer cases has increased by 65%[4].

This phenomenon of an increase in the number of cancer cases, with a stable incidence rate, is essentially linked to the increased population and its ageing, and to a lesser extent to a greater risk of cancer per se.

In women, conversely, during this same period, the cancer incidence rate (SMR) increased more than in men: + 1.1% per year, and the number of new cancer cases increased by 93%[4].

Half of this phenomenon is linked to the greater risk of cancer, especially lung cancer (+ 5.3% per year on average between 1990 and 2018), as well as the increase in incidence of breast cancer (stabilization between 2003 and 2010, then another increase of + 0.6% per year on average between 2010-2018), and the other half is linked to the increase in and ageing of the population[4].

However, during this same period, cancer mortality rates decreased, in proportion with screening and therapeutic advances, in a more pronounced way in men (- 1.8% per year on average) than in women (- 0.8% per year on average)[4].

Cancer is a disease whose incidence increases with age, both in France and at European level.

In France, the median age at diagnosis is 68 in men and 67 in women, and the median age at death is 73 in men and 77 in women[6].

In 2017, in France, 62.4% of all cancers affected the over-65s and 11.5% the over-85s (9.3% in men and 14% in women)[4], whereas 75.3% of total cancer deaths occurred in the over-65s and 24.8% in the over-85s[8].

In 2020, at European level, 60% of new estimated diagnoses and 73% of estimated deaths occurred in people aged 65 and over[3].

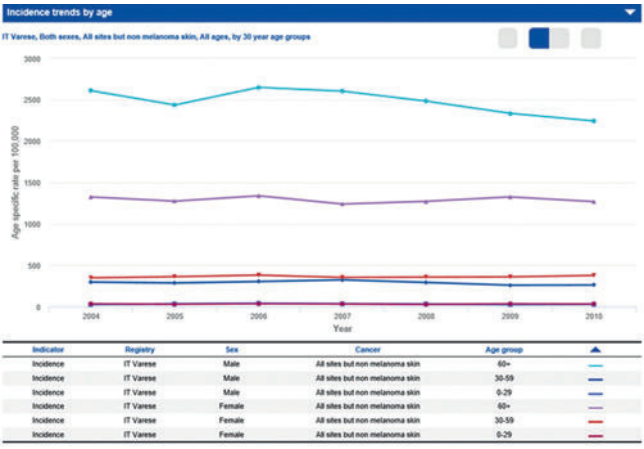


Figure 1: *Incidence and mortality statistics, by registry and cancer sites - Incidence trends by age - European Cancer Information System - ECIS.*

This graph, using data from the European Cancer Information System - ECIS, clearly illustrates the fact that in Europe too, cancer is a disease that affects older people.

As the European population ages, estimates of the number of people diagnosed with cancer could reach 18% in 2040, with incidences of new cancer cases increasing by 2% to 65.3% depending on the country[3].
In 2020, the most common cancers[1] worldwide were:

- breast cancer (2.26 million cases), with 685,000 deaths
- lung cancer (2.21 million cases), with 1.80 million deaths
- colorectal cancer (1.93 million cases), with 916,000 deaths
- prostate cancer (1.41 million cases)
- skin cancer (non-melanoma) (1.20 million cases)
- stomach cancer (1.09 million cases), with 769,000 deaths.

Worldwide, cancers with the greatest incidence are the same as in Europe: breast, lung, colorectal and prostate.

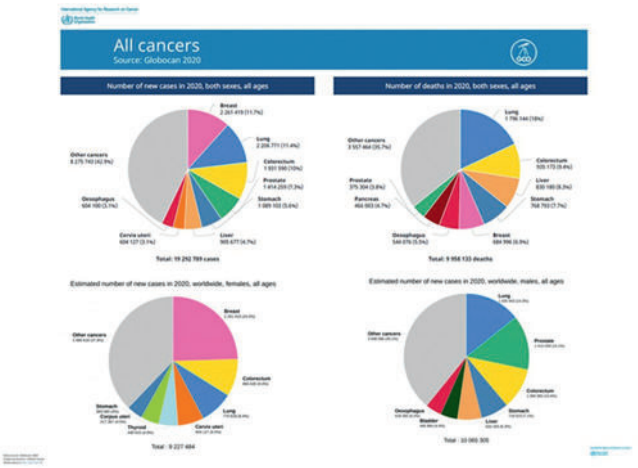


Figure 2: *Incidence and mortality by cancer type worldwide in the general population and by sex. IARC - 14 December 2020 - the updated Globocan 2020*[9].

At national level in France, in men, the most common cancers, in terms of new cancers, concern the prostate, lung and colon-rectum. They are responsible for 46.5% of deaths in the over-65s.

In women, breast, colorectal and lung cancers are the most common and are responsible for 43.2% of cancer deaths in the over-65s[7,8].

Net survival (survival that would be observed if cancer was the only cause of death) at 10 years for prostate cancer is 61% for 75- to 84-year-olds and 32% for the over-85s, whereas it is 83% for 55- to 64-year-olds and 79% for 65- to 74-year-olds[7].

10-year net survival for colorectal cancers decreases with age, falling from 60% in 15- to 44-year-olds to 45% in the over-75s[7].

For breast cancers, 10-year net survival is 65% in the over-75s, whereas it is 83% in 45- to 54-year-olds[7].

10-year net survival in lung cancers is 9%, in all age groups. It has fallen from 17% for 15- to 44-year-old patients (13% in men and 25% in women) to 5% in the over-75s (5% in men and 4% in women)[7].

Table 1 below lists the 5-year net and observed survival rates of the main cancers: breast, prostate, lung and colorectal. We can see that net survival, whether 5-year

Table 1: *5-year net and observed survival of patients diagnosed between 2005 and 2010 depending on site and age*

Net and observed survival for 2005-2010 diagnoses by age category - HCL/Francim/SPFrance/INCa					
Site	Age category	5-year net survival in patients diagnosed between 2005 and 2010	95% CI of 5 year net survival	5-year observed survival of patients diagnosed between 2005 and 2010	95% CI of 5-year observed survival
Breast	15-45	90	[89-91]	90	[89-90]
Breast	45-55	93	[92-93]	92	[91-92]
Breast	55-65	92	[91 -92]	89	[89-90]
Breast	65-75	92	[91 -92]	87	[86-88]
Breast	75-+ +	76	[74-77]	58	[57-59]
Prostate	15-55	96	[95-97]	93	[92-94]
Prostate	55-65	98	[97-98]	93	[92-93]
Prostate	65-75	97	[97-98]	87	[86-87]
Prostate	75-85	89	[88-90]	67	[66-67]
Prostate	85-++	65	[61 -70]	28	[27-30]

Table 1 (continued): *5-year net and observed survival for patients diagnosed between 2005 and 2010 depending on site and age.*

Net and observed survival for 2005-2010 diagnoses by age category - HCL/Francim/SPFrance/INCa					
Site	Age category	5-year net survival in patients diagnosed between 2005 and 2010	95% CI of 5-year net survival	5-year observed survival of patients diagnosed between 2005 and 2010	95% CI of 5-year observed survival
Lung	15-45	25	[22-28]	25	[22-28]
Lung	45-55	21	[20-22]	20	[19-22]
Lung	55-65	19	[18-20]	18	[17-19]
Lung	65-75	17	[16-18]	16	[15-16]
Lung	75-+ +	10	[9-11]	8	[7-8]
Colon-rectum	45-55	70	[69-72]	69	[67-70]
Colon-rectum	55-65	68	[67-69]	65	[64-66]
Colon-rectum	65-75	66	[65-67]	60	[59-61]
Colon-rectum	75-++	50	[49-51]	36	[35-36]

or 10-year, is lower in older patients compared to the rest of the population.

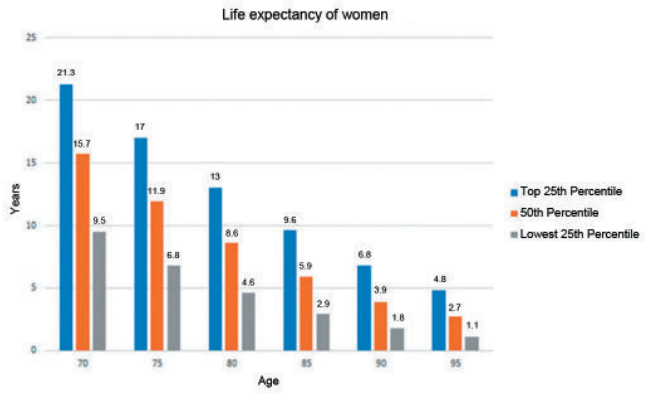
There are several explanations for this: later diagnosis, comorbidities limiting the possibility of a cure, less benefit from therapeutic advances, and less aggressive treatments being suggested.

Older patients are also rarely offered screening, or even not at all, and do not always receive the same medical follow-up as younger patients[10,11].

It is true that in the older population, who are often frail, the therapeutic index is narrower and the risk-benefit ratio of treatments is harder to evaluate.

The life expectancy of older patients with cancer also depends on their comorbidities and their sex, as shown by the figures below. At the age of 80, a patient without any major comorbidity (in other words in the Top 25th Percentile - 80-year-olds in excellent health) has a life expectancy of 10.5 years (13 years for a woman). At the same age of 80, a patient with major comorbidities such as advanced dementia accompanied by loss of independence (in other words in the Lowest 25th Percentile - 80-year-olds in less good health) has a life expectancy of 3.3 years (4.6 years for a woman) (Figure 3).

Net survival is survival that would be observed in the hypothetical situation where the only possible cause of death was cancer.



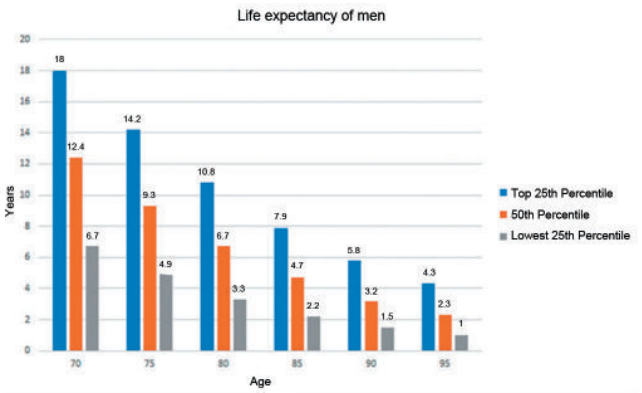


Figure 3: *Life expectancy between 70 and 95 depending on sex and level of health.*

Life expectancy associated with comorbidities other than cancer also varies according to the individual. Indeed, if we observe life expectancy associated with dementia, this can vary from 3 to 12 years according to the type of dementia (lower life expectancy in vascular dementia cases compared to Alzheimer's disease), level of education (greater life expectancy among high socio-cultural groups), and sex (greater life expectancy in women)[13,14].

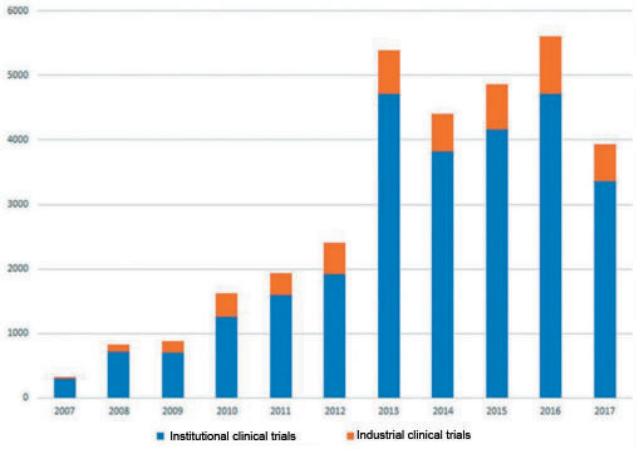
All these factors underline the importance of conducting therapeutic trials in this population.

For several years, measures have been put in place to promote trials in older patients: international guidelines encourage their inclusion in clinical trials, and in France, national incentives arising from the various "Cancer Plans" are designed to improve their care and how the specific needs of older people are taken into account.

In 2005, the INCa created a register of clinical trials in cancer treatment which lists both academic and industrial trials (Figure 4).

We can see that trials which include patients aged over 75 are mostly run by institutions.

In 2013, analysis of this register listed 122 open trials for patients aged over 18 with no upper age limit, without being able to specify the number of patients aged over 65 included in these trials. Only 14 of them were dedicated exclusively to oncogeriatrics (open only to patients aged over 65)[15].



Source: ONCOG_EC19
Treatment: INCa - lesdonnees.e-cancer.fr
http://lesdonnees.e-cancer.fr/Themes/Soins/La-prise-en-charge-des-populations-specifiques/Oncogeriatrie#ind23083

Figure 4: *Evolution of inclusion of older patients aged over 75 in a clinical trial.*

A study themed around inclusion of older subjects in clinical trials for colorectal cancer showed that older patients rarely met the criteria for inclusion, mainly due to their comorbidities. Hence, out of the 577 patients aged 65 or over followed in this study, only 27% of them met the criteria for inclusion in the current trials, and when they were eligible, only 2/3 of them were invited to take part in the trial.

In total, 12% of patients with colorectal cancer, aged at least 65, were included in a trial. This proportion varied from 43% for 45- to 60-year-olds to just 6% for older patients aged at least 80, and was not explained by the single variation of Performance Status according to age[16].

This phenomenon of under-representation of older populations is found in clinical trials worldwide, as illustrated by this study published in 2016, which collected the proportion of older patients included in trials run by the Alliance for Clinical Trials in Oncology focusing on systemic treatments for breast cancer between 1985 and 2012[17].

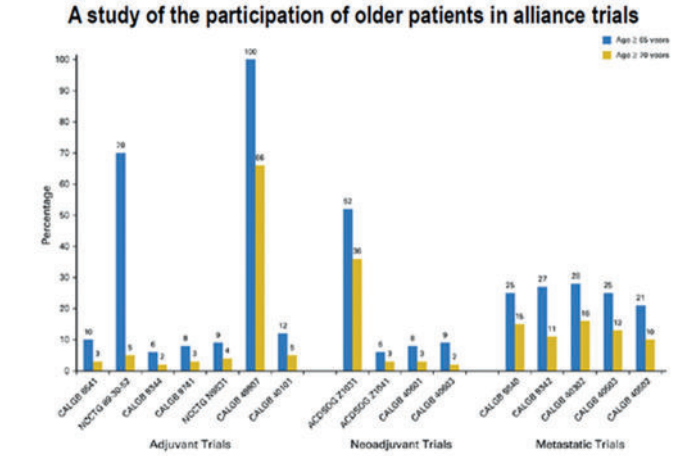


Figure 5: *Participation of older patients in trials run by the Alliance for Clinical Trials in Oncology on systemic treatments for breast cancer* [17].

Even though, over the course of the last 20 years, an improvement has been seen in the number of phase I, II and III clinical trials devoted to cancer treatment in older patients[18], too few studies have been devoted to them. The conclusion remains the same: new strategies aimed at increasing the level of participation are essential if the evidence base for this growing population of patients is to change in a meaningful way.

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CONCEPT OF FRAILTY

Johanne Poisson, Olivier Saint-Jean, Mathilde Gisselbrecht

3

Analysis of the literature on frailty shows the historical background to how it is defined. In the 1980s it was described as polypathology and loss of functional independence, and in the 1990s as a cognitive decline and malnourishment through the sarcopenia resulting from it. This last element was included in prospective cohorts and led in 2001 to the publication of Fried's 5 criteria[1], which set out the parameters of physical frailty and attempted to impose itself as a single definition of frailty. However, in 2006 a conference held under the auspices of the American Geriatrics Society proposed a wider definition: reduction in homeostasis and resistance to stress which increases vulnerability and risks of harmful effects such as progression of a disease, falls, incapacity and premature death due to a lowering of functional reserves[2].

Although somewhat fluid, this definition puts two essential concepts at the heart of frailty: prognosis and the concept of functional reserves. Frailty could therefore be likened to factors such as poor prognosis, or more exactly to factors which would explain observable gaps in prognosis between a young person and an older person, or between two older people, suffering from the same health event. We therefore understand the

complexity of the concept and its diversity, because it depends on the type of event studied (an acute or chronic disease, increasing age), and on how it is measured and the length of prognosis. Frailty can therefore only have multiple causes. The variables and terms of results are manifold in geriatrics: death, changes in living environment, physical and instrumental functional independence, quality of life, rehospitalisation, etc., either in the short, medium or long term. In two extreme examples (non-metastatic breast cancer and an aggressive stage 4 lymphoma in an 80-year-old woman without comorbidity), frailty, indisputable in the sense of what will affect the prognoses, will be measured completely differently. As for the reference to functional reserves, as exciting as it is, this only underlines our incapacity to measure them. Based on long-term prospective cohort studies, the current variables for frailty tell us about the long-term predictive factors for loss of independence, falls, hospitalisations. They are measured by predictive static tools (this is the basis of the standardised geriatric assessment). But these static tools, if they are measuring a current status comparable to an average reference, tell us nothing about a person's functional reserves which can only be measured by real-life tests that mobilise these resources. Although we can associate the idea of the risk of post-operative confusion in an older patient without cognitive decline with cognitive frailty, how can we measure this reserve in an individual, and thus select those who could benefit from preventive action? The same goes for the capacity to withstand the risk of aplasia after chemotherapy or anthracycline-induced cardiac dysfunction. Whereas in the past some people had suggested treating these diseases aggressively with pharmacological solutions (for example high doses of scopolamine to unmask the cognitive reserve threshold), these proposals were rarely felt to be acceptable from the ethical point of view. Sarcopenia and malnutrition, cognitive and functional decline, mood disorders are among the most common long-term risk factors. Despite a degree of overlap between short and long-term prognostic factors, these factors are poor predictors of short-term frailty. The matter of biological markers of functional reserve is now essential and needs to be high up the research agenda.

Moreover, frailty is currently only concerned with intrinsic patient-specific factors. The availability of the domiciliary

care system is much talked about, but it is inadequate to describe the role played by extrinsic and psychosocial factors in the medical journey of an older person. The nature of the healthcare system, the capacity for optimal use of health and social care provision, and patient strategy with regard to their state of health have a profound impact on the prognosis. Therefore if someone suffers a fracture at the upper end of the femur, whether they go to orthogeriatrics or orthopaedics will have a huge impact on their life prognosis 6 months later[3], even with the same frailty!

Finally, the literature has an abundance of assessment or screening tools for frailty, with each institution vaunting the merits of their tool. The diversity of the concept of frailty means that these tools are neither universal, nor comparable. Hence, applied to a cohort of more than 27,000 subjects aged over 65, eight frailty scales measure its prevalence in a range between 6.1 and 43.9%[4].

Ultimately, what we understand best is the importance of the concept of a global geriatrics approach, which can bypass standardised tools based on a full clinical and biological analysis of an unwell older person, their environment and their capacity to follow a disease management pathway including the optimal resources for their treatment. This approach should lead to an integrated care and services plan, the only thing that can guarantee efficacy when determining the prognosis[5].

In total, there is not just one frailty but areas of frailty, and our capacity to intervene in these will be diverse and the benefit somewhat mixed.

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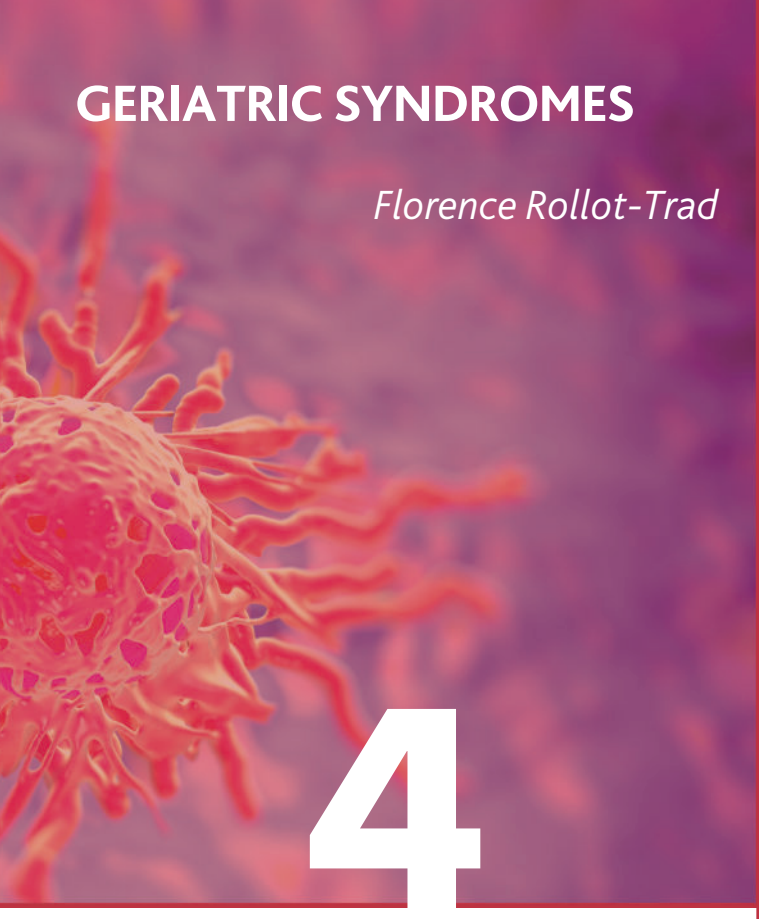
GERIATRIC SYNDROMES

Florence Rollot-Trad



4

What is a geriatric syndrome (GS)?

A geriatric syndrome (GS) is a health situation with multiple causes and consequences.

It is neither a disease, nor a conventional medical syndrome. The frequency of GSs increases with age.

Several factors are involved:

- chronic contributory factors (e.g. falls and Parkinson's disease), including the effects of ageing (e.g. sarcopenia and falls)
- acute precipitating factors (e.g. infection, iatrogenic condition) or intermittent factors (e.g. repeated hospitalisations).

The list of GSs is not exhaustive: repeated falls, incontinence, protein-energy malnutrition, loss of independence, dementia, delirium, osteoporotic fractures, bed sores, visual and auditory impairment, depression, social and family isolation, abuse, illness-fainting, sleep disorders, swallowing problems, temperature regulation problems, etc.

Taking account of geriatric syndromes in Oncogeriatrics is essential

In the older population, the prevalence of GSs is likely to be higher in patients with cancer.

As well as cancer, GSs have consequences for morbi-mortality, life expectancy and quality of life (QOL).
GSs have an impact on:
- the feasibility of cancer treatment
- the organisation and establishment of the cancer treatment pathway
- the efficacy, tolerance and continuance of treatment.

Cancer and its treatments can be precipitating factors for GSs that need to be anticipated as well as possible.

How can we IDENTIFY geriatric syndromes?

This exercise requires a rigorous process:
- taking a global multidimensional approach
- asking questions (patient, friends and family, carers), watching, listening, examining
- using scales (e.g. ADL, IADL) which should be repeated during monitoring to estimate how much the patient's capacities have changed and the risks during treatment
- using tests such as for example standing on one leg and walking speed to assess the risk of falling, the MMSE + clock-drawing test or MoCA to assess the risk of post-operative confusion, etc.
- running biological tests (e.g. albuminemia, electrolyte test, corrected serum calcium, TSH, iron and saturation coefficient, CRP, etc.) which will be guided by the clinic.

How can we FACE UP TO and DEAL WITH geriatric syndromes in Oncogeriatrics?

The concept is to:
- conduct a causative investigation to correct any factors that can be changed (e.g. metabolic and/or diet-related deficiencies, physical deconditioning, depression, etc.)
- guard against aggravation and accumulation of GSs, prevent organ failure and a cascade of pathologies
- ensure adherence to the timetable for systemic treatments (chemotherapy, targeted therapy, immunotherapy) and radiotherapy, in optimised conditions

- coordinate multidimensional care, leading to organised interventions. This requires a global approach to the level of health, ranking/prioritisation of problems and the person's needs
- propose appropriate interventions (non-exhaustive list): motor rehabilitation, nutritional or psychological support, equipment (e.g. hearing aid, spectacles, night ventilation), speech therapy, installation or reorganisation of professional or material aids, adjustment of prescriptions, adaptation (type, place) of care (teeth, dressings, medicines), etc.

The purpose of identifying and taking account of GSs is to preserve functional independence and independent living, delaying entry to a care home and guaranteeing the best possible quality of life. Taking a multi-professional view and actions, it is a question of contributing to efficacy and better tolerance of the cancer treatment, when possible.

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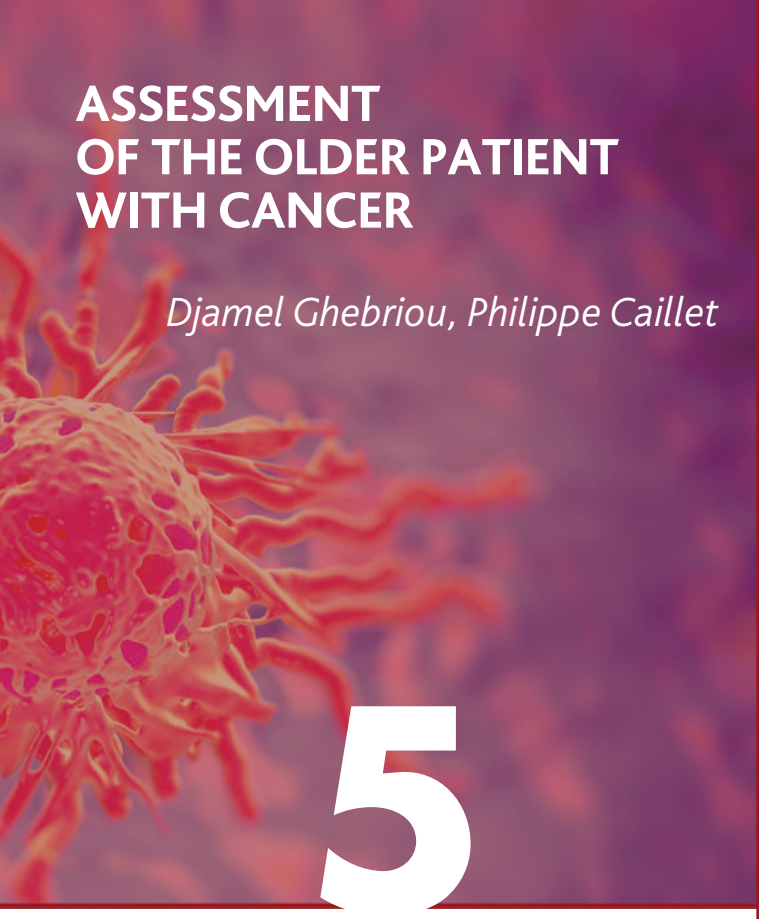

ASSESSMENT OF THE OLDER PATIENT WITH CANCER

Djamel Ghebriou, Philippe Caillet

5

Screening

Djamel Ghebriou

One-third of cancers occur after the age of 75. It is important to identify older patients with cancer who have some vulnerability or geriatric frailty and offer them a specialist consultation so they can have a comprehensive geriatric assessment (CGA) before starting their cancer treatment. G8 is a geriatric screening tool approved by the ONCODAGE[1] study for use by cancer care teams for any older patient with cancer prior to treatment (Appendix 1).

It was a multicentre study conducted between August 2008 and March 2010 that included 1,674 patients, 1,597 of whom were eligible with an average age of 78.2 years. The G8 test could be administered by a nurse or a clinical research associate on average in less than 10 minutes, whereas the CGA performed by a geriatrician took around 1 hour.

The G8 score was abnormal for 68.4% of patients. The CGA was abnormal for more than 80% of patients. The primary cancer site had an influence on the percentage of abnormal CGAs and G8s. The G8's sensitivity was 76.5% and its specificity was 64.4%.

Appendix 1: *G8 score*

Items	Score
Is the patient experiencing loss of appetite? Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0: severe decrease in food intake 1: moderate decrease in food intake 2: no decrease in food intake
Weight loss during the last 3 months	0: weight loss > 3 kg 1: does not know 2: weight loss between 1 and 3 kg 3: no weight loss
Mobility	0: bed or chair bound 1: able to get out of bed/chair but does not go out 2: goes out
Neuropsychological problems	0: severe dementia or depression 1: mild dementia or depression 2: no psychological problems
Body Mass Index (BMI = weight in kg/height in m^2)	0: BMI < 19 1: BMI = 19 to BMI < 21 2: BMI = 21 to BMI < 23 3: BMI = 23 and > 23
Takes more than 3 medications per day	0: yes 1: no
In comparison with other people of the same age, how does the patient consider his/her health status?	0: not as good 0.5: does not know 1: as good 2: better
Age	0: > 85 1: 80-85 2: < 80
TOTAL SCORE	0-17

A score ≤ 14 reveals a geriatric vulnerability or frailty that should lead to a bespoke consultation.

A modified G8 score[2,3] with modification of the polypharmacy threshold to 6 medications per day and the addition of 4 IADL items seems more specific than the G8 when detecting frailty in older patients. This test is currently being validated.

It should be noted that the G8 tool appears to be less suitable in terms of its screening function in older patients with ENT cancer, since 82% of patients have a score? 14 according to the results of the ELAN-ONCOVAL study.

Studies have attempted to demonstrate the prognostic value of tests that screen for frailty such as the G8 or the VES 13 in the context of chemotherapy treatment for various cancers, or to predict post-operative or post-chemotherapy complications. Nonetheless, these tests have as yet no other indication than screening for frailty which is recommended for older patients. At the present time, they do not change the decision-making algorithms for cancer beyond the screening stage.

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■ Comprehensive geriatric assessment

Philippe Caillet

Chronological age alone cannot define the state of health of an older patient with cancer, their life expectancy, or tolerance of an anti-tumour treatment. Indeed, the older population represents a diverse population in terms of social environment, independence, nutritional status, cognitive and mood status, or even in terms of comorbidities, the incidence and number of which often increase with advancing age, leading to high levels of polypharmacy. This diversity explains both the significant variations in life expectancy at a given age, and the difficulty of establishing treatment recommendations in older patients with cancer. This is why it is currently recommended that you make a comprehensive geriatric assessment CGA) in older patients with cancer before deciding on the treatment[1], particularly when it involves systemic treatment with chemotherapy[2], because the CGA constitutes the best way of dealing with this diversity.

The CGA is a multidimensional, multidisciplinary, diagnostic interventionist procedure, which is used to assess the overall state of health of an older patient and suggest appropriate care for this **health status** and the problems identified. It is based on the use of validated tools which analyse the main dimensions of the older patient (socio-economic environment, physical and mental independence, nutritional status, mood status, comorbidities, treatments). The CGA is used to make an individual estimate of the risk-benefit ratio to the extent that its components are correlated to the toxicity of treatments and mortality[3].

Advantages of the comprehensive geriatric assessment

- *Social environment*

Social isolation constitutes a separate mortality risk in the older general population, and also in in older patients with cancer. Assessment of the social environment (living conditions, family situation, home help, resource persons in the friends and family) can help define practical treatment arrangements (transport, dealing with emergencies, keeping the patient at home during treatment), and anticipate putting in place the help needed to implement and/or follow up treatment.

• *Independence*

In oncology, functional status is assessed using the ECOG-PS (*Eastern Cooperative Oncology Group Performance Status*). In geriatrics, functional status is evaluated using ADL (*Activities of Daily Living*) and IADL (*Instrumental ADL*) scores, which assess the patient's level of independence on the basis of their ability to look after themselves in activities of daily living.

In the general population, dependence for one ADL or more is associated with reduced life expectancy. Deterioration of the ADL, IADL and PS is correlated to an increased risk of post-operative complications in older patients with cancer treated with surgery. Dependence for one IADL or more can adversely affect tolerance of chemotherapy. In the longer term, dependence is associated with increased mortality, regardless of age, type and stage of the tumour, and the treatment.

The existence of problems with walking, falls and/or a risk of falling are also signs of loss of independence (assessed by the Timed Get Up and Go Test and the standing on one leg test). The risk of falling is correlated to higher mortality in older patients treated with chemotherapy[4].

Looking for dependence issues and/or risk of falling allows the necessary aids to be put in place to make life less difficult for the patient, including active physical therapy with the goal of keeping the patient at home during treatment.

• *Nutritional status*

Common in older patients, malnutrition constitutes a negative prognostic factor associated with a reduction in quality of life, loss of function, longer stay in hospital, and increased mortality. In older patients with cancer, it is associated with increased risk of toxicity from chemotherapy, a reduced response to these treatments, and decreased survival. Weight loss (< 5%) in the six months preceding chemotherapy is correlated to decreased survival and the chemotherapy response rate. A low score on the MNA (Mini-Nutritional Assessment) is associated with increased risk of mortality in older patients treated with chemotherapy[4]. Hypoalbuminemia, correlated to an increase in mortality from all causes, also constitutes

a toxicity factor in chemotherapy. In the event of malnutrition, clinical and biological nutritional monitoring, ideally supervised by a dietitian, should be instigated and a nutritional supplement should be prescribed.

- *Cognitive status*

Cognitive pathologies are associated with decreased overall survival in the older general population, like in older patients with cancer. More specifically, pre-existing cognitive impairment may get worse over the course of chemotherapy, be associated with poor tolerance of the chemotherapy, or even impossibility of completing the treatment in full. Cognitive impairment may reduce treatment compliance due to lack of understanding, or compromise some imaging tests or radiotherapy sessions which require patients to lie still. Cognitive disorders lead to an increased number of mistakes when taking medication, resulting in possible lower treatment efficacy or increased toxicity.

In clinical practice, the usual mechanism for screening for cognitive disorders is the MMSE (Mini Mental State Examination). Identifying cognitive impairment is useful when assessing treatment compliance, and can improve therapeutic follow-up by suggesting, for example, nurse supervision at home and boosting joint follow-up by the attending physician, oncologist and the geriatrician. The memory consultation follow-up should be discussed on the basis of the overall prognosis.

- *Mood status*

Depression is associated with impaired quality of life and constitutes a risk for morbidity and mortality in the older general population. In older patients with cancer, it constitutes a separate risk factor for treatment toxicity, but also for overall progression-free survival.

In the event of depression, psychological follow-up and/or antidepressant treatment can improve the patient's quality of life, and their treatment compliance.

- *Comorbidities and polypharmacy*

Comorbidities constitute a major prognostic factor correlated to reduced life expectancy in the older general population. In older patients with cancer, they are also

a separate mortality factor for cancer, and are associated with worse treatment tolerance[3]. Cardiovascular disease, chronic obstructive pulmonary disease, chronic renal insufficiency and anaemia are more specifically associated with a reduction in overall survival and progression-free survival in older patients with cancer. Assessment of comorbidities can be made easier by using scales such as the CIRS-G (Cumulative Illness Rating Scale for Geriatrics) or the Charlson index, which both help with prognosis.

Assessment of comorbidities is essential when estimating life expectancy and looking for contraindications to the treatment(s) envisaged. Identifying comorbidities improves how they are managed by conducting additional explorations which may lead to a better assessment of their severity and the therapeutic adjustments needed whenever their condition is not stable, or risk interfering with either the cancer itself, or with its treatment.

Comorbidities are often the reason for polypharmacy. The usual treatment should be reassessed according to the hierarchical importance of comorbidities, cancer treatments and the iatrogenic risk, in order to detect any drug-drug interactions in the usual treatment and anticipate possible interactions with cancer treatments (risk of lower efficacy or increased adverse events). Non-essential treatments should be halted in order to minimise the iatrogenic risk[5].

- *Summary of the CGA*

Because of its prognostic value, the CGA constitutes a therapeutic decision aid, by allowing more accurate assessment of the risks and benefits linked to oncological treatment, as well as the overall care of older patients with cancer, thus optimising any non-oncological treatment[6,7]. Balducci and Extermann's concept of dividing patients into three groups defined by the CGA data has evolved considerably over time. The recommendations of the International Society of Geriatric Oncology (SIOG) distinguish four groups of patients whose personalised care plan is defined by the patient's capacity to withstand the cancer treatment[8].

Patients in good health ("**healthy ageing**"), without significant comorbidity and living independently (normal

ADL and IADL) are deemed suitable to receive exactly the same treatment as that offered to younger patients.

"**Vulnerable**" patients, with one or two significant comorbidities (level 3 on the CIRS-G score), whether or not associated with one or more dependencies for IADLs (independent for ADLs), are still in principle eligible for standard treatment after starting specific geriatric interventions.

For "**frail**" patients, with three or more significant comorbidities (level 3 on the CIRS-G score) or one major comorbidity (level 4 on the CIRS-G), combined with one or more dependencies for ADLs, cancer treatment can still be envisaged in certain conditions if adaptations are made to the patient's general health, and only after setting up specific geriatric interventions. Some frail patients may indeed have a fairly significant life expectancy despite their comorbidities, which may exceed their cancer prognosis. Certain specific treatments, including chemotherapy, can therefore be discussed for palliative care, with the aim of preserving quality of life.

Finally, "**highly impaired**" patients, with serious comorbidities, who are insufficiently stable and/or at very high risk of decompensation due to cancer or its treatment, who have lost much of their independence and whose general health has deteriorated significantly, are deemed too frail to receive dedicated cancer treatment. Their care relies on treating the symptoms and supportive care, with the exclusively palliative aim of preserving quality of life.

Conclusion

The CGA has multiple aims:

- estimating life expectancy according to comorbidities and geriatric syndromes
- ranking comorbidities, how they are managed, and their specific prognostic value in relation to cancer care
- determining which geriatric factors and comorbidities might interfere with the cancer treatment
- implementing corrective actions to normalise the problems identified, as part of a personalised care plan
- providing medical and psychosocial follow-up throughout the cancer treatment.

Thanks to its multidisciplinary and multidimensional nature, the CGA identifies problems about which little is often known before this routine assessment, but are likely to interfere with the treatment or cancer progression. It enables the supportive care needed for optimal treatment to be put in place very early, and can improve tolerance of cancer treatments and preserve the quality of life for older patients with cancer.

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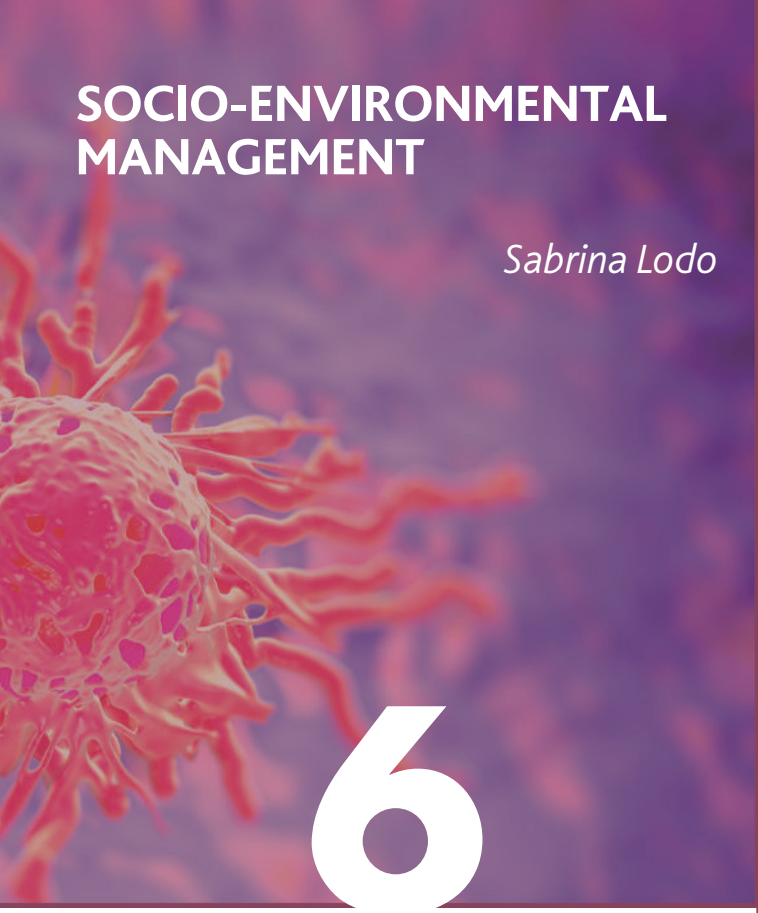
SOCIO-ENVIRONMENTAL MANAGEMENT

Sabrina Lodo



6

Introduction

On 3 February 2021, the European Commission presented its Beating Cancer Plan. A €4 billion budget will be dedicated to various specific programmes such as "EU4Health" and four areas of activity aimed at:

- expanding a sustainable prevention policy
- improving early detection of cancer
- improving diagnosis and treatment by taking action to reduce inequalities in access to cancer care across the EU
- improving quality of life for patients with cancer, for those who have survived cancer, also taking carers into consideration.

Not forgetting the development of new technology and a particular focus on childhood cancers.

On **4 February 2021**, France unveiled its ten-year cancer control strategy for 2021-2030. This strategy will be coordinated by the National Cancer Institute, which drew up the fifth report on the 2014-2019 cancer plan in 2019. It will have a €1.74 billion budget for its first 2021-2025 roadmap.

Four ambitious goals:
- To reduce the number of avoidable cancers by 60,000/year before 2040.
- To screen 1 million more people per year from 2025.
- To reduce the number of patients with sequelae 5 years after diagnosis from 2/3 to 1/3.
- To significantly reduce the slowdown in survival rates for cancers with the worst prognosis by 2030.

Four strategic messages:
- Improving both primary and secondary prevention
- Minimising sequelae and improving quality of life for patients during and after treatment
- Combating cancers with the worst prognosis in adults and children
- Ensuring that advances in combating cancer benefit everyone.

France's commitment will run alongside the European commitment and will result in consolidated and deeper European and international cooperation.Erreur ! Référence de lien hypertexte non valide.

In France, more than 3.8 million people are or have at one time been living with cancer. They constantly come up against multiple difficulties in organising their daily life. We will present here the main tools and the various professionals who may be asked to intervene in supporting and providing social care for an older person.

The main venues and sources of information

- *Communal social welfare centre (CCAS)*

Its mission is to organise general prevention and social development action in the community alongside public and private institutions. It may intervene in the form of making reimbursable or non-reimbursable payments (Art. L123-5 of the Casf). The person concerned can submit an application for social welfare (contribution to housing costs, or help in the home). The application is forwarded to and actioned by the department's General Council. At the CCAS, the person can ask the home support service to put in place a home support package, meals on wheels, or remote assistance. They can also ask a social worker to support them with various tasks, [applying for Supplementary Universal Health Insurance (CMUC), requesting financial assistance].

DAC coordination support package: at the end of July 2022 the aim was to consolidate the different packages mentioned below into a one-stop shop for any age or pathology, regardless of the complexity of the situation.

• Home for seniors and caregivers

Exists in every department in France. The aim is to centralise all three geriatric support packages:

- Local Information and Coordination Centre (*CLIC*): information and support hub dedicated to older people and their friends and family. Depending on the CLIC label level, its role is:
- level 1: to inform, welcome and listen
- level 2: to perform a needs assessment and draw up a care plan
- level 3: to implement the care plan and document the person's situation.

It is also a coordination hub for all professionals working with older people. They exercise vigilance concerning the state of the offer and needs in their area of operation. Professionals attached to the CLIC are mainly trained as social workers [ANCCLIC, Association nationale des coordinateurs et coordinations locales, ancclic.fr *www.pour-les-personnes-agees.gouv.fr/resultats-annuain*)]. With good knowledge of packages and the various service providers (home support service, meals on wheels, remote assistance, home adaptations, etc.), they are an effective source of information.

- Action method for integrating care and assistance services for independent living (MAIA): the aim is mainly to ensure continuity of pathways for people aged 65 and over, in order to avoid interruptions in care. A leader is assigned to running the project, identifying resources, pointing out inefficiencies and developing links between the various participants. A case manager is assigned to overseeing individual complex situations. They then become the direct contact for the person and their friends and family, to coordinate the various actions by all professionals who may need to intervene.
- *Parcours de santé des personnes âgées en risque de perte d'autonomie (PAERPA)*: this has been deployed since 2014 in pilot regions. The aim is to maintain

maximum independence, for as long as possible, in the over-75-year-old's usual living environment. "Having the right care, delivered by the right professionals, in the right structures at the right time and all at the best cost".

• Social protection schemes

These are a social service within health insurance funds whose mission is to promote access to care, contribute to keeping people at home, support people with long-term serious illnesses: for example in recognising cancer as an occupational illness. They are a specialist service working in a defined geographical sector (*www.ameli.fr*, telephone 3646, *www.msa.fr*, *www.secu-independants.fr* telephone 3648, *www.regimesspeciaux.org*).

When travelling in an EU country, in the European economic area or in Switzerland, people must have a European health insurance card (from outside France, call +33 811 703 646).

• Care facilities

In these structures, the hospital social service helps to prevent social or medico-social difficulties. Its mission is to assist patients and their next of kin with the various administrative procedures, and support them in organising and running their project.

• Other sources of information for France

- Family allowance fund: one per department (*www.caf.fr*). Depending on the person's situation, different allowances may be paid (income support (*RSA*), disability allowance, housing allowance, etc.)
- Centre for people with disabilities (*MDPH*): one per department where a multidisciplinary team is in place and reports to the Commission for the Rights and Independence of Persons with Disabilities (*CDAPH*). This body makes decisions concerning specific rights or benefits for people with disabilities (disability compensation benefits (PCH), inclusion mobility cards which have replaced priority cards or parking cards for adults with disabilities, etc.)
- The *Comité départemental de la ligue contre le cancer* (*www.ligue-cancer.net*, telephone 0800 940 939 to

call the legal department and arrange a meeting with a duty lawyer, press 3)

- Regional cancer networks, cancer information kiosks (*www.e-cancer.fr*), cancer centres in the city of Paris (*www.paris.fr*), as well as Meeting and information spaces (ERI) hosted by cancer centres or hospitals (contact details available on *www.e-cancer.fr/patients-and-proches*).

The main personal assistance schemes

• Home help and support service (SAAD)

Home help services must be approved before they can work with older people. There are two possible response statuses: service provider and/or authorised representative. With service providers, the SAAD acts as an employer. With authorised representatives, the SAAD offers technical support for all administrative matters but the older person is the employer (*https://monaideado- micile.paris.fr*). The SAAD employs professionals who may be involved as:

- a home help to assist purely with everyday tasks (housework, shopping, going outdoors, etc.)
- homecare assistant to help with everyday living. They are also authorised to supervise taking medication (prepared by a nurse) and carry out simple hygiene tasks
- live-in nurse to help the person day and night.

The older person can choose to employ this person directly. In this case, they are responsible for all employer obligations, as well as all the administrative processes around this status (Social Security declaration, contract of employment, redundancy, etc.). To help with all these processes, in France the person can use the voucher-based system (CESU, *https://www.cesu.urssas.fr*) and consult the following websites for information: *www.pole-emploi.fr*, *www.entreprises.gouv.fr/services-a-la-personne*, *www.service-public.fr*. The presence of supportive friends and family is often vital when organising keeping an older sick person at home, and French law offers the following:

- Caregiver leave can allow, in certain conditions, a private sector employee to suspend or reduce their professional activity to look after a family member who has lost much of their independence and lives in

France. For public sector employees, two similar processes are availability and right to part-time working. The employer cannot refuse this leave and its maximum length is one year in the whole employee's career. This leave is not paid by the employer but the employee is eligible for up to 66 days of daily carer's allowance at a rate of €58.59 per day and €30.47 per half-day

- The aim of family care leave is to allow carers who wish to halt their professional work temporarily in order to take care of a relative who is sick or dying (*http://www.pour-les-personnes-agees.gouv.fr/aider-un-proche/travailler-and-aider-un-proche*). The employer cannot refuse this leave, which is a maximum length of three months and can be renewed once all the conditions have been fulfilled. This leave is not paid by the employer but the employee can ask for a daily allowance for looking after a dying person at home which amounts to €59.63 per day and €29.82 per day for switching to part-time work.

The main home care schemes

• Home care nursing services (SSIAD)

Like private nurses, these get involved as a result of a medical prescription. The prescription specifies how often they should visit and what action they should take. Auxiliary nurses also come under this category, as do occupational therapists and psychologists, etc. (Union nationale de l'aide, *www.una.fr*).

• Hospital at Home (HAD)

Provides round-the-clock care, with installation of medical and technical equipment if necessary (*Fédération nationale des établissements d'hospitalisation à domicile www.fnehad.fr*). This is most commonly put in place at the hospital doctor's request with the agreement of the HAD coordinator and approval of the attending physician. A number of health professionals work together (psychologist, therapist, speech therapist, social worker, etc.).

• Home healthcare providers

These are companies that specialise in medical technology for home care. They hire out or sell equipment (adjustable bed, incontinence protectors, walking frame,

etc.), ventilators, products and services for perfusions or nutrition. The cost of installing this equipment will be covered by the health insurance fund on production of a medical prescription.

• *Day hospital*

Covers the cost of treatment during the day by health-care professionals. The person can travel in an ambulance or using their own transport.

These schemes are covered by the health insurance fund on production of a medical prescription (100% reimbursed when the disease appears on the list of long-term conditions).

The main types of technical assistance

• *Meals on wheels*

This may be offered by social welfare centres or other service providers chosen by the individual. These meals are adapted to different diets and they are packed in a way that allows them to be reheated and opened very easily.

• *Remote assistance*

The provider chosen by the individual installs an alert system which is triggered by simply pressing a transmitter worn permanently by the person. This signal is relayed to a remote assistance centre which warns friends and family or contacts the appropriate emergency service. Technical advances have led to the development of geolocation systems which also work outside the home, and automatic fall detectors.

• *Home adaptations*

These are used to make safe the older person's immediate environment, for example by minimising the risk of falling, using a remote control to open and close shutters automatically, buying or renting special equipment (toilet seat riser, hospital bed, non-slip floor covering, etc.). Some of these devices require a medical prescription for this to be covered in full or partly by the health insurance fund. For more substantial adaptations, the department PACT or ANAH (French national agency for

housing improvement, telephone: +33 (0)820 15 15 15; *www.anah.fr*) can be asked to make a financial contribution in certain conditions.

The main funding schemes

There are several types of financial support. Applications can be made to bodies such as the CCAS, the department, pension funds, health insurance funds, private health insurance companies (depending on the contract), CAF (*www.caf.fr*), etc.

- *Personalised autonomy allowance (APA)*

This is aimed at people aged over 60 who are losing their independence. It is intended to contribute to the expenses associated with loss of independence. In France, the application for APA is lodged with the General Council in the applicant's locality. Independence is assessed according to the AGGIR national grid (Iso Resource Group (GIR) from 1 to 6, CERFA form no. 11510*01). Only a GIR assessment of 1 to 4 gives the right to receive the allowance. The amount of financial contribution takes into consideration the degree of dependence and the applicant's economic circumstances. If their income is less than €816.65/month, no financial contribution will be asked for. Therefore for a GIR of 1 the amount allocated is €1,807.89/month, for a GIR of 2 it is €1,462.08/month, for a GIR of 3, €1,056.57/month and for a GIR of 4, €705.13/month.

For income between €816.65 €/month and €3,007.51/month, the financial contribution is reduced according to the proposed cost of the care plan.

For income above €3,007.51/month, the beneficiary will only receive 10% of the allocated sum.

The assessment of loss of independence is conducted at the person's home by the APA medico-social team before the care plan that will be proposed to the applicant is drawn up. Once the dossier is complete, the department has two months to give a response. However, an emergency application for an APA can be requested when the person's situation requires it.

Since January 2017, the French inclusion mobility card (*www.cnsa.fr/documentation-and-donnees/formulaires*) allows people to apply for a European parking card and

disability card at the same time as applying for an APA depending on the GIR applicable to that person.

If the person is ineligible for an APA, they can request benefits from their pension fund: for example, the CNAV offers help with going home after a stay in hospital (ARDH) or help with emergency situations (ASIR). It can quickly allocate funding for a maximum of three months with a ceiling of €1800 (telephone 3960; from outside France, from a booth or a mobile +33 9 71 10 39 60, *www.lassuranceretraite.fr*). This sum is intended, after implementation of a personalised care plan, for putting in place home support, technical equipment, meals on wheels, remote assistance, etc. It is incompatible with APA.

- *Social care at home*

This is aimed at people over 65, or 60 if they are unfit for work, who do not have sufficient resources to pay for the expenses resulting from loss of independence. The application for social care is lodged with their local communal social welfare centre. It is then sent to the general Council for a decision on whether it is granted or rejected. Home support helps to pay for the provision of home help services and/or meals. Unlike the APA, the cost of social care is recoverable from the applicant's estate according to the conditions defined by the department.

- *National Fund for Health-related and Social Action (FNASS)*

This is aimed at people receiving palliative care certified by the doctor who is monitoring their palliative treatment *(www.sfap.org)*. This financial support is means-tested. It is used to fund services and provisions not covered elsewhere. It is paid on top of the APA, ARDH, etc. The application is filed with the patient's local sickness insurance fund. It is managed by the CNAVTS.

However, in certain circumstances, keeping the older person at home is no longer feasible. They may then need to be admitted to a nursing home or long-term care facility (LTCF). The possibility of going to live with family can also be explored. The person can live with a "foster carer" approved by the department in exchange for

remuneration (*www.pour-les-personnes-agees.gouv.fr/choisir-un-hebergement/vivre-en-accueil-familial*).

The main accommodation schemes

- *Nursing homes*

These must provide their residents with quality of life and look after their medical needs appropriately. They take in older people who cannot or no longer wish to stay in their homes. When the application for admission (CERFA no. 14732*01) is lodged, it comes into effect after being reviewed by the home's coordinating physician and confirmed by the applicant.

- *Long-term care facilities (LTCFs)*

These must provide their residents with ongoing medical care. They are aimed at older people with multiple conditions who have lost much of their independence and require prolonged treatment. These are healthcare institutions, usually attached to a hospital structure. Like for nursing homes, admission happens after a medical opinion.

The main funding schemes

Nursing home pricing is similar to that of an LTCF, and includes the cost of care, accommodation and dependence. The cost of care is covered by the person's health insurance fund, the cost of accommodation is paid by the person and cost of dependence is calculated according to their level of dependence on nursing care. If the older person has insufficient income to pay for the accommodation element, they can apply for social housing assistance, provided that this is approved by the department. As concerns the cost of dependence, they should apply for a personalised autonomy allowance in an establishment.

- *Social support with accommodation*

The application is made, in part, in the same way as social care at home. The beneficiary contributes up to 90% of their income (when there is a spouse, the percentage contribution may be calculated differently). The spouse contributes as a duty to pay their part. Parents and children are obliged to pay maintenance. After

assessing everyone's financial situation, the family court sets the amount for everyone to contribute. In addition, a legal mortgage is taken by the department on the property, and this is recovered from the applicant's estate from the first euro.

- *Personalised autonomy allowance (APA) in an establishment*

The application is made, in part, in the same way as for the APA at home. The establishment's coordinating physician assesses the applicant. There are three dependence tariffs: 1-2, 3-4 and 5-6. The amount of the APA in an establishment equals the difference between the establishment's dependence tariff corresponding to the resident's GIR and the contribution they still need to make. There are calculation simulators for assessing the amount of their APA, especially on the website *www.pour-les-personnes-agees.gouv.fr*. If the person is already benefiting from an APA at home, the amount awarded for an APA in an establishment will be different.

Putting these schemes in place requires the older person to sign up and give their approval. If they are incapable (physically or intellectually) of expressing their wishes and acting for themselves, it may sometimes be necessary to apply for legal protection. The legal representative, appointed by the guardianship court judge can then act in the interests of the adult in need of protection.

The main types of legal protection

The application is made by registered mail, sent to the guardianship judge at the family court local to the adult in need of protection, when it has been formulated by the person or by their close family. The application is made to the public prosecutor when it has been formulated by a third party, such as someone in a medical or social establishment. The public prosecutor assesses whether the application should be sent to the guardianship judge. It contains the expert medical report on the list drawn up by the public prosecutor, a single application form, filled in with the information which explains the need to resort to legal protection. The guardianship judge will rule on the most appropriate legal

protection measure, thus allowing a personalised approach to the measures that he will make a decision on (law 2018-222 of 23 March 2019 on reform of the justice system, family law and people's rights) (*www.service-public.fr/particuliers/vosdroits*).

• *Court order*

This is an emergency temporary legal protection measure lasting for a year, which can be renewed once. It allows the person to continue to participate in civil affairs to some extent. In some complex situations, the guardianship judge can appoint a special representative who then undertakes all the actions mentioned in the order. This measure gives the option of challenging certain actions that are not in the interests of the adult.

• *Guardianship*

This is a legal protection measure which is chosen for people who, although not totally incapable of acting for themselves, need to be advised or monitored continuously in their civil affairs. It lasts for a maximum of five years. The magistrate can renew it.

Types of guardianship in France:

- simple guardianship: the adult will only be assisted with disposal of assets
- enhanced guardianship: the adult will be assisted with disposal of assets, but their guardian also has access to the adult's resources in an account opened in the latter's name
- modified guardianship: the judge determines on a case-by-case basis which actions the person can perform on their own.

• *Ward of court*

This is a legal protection measure which is used for people who are totally incapable of acting and who need to be represented for all their civil affairs. The judge can decree that the adult in need of protection takes decisions concerning them on their own (choosing where to live, for example). Like guardianship, it lasts for a maximum of five years, and can be renewed.

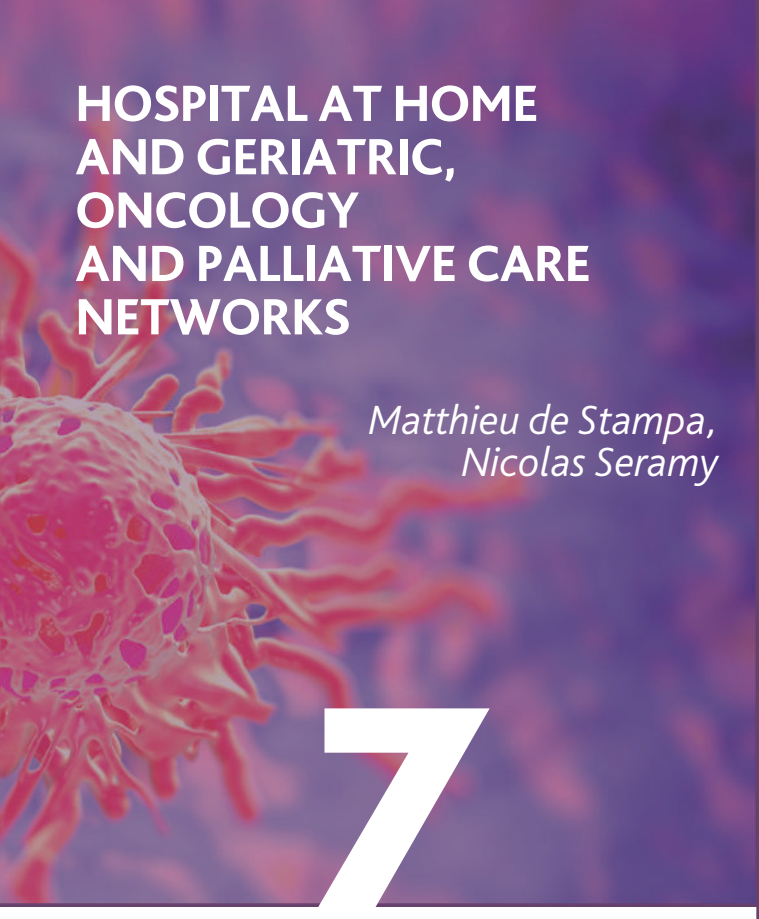
The reform of 2007, applicable in 2009 after having modified the legal protection system, established the lasting power of attorney. This is a contract which allows

someone (the donor) to organise, in advance, protection (of their property and/or person) by appointing another person (the attorney), with their permission. Power of attorney can be drawn up by private agreement or a notarised deed (CERFA no. 13592*02, no. 51226*02). It comes into effect when a medical expert certifies the donor's incapacity to act for themselves and this is authenticated by the registry of the district court. The law of 23 March 2019 confirms the primacy of the lasting power of attorney once this has been put in place.

With order no. 2015-1288 of 15 October 2015 applicable from 1 January 2016, the legislator has empowered families. This legislation makes it easier for the next of kin to act on behalf of someone who has lost the capacity to express their wishes. The law of 23 March 2019 extends this measure to people who can't make decisions for themselves due to impairment, with medical evidence, of their mental faculties, or their bodily faculties. Family empowerment can be requested directly from the magistrate (standard request form: *https://www.service-public.fr/particuliers/vos-droits/R45193*) with a medical certificate provided by an approved medical expert. However, it is not a legal protection measure. Once the authorised person has been appointed, the guardianship judge does not get involved again. The person's representation may be limited to a few actions or may be general. It therefore requires a good understanding between the various family members involved (*http://www.pour-les-personnes-agees.gouv.fr/aider-un-proche/protegerson-proche-les-differentes-mesures/lhabilitation-familiale*).

Conclusion

Supporting and caring for an older person who has become frail as a result of illness is often complex. It is vital to have a good understanding of what their situation requires, taking all the different elements into account (pathological, social, economic, environmental, etc.) that interact in their day-to-day life and affect their well-being.



HOSPITAL AT HOME AND GERIATRIC, ONCOLOGY AND PALLIATIVE CARE NETWORKS

Matthieu de Stampa, Nicolas Seramy

7

Healthcare networks

These have had the benefit of long-term funding and have expanded since the early 2000s. Their missions are clearly defined in the founding legislation, especially in the French Public Health Code.

Since 4 March 2002, healthcare networks have been given an official definition (translation of Article L 710-1-1 of the Public Health Code below): "*healthcare networks are intended to facilitate access to care, coordination, continuity or interdisciplinarity of healthcare services, especially those specific to certain populations, diseases or health activities. They provide care adapted to the person's needs both in terms of health education, prevention, diagnosis and treatment. They may participate in public health initiatives. They perform appraisal activities in order to guarantee the quality of their services*".

Healthcare networks which are, for the most part, set up as associations (1901 law) do not have a role in prescribing, nor do they replace existing professionals. Their added value lies in their expertise, especially in palliative care and gerontology, and above all in supporting professionals in the community, including in structures such as Hospital at Home.

In these types of network, multidisciplinary home assessment and coordination of those involved in care are essential.

Through their comprehensive multidisciplinary assessments and their actions to coordinate those in the care sector, healthcare networks participate in improving the quality of care and services delivered to patients and families.

They consolidate the continuity of home care, make it possible to take account more comprehensively of patients' needs wherever they live, facilitate care in the community, circulate and encourage compliance with good practice by primary care professionals, and facilitate "community-hospital" links.

Healthcare networks, in their role as "support coordination structures", support the patient's coordinated care pathway, especially for so-called "complex" health situations requiring joint intervention from medico-social and social health professionals.

Coordination of the disease management pathway, the primary goal of a healthcare network's mission, organises better care in terms of orientation in the system, use of tools for managing a territory, programming diagnostic and therapeutic steps, and organising follow-up.

This coordination is different from clinical coordination, which refers strictly to medical aspects and falls within the remit of health professionals in the field and of attending physicians on the front line (attending physician reform of 13 August 2004).

Healthcare network teams may include doctors: palliative care and/or specialist pain relief doctors, nurses, social workers, psychologists, a secretary.

Due to the choices made by the network sponsors and/or financiers, these teams are often much less multidisciplinary in nature.

Healthcare network professionals jointly construct the patient's disease management pathway with all the professionals involved in the patient pathway, especially with the general practitioner, through the Personalised Healthcare Plan (PPS) suggested by the HAH (July 2013), adapted at territory level if applicable on the basis of any problems encountered.

A number of actors/mechanisms/structures may be involved in the support process coordinating complex disease management pathways. Healthcare networks are responsible for ensuring, with the regional health authority and all their partners, that each of their missions is well defined and implemented in a complementary manner, in order to provide coordination and an optimal service offer that is clear to both professionals and patients on every territory.

Current developments

From their mono-thematic origins, the networks are changing due to pressure from the French Directorate General of Healthcare Provision (DGOS) and Regional Health Authorities, into multi-thematic networks.

It has to be said that the number of diseases becoming chronic, the development of polypathological conditions, the rise in dependence associated with age or disability, isolation, and social insecurity are all contributing to the creation of increasingly complex and interrelated health pathways, expanding coordination to multiple thematic fields.

It has since appeared necessary for healthcare networks to evolve towards a core mission supporting primary care teams, and towards more comprehensive versatility of response and multiple themes.

The concept of multi-thematic support covers support with complex conditions combining several diseases and/or age brackets, without necessarily concerning them all (example: gerontology, cancer treatment and palliative care, but not diabetology).

The majority of existing networks are skilled in palliative care, geriatrics and cancer treatment.

The purpose of these groupings is to improve clarity for professionals and patients and, of course, to lower costs by pooling resources.

These groupings also offer an opportunity to redraw the map of their locations in order to make this consistent in geographic terms and in population areas of equivalent size (territory adjacent to territories defined for MAIAs).

These changes to healthcare networks are entrenched in the plan to set up "territorial support platforms for coordination" as defined by Article 14 of the draft Health Act, or more recently of coordination support facilities expanded to the "all ages, all diseases" health pathway deemed to be complex by any professional in the field who works in a patient's home.

These coordination support facilities, the first fruits of pooling network and MAIA resources (and for certain territories in the CLICs) no doubt presage the forthcoming coordination support tool, incorporating several levels of patient coordination and intervention (simple patient orientation in the medico-social system, medico-social assessment, insertion in the identified care sector in a territory, follow-up of complex conditions).

The gradual roll-out of a digital coordination tool among healthcare professionals (TERR-eSANTE) is consolidating these new orientations and reorganisations of support for health pathways.

In this context, the future of healthcare networks in their existing form is still emerging and most likely to be envisaged in a form integrated in the coordination support facilities, in close collaboration with the mobile intra- and extra-hospital teams who will have the various types of expertise mentioned below.

Healthcare and palliative care networks

Their mission and modus operandi have remained unchanged since their creation.

They provide medico-psycho-social expertise to patients in the home and also support patients and their loved ones.

Since palliative conditions sometimes evolve over a short period of time, conditions are reassessed more frequently than in geriatrics or oncology.

Support for professionals in the community in these situations carrying a heavy clinical and emotional burden is fundamental to ensure they do not feel isolated and are able to provide high-quality treatment.

Palliative care networks are supposed to provide a 24/7 on-call service by telephone as a minimum.

Healthcare and geriatric networks

Multidisciplinarity brought to patients' homes also has huge importance.

Apart from the specific issues of keeping patients with major cognitive disorders at home for the long term who sometimes refuse care, gerontological treatment, which is in essence overall care, often intimately linked with social and medical issues, already brings expanded social, health-related and medical responses from the networks into the home.

Their support and vigilance with regard to disruptions in the pathway with serious consequences for older patients have always been a significant part of the gerontological networks' activity.

Similarly, their support for the primary care teams in these complex situations, whether medically, socially or environmentally, still dominates their action and support for healthcare professionals, users and their carers, often exceeded either by the parcelling out of professional skills (medical/social/legal, etc.), or due to ignorance of the treatment tools proposed by the hospital-based gerontological sectors and territorial non-hospital sectors.

Organising patient pathways in the use of geriatric hospital resources is a significant part of the networks' activity on the gerontological theme (patient follow-up is not as constant as in palliative care).

The link with social services is fundamental (support for professionals in the community can be an expert geriatric assessment in the home when this is essential, but consists primarily of using all the geriatric and social services correctly).

Healthcare and cancer treatment networks

There is not yet a precise specification for cancer treatment networks, so the actions they undertake are fairly variable depending on the territories.

However, the majority provide supportive care, which is fairly close to the missions of palliative care networks. It therefore makes perfect sense to associate the two.

Their other missions can range from organising screening for certain cancers to organising monitoring of chemotherapies, especially oral.

Some have a specific oncogeriatric activity.

The added value of palliative care, gerontology and cancer treatment networks

These networks are not healthcare facilities and their role is neither prescription nor direct treatment, even if their advice may be similar.

Their value lies in their huge expertise in complex treatments.

Intrinsic complexity, due to patient pathways between the community and the hospital being difficult to manage without an adequate coordination structure. Complexity, due to the chronic nature of diseases with ever-changing repercussions on daily life. Complexity linked to multiple medico-psycho-social facets.

The networks' expertise is not limited to purely medical expertise, it comes from their consummate familiarity with the territory where they are working, not just familiarity with resources but also familiarity with the various regulations, areas of expertise and constraints of the other professionals.

Establishing close personal links with professionals in the territory (including hospitals) is an ongoing task but one that make perfect sense for the concept of a "network".

It is worth noting that in regions where networks have existed for a long time, patients and professionals have taken ownership of them and could not imagine the healthcare network without them.

Place of HAH in the care pathway for patients in geriatric oncology

- *Introduction*

Hospital at Home (HAH) is a **special type of hospitalisation** with, as its name suggests, the patient concerned being cared for at home. It is an alternative to a conventional hospital stay which can **avoid or shorten hospitalisation as an in-patient**. Continuous coordinated

medical and paramedical care is provided in the patient's home. The care delivered in HAH is distinguished from that usually dispensed at home by its **complexity**, **duration** and the **frequency of procedures**. Continuity of care is provided 24 hours a day, 7 days a week.

HAS facilities are healthcare establishments, bound by the same obligations as hospitals with accommodation[1].

In 2019, there were 288 HAS facilities in France. 122,000 patients were recorded as being cared for at home, by their family and next of kin. The average cost of a day in hospital for health insurance purposes is €199[2].

HAS is prescribed on the basis of the amount of care required by the patient's state of health. It is totally integrated in care pathways and concerns **patients of all ages** with serious, acute, or chronic diseases which are often multiple, progressive and/or unstable, including cancer. The proportion of older people benefiting from HAH is growing rapidly. Patients in **nursing homes** or in social or medico-social facilities can be treated by HAS and represent 10% of the population looked after in HAH.

Since 2005, a proactive attempt to make the HAH offer more mainstream was made on the territory in order to help meet the growing demand from the population to be cared for at home, the impact of population ageing and an increase in chronic diseases.

However, although the number of days in HAH has grown significantly since 2005 (+ 194% between 2005 and 2014), with activity particularly focused on palliative care, complex dressings and onerous nursing care, its growth has slowed year on year (+ 3% in number of days between 2013 and 2019, with the number of stays actually falling by - 1%). HAH is still relatively rare in France but is expanding strongly compared to the majority of other countries

- *Admission to HAH*

Patients are admitted to HAH **on medical prescription from a hospital doctor, an attending physician in the community, a healthcare network coordinating doctor, a hospital mobile team or a nursing home**, after a consultation/assessment, or following a stay in hospital (MSO, FCR). Hospitalisation at home is in theory always

subordinate to agreement from the patient's attending physician and also the consent of the patient and/or their friends and family. A patient's eligibility for and feasibility of HAH is assessed by a nurse care coordinator (NCC), often present within the prescribing institution. The NCC acts as the interface between the HAH and the hospital. Admission to HAH is decided by the HAH coordinating doctor on the basis of a **treatment protocol, within 24 to 72 hours, depending on the patient's condition and the degree of urgency**.

A specially trained multidisciplinary team (doctors, nurses, auxiliary nurses, healthcare executive, social workers, medical secretaries, dietitians, occupational therapists, physical therapists, psychologists, etc.) provides care in the home with secure organisation. The coordinating doctor is the medical consultant for the HAH healthcare team working in the patient's home.

Logistics organisation in HAH requires numerous checks and a high level of traceability. This work of checking, traceability and coordination is particularly onerous in the HAH organisation system, since it is long and tedious for the various participants and must be done 24/7 at any time of day. Nurses giving care at home have a certain autonomy in organising their shifts and, on the whole, they try to provide continuity of care with the same patients to make it easier to monitor them. They organise themselves according to the number of patients on their list, the time required by each for their care, the distance between the different homes and time constraints that have to be respected.

- *HAH care for adult patients excluding women giving birth*

Care delivered at home in HAH may be for more than one condition and is subject to regulation according to payment per treatment, based on the reason for care, not the disease. Those most frequently associated with cancer treatment are as follows:

- administration of chemotherapy
- post-chemotherapy, post-radiotherapy monitoring with supportive care
- post-surgical monitoring
- pain management
- parenteral and enteral feeding
- complex dressings

- administration of intravenous treatment (usually hospital drugs reserved for hospitals, including IV antibiotic therapy)
- support with palliative care
- motor and neurological rehabilitation.

• Chemotherapy at home

Chemotherapy at home is prescribed by the hospital doctor who is looking after the patient in the healthcare facility. For safety reasons, the first chemotherapy session is administered in a day hospital, in order to identify any particular reactions to the treatment, which allows the prescribing doctor to adapt the protocol and the dosage regimen.

As concerns eligibility for chemotherapy at home, the NCC looks at whether it is feasible and in particular assesses:
- conditions at the patient's home to ensure that they are suitable for HAH
- the patient's tolerance profile and the data needed for follow-up in HAH (cancer history, minutes of multidisciplinary team meeting: MDTM, etc.)
- the patient's cognitive ability to understand how it works and the challenges associated with administration of chemotherapy at home.

If the patient's social situation and home living conditions (particularly sensitive subjects when it comes to older patients) lead the NCC to doubt the feasibility of HAH (social isolation, unfit housing, inadequate care plan, etc.), the NCC can ask the HAH social worker and/or occupational therapist to visit the patient's home and conduct a medico-social assessment to make the patient eligible for HAH.

Once the patient has been admitted to HAH, the NCC updates the patient's records with each hospital visit and any change or event that has occurred, in order to maintain traceability of their care pathway, in conjunction with the HAH healthcare team working in the patient's home.

The attending physician, in conjunction with the prescribing doctor and the HAH coordinating doctor, is responsible for regular follow-up of the patient at home between each session. The HAH coordinating doctor

oversees medical coordination of all patient follow-up in conjunction with the referring hospital team, attending physician and if applicable the healthcare network involved in the patient's care pathway.

Older patients do gain some benefit from having chemotherapy administered in HAH. Chemotherapy in a day hospital is often too difficult because it is repetitive and involves frequent travel (often daily) for short-term product administration (mostly subcutaneously, especially in haematology). Whether prescribing doctors choose to "outsource" chemotherapy to HAHs depends on the dosage regimen. Some chemotherapies, especially those involving haematology protocols often need administrations close together and must be administered very frequently (e.g. subcutaneous injections of azacitidine for 7 days in a row or subcutaneous injections of bortezomib on D1, D4, D8 and D11).

These very frequent, relatively "light" methods of administration in terms of nursing care are particularly suitable for HAH treatment at home of older patients who would find it uncomfortable to travel to a day hospital. This can also free up spaces in a day hospital so it can take new patients.

However, hospital prescribers can feel they have lost control if a patient is being followed up in HAH. As the patient travels less often to the healthcare facility where the prescriber works, they may have a feeling that they have "lost sight" of the patient. The conventional hospital care team and the HAH team need to learn to work together and coordinate their tasks, since they will not necessarily have the same way of doing things. In addition, it sometimes happens that patients revise their perception of HAH care, especially of having their chemotherapy at home over time. They may wish to return to a day hospital because they realise that the HAH actually involves them in a lot of effort, particularly in receiving or returning the various packages and medical devices. This means that they have to manage a lot of logistics at home[4]. It is therefore necessary to implement procedures to support and update the teams, and work to optimise logistics, which is a major challenge for HAH.

Intervention by a multi-thematic healthcare network (geronto-onco-palliative care) can be helpful in coordinating

the patient's care pathway. It can get involved upstream and downstream of the HAH intervention. This should not complicate coordination but on the contrary should be a strength. This collaboration allows for a more fluid approach to care. It makes the care pathway less complicated when the HAH has a technical role in applying the treatment recommended by the healthcare network and prescribed by the hospital doctor or attending physician.

• *Conclusion*

The trend for hospitals to shift towards ambulatory care and therapeutic advances will probably mean there are increasing indications for HAH, especially in the field of cancer treatment and palliative care. This means that even more patients can be treated, including those treated with oral chemotherapies for which the indications are expanding, even if financial and medico-economic issues need to be taken into consideration.

Good collaboration between the community and the hospital (for which the HAH acts as an interface), and a good understanding of the roles of everyone helping to care for the patient, in hospital or at home, will allow patients with cancer (whose average age is constantly increasing) to be supported right from the start of the disease until end-of-life care is needed, which can now be given at home.

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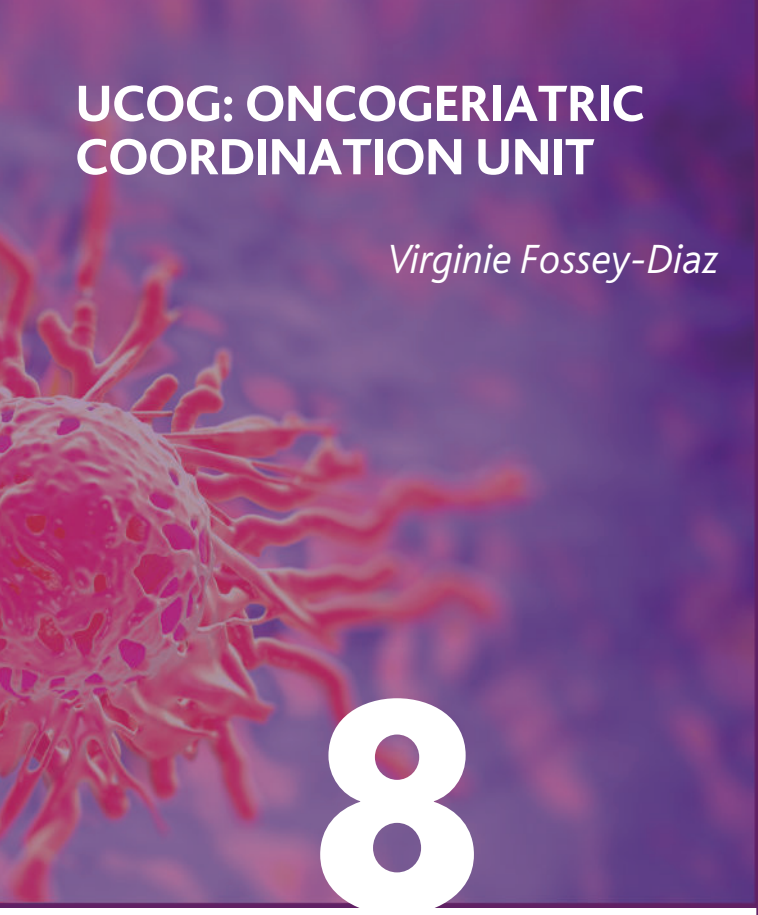
UCOG: ONCOGERIATRIC COORDINATION UNIT

Virginie Fossey-Diaz



8

At the outset: a visible statistical context

The incidence of cancer increases as people age.

In 2017, cancers in the over-65s represented 62.4% of estimated cancers in all age groups.

In the over-85s, there were 45,993 estimated new cancer cases, accounting for 11.5% of all diagnosed cancers (9% in men, 14% in women)[1].

In 2012, 53,389 women in the same age bracket were given a cancer diagnosis.

Almost 10% of all diagnosed cancers were in the over-85s.

In terms of incidence, we find the same distribution of cancer types as in the general population. The most common cancers in men are, in the over-65s: prostate cancer (34,060 estimated new cases in 2013), lung cancer (20,214 estimated new cases in 2017), colorectal cancer (17,366 estimated new cases in 2017)[2].

In women aged over 65, breast cancer was still the most common (28,799 new cases according to the 2017 forecasts), followed by colorectal cancer (15,376) and then lung cancer 9,328)[2].

In parallel, the 10-year net survival for prostate cancer was 61% for 75- to 84-year-olds and 32% for the over-85s, as opposed to 83% for 55- to 64-year-olds and 79% for 65- to 74-year-olds. Late diagnosis and comorbidities explain the poor prognosis.

The same goes for colorectal cancers: 60% in 15- to 44-year-olds as opposed to 45% in the over-75s.

For breast cancers, net survival was 83% in 45- to 54-year-olds and 65% in the over-75s.

Finally, for lung cancer, net survival was 17% for 15- to 44-year-olds and 5% in the over-75s. This cancer is diagnosed late regardless of the patient's age.

Geriatricians, oncologists and other organ specialists often need to discuss records of patients aged over 75 in a multidisciplinary team meeting (MDTM).

An initial response: creation of the UPCOG structure

Hence, given the increase in life expectancy and the increased incidence of cancer in the geriatric population, measure 38 of the cancer plan (2003-2005) envisaged adapting care methods and treatments to better suit the specific needs of older people.

In 2006, 15 oncogeriatric pilot units (UPCOGs) were created, spread throughout 13 of the 27 French regions. The INCa specification stipulated:

- improving training of carers so they can better assess patients aged over 75
- increasing the number of staff trained in oncogeriatrics
- allowing patients aged over 75 to have an oncogeriatric assessment before starting treatment.

Funding was provided by the French National Cancer Institute (INCa), paid in the form of general interest mission (MIGAC) funds to the finance departments of the hospitals sponsoring the project.

The UPCOGs defined operational care programmes by focusing on 3 areas:

- training/information
- access to care and oncogeriatric assessments
- inclusion of older people in research protocols[3].

These programmes consisted primarily of developing a partnership between the geriatric and oncology departments.

Nowadays: UCOGs

The second cancer plan (2009-2013) decided to boost this initiative. A new call for projects was launched by INCa in 2011.

In August 2013, 28 coordination units, including 4 oncogeriatric centres (Rouen, Tours, Besançon, Clermont-Ferrand) were approved (source FINESS, Organisation des Soins department, INCa Pôle Santé Publique et Soins).

Funding was provided by INCa, under the same arrangements.

The missions were restated:
- optimising oncological treatments in the older population, thanks to oncogeriatric assessment
- boosting the number of oncogeriatric studies
- informing healthcare workers/patients/the general public
- encouraging UCOGs to self-assess.

Action 2.16 of the 2014-2019 cancer plan stresses the priority of caring for the geriatric population and the role of the UCOGs in circulating good practice with a view to homogenising research and training throughout the regions[4].

In order to comply with the specification, every UPCOG/UCOG developed organisation of their territories in line with existing structures.

Some UCOGs joined regional oncology networks. This still varies a lot from one region to another.

The way each UCOG operates is still based on collaboration between the oncologist and the geriatrician: the oncologist usually gives the cancer diagnosis and suggests the treatment (which is then validated in the MDTM).

The geriatrician diagnoses the associated pathologies, ranks comorbidities, assesses the functional status and social environment, proposes a care plan in order to

optimise treatment and, in an ideal world, is responsible for patient follow-up.

Getting both these experts together should improve overall care: choice of treatment, need for and putting supportive care in place (nutritional management, physical therapy, adaptation of the home, psychological support, etc.), geriatric care.

In 2014, the regional health authorities (ARS) asked all the UCOG leaders to ensure that all centres with an oncology activity are attached to a UCOG. The goal was to share tools and recommendations in order to optimise care of older patients who have been diagnosed with cancer.

Thanks to the work of learned societies (SOFOG, SIOG, etc.) or geriatric oncology discussion groups (FROG), the impact of oncogeriatric care has been recognised. Intergroups within learned societies, with advisers from the UCOGs, participate in making recommendations to national bodies (INCa), oncogeriatric sessions take place during national (SFGG) and international (ASCO) geriatric congresses.

UCOG leaders are regularly asked to participate in hospital clinical research programme (PHRC) projects, and indeed often sponsor these.

As a general rule, UCOGs are organised as follows, developed according to needs and resources:

- management: steering committees with local committees to create joint projects, assess them, disseminate information, during multi-year meetings
- assessments and follow-up:
  - performed by consultant medical assessors, at the patient's bedside, in day hospitals and through expansion of mobile teams
  - participation of geriatricians in MDTMs
  - use of the G8 tool (Oncodage study) and standard geriatric assessment, and also recruitment of nurse care coordinators who get involved in assessing and coordinating the patient pathway between the local authority and hospital
  - boosting of some teams with the arrival of RNs-APNs (advanced practice nurses) who take part in liaison, follow-up and consultation activities

  - developing links with local authority networks for supportive care, palliative care, as well as with social workers and pain clinics.
- **training/information:** creation of university diplomas in geriatric oncology open to doctors and paramedics, participation in geriatric oncology conferences (SOFOG, SIOG, MAO, Journées Arpège, etc.), organisation of themed cancer days, creation of a website presenting the UCOG, directories listing all the contact people, etc.
- **research**: sharing assessment tools, PHRCs, clinical trials, recruitment of a clinical research associate.

Obstacles to implementation

At the end of the day, despite a real desire for national coverage, the UCOGs have had to face a number of limiting factors:

- extensive geographical territories and insufficient geriatric medical representation compared to needs
- comprehensive geriatric assessment is very time-consuming and the number of trained geriatricians is insufficient to meet the need
- as a result, problems in freeing up time to work on topics in a group
- patient follow-up is difficult to achieve. Local authority/hospital links still need to be strengthened
- lack of a pricing structure for oncogeriatric assessments is holding back expansion of this activity.

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SURGERY AND INTERVENTIONAL IMAGING

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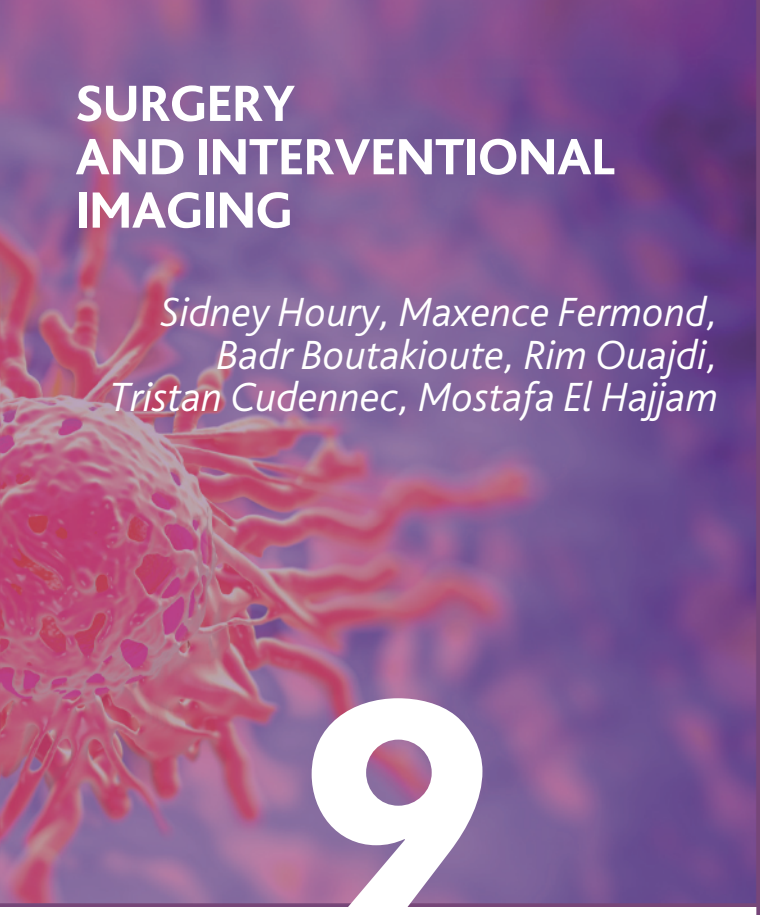

9

■ Specific features of cancer surgery in older patients

Sidney Houry

First of all, we thought we should define the older patient. Numerous publications use an age of 70 or 75. In reality, medically speaking, and this is consistent with healthcare expenditure, it is octogenarians who should be viewed as older people[1]. This is the concept that has been chosen by geriatricians and geriatric oncologists. We have tried to use this age as a benchmark for the specificities of treating digestive cancers. According to INSEE sources as at 1 January 2022, people aged 80 and over represented almost 8.5% of the overall population in France. The last national census recorded 67,813,936 people, including 4,546,481 octogenarians, 1,174,662 nonagenarians and 31,037 centenarians. Moreover, the risk of developing cancer increases with age. Cancer is still the main cause of death in France. Given these data, cancer surgery in older patients is a real strategic challenge for the nation. Surgical indications pose the basic question of whether an older patient will die from age or from cancer. A clear response was provided by the French National Institute of Statistics and Economic Studies. This shows that the risk of dying within the year is

only around 5% in octogenarians. The same sources show that the average number of years octogenarians have to live is 10.9 years for women and 9 years for men (Table 1). The patient is therefore more likely to die from their cancer.

Table 1: *Average number of years yet to live in people who have reached the stated age. INSEE, statistics on marital status and estimated population. Provisional results determined at the end of 2021*

		80 years	85 years	90 years	95 years	100 years
Female	2018	11.18	7.82	5.19	3.39	2.37
	2019	11.26	7.90	5.23	3.44	2.43
	2020	10.90	7.60	5.01	3.30	2.32
Male	2018	8.80	6.13	4.14	2.88	2.44
	2019	8.96	6.24	4.21	2.86	2.34
	2020	9.00	6.26	4.22	2.94	2.78

Talking about the specificities of digestive surgery in older patients means that the surgical indication is already on the table.

Pre-operative specificities

- *Diagnostic explorations*

Diagnostic explorations should only be undertaken if a treatment plan is feasible. Upper endoscopy can be performed without sedation. No more complications occur in upper endoscopy in older patients, indeed it appears to be tolerated better by them. A study involving 420 patients showed better acceptance and a better success rate in patients aged over 75[2]. Colonoscopy poses problems from the general anaesthetic, and a higher risk of complications. The risk of perforation was, in the work of Arora *et al.*, 0.7 in one thousand under the age of 65 and 1.1 after 80 years of age ($p = 0.016$)[3]. However, it is still advisable to perform a colonoscopy in octogenarians because of its diagnostic performance. The number of lesions discovered at this age was around 15%, much higher than in patients aged under 70. However, there is much less advantage in performing a colonoscopy in

nonagenarians[4]. Colonoscopy also poses the problem of the need for good intestinal preparation, which is difficult to achieve in older patients. In these cases, impossibility or failure should not however contraindicate surgical intervention. This may not be on a CT colon scanner which also needs rigorous preparation, but instead on a scanner which is sometimes easier for an octogenarian to accept. Endoscopic screening is only offered up to the age of 74 in France. A very recent review on the usefulness of the quantitative immunochemical screening test underlined the benefit of extending this test on prescription in over-75s without significant comorbidity[5].

The scanner, indicated when a parenchymal tumour is suspected or in the staging, must be injected, provided there is no renal insufficiency. Multi-camera scanners allow examinations to be carried out in a very short time, as holding breath is sometimes difficult to achieve in older patients. It must constantly be borne in mind that an older person is someone with often very reduced mobility, someone in pain, and that this person often has hearing problems. Due to its non-invasive nature, ultrasound scanning can be attractive to older patients. However, the application of ultrasound to the geriatric condition poses very serious problems linked to the physics of sound waves being incapable of travelling through bony or gaseous structures. Ultrasound scanning for the third age is often unproductive or unsuccessful.

- *Preventing emergency care*

Emergency surgery significantly increases post-operative mortality and morbidity. Over a series of more than three hundred colorectal resections, Webster *et al.* reported post-operative mortality of 13% and cardiopulmonary morbidity of 36% in octogenarians operated on as an emergency, whereas these figures were 6% and 7% respectively in non-emergencies[6]. In this study, the curative resection rate was only 49% *(versus* 72%). A French study in a reference centre looking at 176 colorectal cancers operated on in octogenarians showed a median recurrence-free survival of 27.2 months for patients operated on as an emergency *versus* 67.2 months for those who underwent elective surgery[7]. This bad luck is even more of a shame since it was shown that in the month preceding intervention, the majority of patients had a significant number of signs suggestive of cancer[8].

• *Digestive prehabilitation*

More than 30% of older people in hospital are malnourished[9]. Malnutrition is associated with a significantly increased risk of mortality and morbidity[10]. It is therefore essential to screen for this and correct it systematically to reduce the risk of post-operative complications. To this end, the HAS recommendations are vital in older patients (sfrar.org): pre-operative administration for 7 days of ORAL IMPACT® immunonutrition (3 sachets per day) before any major digestive surgery, regardless of the patient's nutritional status. Any patient with nutritional grade NG 4 should receive pre-operative nutritional assistance for at least 7 to 10 days. Enteral feeding should be prioritised in any patient with a functioning GI tract, and in this case, parenteral feeding is not recommended.

Moreover, numerous controlled trials and meta-analyses showed the futility of mechanical bowel preparation prior to surgical intervention, which is particularly useful in older patients[11].

• *Neoadjuvant treatments*

For several years, the consensus recommendations have highlighted the idiosyncrasies of older patients. These elements have been codified for every type of cancer in France's national digestive cancer thesaurus.

For stage I and II oesophageal cancers, the current recommendations are to perform an oesophago-gastrectomy[12]. A few sets, involving a limited number of cases, showed the possibility of oesophagectomy in octogenarians[13]. These results can never be extrapolated to all octogenarians because patients were selected and were operated on in experienced centres.

For squamous cell stage III types, chemoradiotherapy exclusively is a grade A recommendation[12]. Nonetheless, cancers of the bottom third of the oesophagus and cardiac cancers are essentially adenocarcinomas, in which case surgery preceded by neoadjuvant treatment is recommended, either chemoradiotherapy (grade A) or chemotherapy (grade A)[12].

However, multimodal treatments can be gruelling for older patients, and numerous studies show that they are only indicated in a limited number of studies. Bakhos *et*

al., in the national American oesophageal cancer database, show that multimodal treatments were only given to 2% of octogenarians, and did not appear to confer a survival advantage compared to surgery only[14]. A recent exhaustive study of the literature also casts doubt on the usefulness of pre-operative treatment in oesophageal cancers[15]. Tougeron *et al.* showed the advantage of chemoradiotherapy exclusively in older patients, with a full clinical response of 58% and two-year survival of 36%[16]. This option of chemoradiotherapy exclusively, with salvage surgery in an expert centre if the tumour is proven to persist after treatment ends or in the event of locoregional recurrence, is a grade B recommendation, but would appear to be relevant to octogenarians[12]. All the studies underline the importance of very rigorous selection of octogenarians to be operated on according to their comorbidities. Otero *et al.,* in a multivariate analysis, showed that the patient's level of dependence was the variable most strongly associated with the post-operative mortality rate. Every additional year over 80 increased the risk of patients not returning home by 17%. Octogenarians should be selected year by year, including their level of dependence, to reduce unnecessary treatment to a minimum[17].

For stomach cancers, a grade A recommendation recommends peri-operative chemotherapy with a benefit in terms of overall disease-free survival which appears to apply to all age brackets; in these randomised studies 20% of the population were aged 70 or over[18]. A recent study showed that the protocol combining 5 FU, oxaliplatin, docetaxel (FLOT) pre- and post-operatively was superior to the initial protocol (ECF) with 45% *versus* 36% 5-year survival, in a patient population in which 25% were also aged over 70[19]. Two recent trials confirmed the long-term advantage of peri-operative chemotherapy (FLOT 4) and neoadjuvant chemoradiotherapy[20,21]. However, none of these studies specifically looks at the advantage of this peri-operative treatment in octogenarians or older patients. The FLOT regimen is difficult to administer in older patients due to its toxicity. In "unfit" patients, 4 to 6 cycles of the FOL-FOX regimen before and after surgery is an alternative[22]. As concerns peri-operative chemotherapy, sarcopenia plays an essential role. Koch *et al.* showed that of the patients included in the FLOT trial, those with sarcopenia had ended chemotherapy considerably earlier, had more serious

post-operative complications, and significantly shorter survival[23]. The patient's nutritional status is still therefore of major importance when it comes to tolerance of adjuvants or peri-operative treatments. These treatments should only be proposed for patients who are not malnourished, with a daily intake of at least 1,500 calories. Without exception, the recommendations are those for initial surgery in cases of stenosis or haemorrhage.

For cancers of the rectum, in order to reduce the risk of local recurrence but without definitely improving survival rates, the recommendations stipulate pre-operative chemoradiotherapy combined with total mesorectal excision for non-metastatic cancers of the middle and lower thirds. This is 50 Gy radiotherapy delivered in five weeks followed by surgery 7 to 8 weeks later. These timescales are long for older patients. A recent trial (NACRE) in patients aged over 75 with a PS? 2 compared the typical pattern with radiotherapy delivered in one week for T3 or cT4 tumours (or cT2 very low down the rectum), M0. Preliminary results are in favour of this short radiotherapy both in terms of survival and serious post-operative complications[24]. However, pre-operative radiotherapy significantly increases post-operative digestive problems, especially urgency, incontinence and need for protection. Hughes *et al.* showed that neoadjuvant radiotherapy before rectal resection with low anastomosis was associated with a 20-fold risk of functional problems that adversely affect quality of life ($p < 0.001$)[25]. These problems usually get better over time. But in an octogenarian, such post-operative problems lead to discomfort that has a very damaging effect on quality of life. Pre-operative radiotherapy also leads to an increased risk of fistulas and stenosis, hence the need for a temporary stoma to protect the anastomosis. In patients aged over 75, there is an additional risk of this stoma not closing. In the study that came out of the Dutch trial, age was, in a multivariate analysis, a separate risk factor of the stoma not closing ($p = 0.029$)[26]. These elements, unless in specific cases, suggest that pre-operative radiotherapy should not be performed in octogenarians unless it is regarded as exclusive treatment. Tumours of 4 cm or less, situated less than 8 cm from the anal margin, assessed as T2-T3, N0-1 could be indications for rectal preservation[27]. Hupkens *et al.* showed that when there was a complete response, the simple monitoring attitude considerably improved quality

of life two years on[28]. Recent results of the GRECCAR 2 phase III randomised trial, for T2/T3 tumours less than 4 cm, comparing rectal preservation with local excision as against total mesorectal excision surgery, showed 80% good responses and 63% rectal preservation. The authors consider that T2N0 tumours should not be operated on, as they benefit from chemoradiotherapy exclusively[29].

Peri-operative specificities

- *Surgical approaches*

Laparoscopy (keyhole surgery)

For oesophageal cancers, studies suggested a reduction in respiratory morbidity when abdominal surgery was performed by laparoscopy, which may be an advantage in older patients[30]. Nonetheless this type of surgery can only be considered in experienced centres. Sdralis *et al*. reported recent results over a period of four years in octogenarians using the minimally-invasive route. Post-operative mortality was zero. The authors considered that minimally-invasive oesophagectomy is a treatment that can be offered even to older people aged over 80[31].

For colorectal cancers, Wang *et al*. published a meta-analysis of 15 randomised trials showing the short- and long-term benefit of keyhole surgery[32]. Although the average age of patients included in the majority of these studies was around 70, these trials did not specifically deal with older patients. Exhaustive studies of the literature, in people aged 80 and over operated on for colorectal cancer, also showed that keyhole surgery had the same advantages as in younger patients, but the majority of studies analysed were retrospective[33,34]. All studies on laparoscopy showed that this approach significantly increased the length of the operation. However, unlike younger patients, the length of the operation has a negative impact in octogenarians. In a cohort study (3,801 patients operated on using open surgery and 2,113 operated on using keyhole surgery), Kennedy *et al.*, in a multivariate analysis, noted that being aged over 85 and surgery lasting longer than 4 hours were independent factors associated with post-operative morbidity[35]. The choice of keyhole surgery should therefore depend on the operator's expertise.

- *Thoracotomy*

A recent national study looking at more than 3000 oesophageal cancers operated on showed the superiority in terms of post-operative mortality of resections with thoracotomy and intra-thoracic anastomosis compared to no thoracotomy with cervical anastomosis[36]. In octogenarians, a very few studies show that in carefully selected patients, without any morbidity, oesophageal surgery with thoracotomy is possible with post-operative mortality identical to that of "younger" patients. These results cannot be extrapolated to all octogenarians because the patients had been carefully selected, corresponding to less than 5% of patients, and had been operated on in highly experienced centres. The authors proposed performing trans-hiatal oesophagectomies to avoid the risks of a thoracotomy in older patients. Paulus *et al.*, in a tertiary referral centre, analysed the results of the trans-hiatal oesophagectomy retrospectively in 33 octogenarians. Compared to younger patients, the post-operative mortality and morbidity rate was significantly different. In octogenarians. 3- and 5-year survival was 56% and 37% respectively. The authors concluded that with appropriate selection, good results can be observed after a trans-hiatal oesophagectomy in octogenarians[37]. A recent study on the same number of octogenarians operated on using the trans-hiatal route confirmed these results[38].

The surgery called hybrid minimally-invasive with laparoscopic gastrolysis and thoracotomy is recommended because it is responsible for fewer respiratory complications and offers oncological outcomes comparable to open surgery[39]. Minimising respiratory complications is essential in older patients.

- *Optimal or suboptimal cancer surgery*

Extending resections

For stomach cancers, a total gastrectomy is only justified, irrespective of age, for cancers of the upper third or linites. In older patients, total gastrectomies should be avoided due to the higher post-operative risk and especially the nutritional risk. Teng *et al.* analysed outcomes for 487 octogenarians, only a quarter of whom had had a total gastrectomy, and 10% an adapted

lumpectomy. In a multivariate analysis, being aged 80 or over was associated with significantly higher post-operative mortality and morbidity. The authors therefore recommended restricting indications for total gastrectomy in octogenarians[40]. A detailed review with meta-analysis of publications concerning gastrectomy in octogenarians confirmed these data. The number of octogenarians dying in hospital was three times higher than that of younger patients. Although the incidence of surgical complications was broadly similar between the two groups, that of essentially cardio-respiratory medical complications was higher. Overall survival was significantly lower in octogenarians[41].

The Japanese authors, to reduce the risks of total gastrectomy in older patients, proposed performing an upper polar gastrectomy for proximal cancers, with equally good cancer outcomes as for total gastrectomy[42]. Broader indications should still apply when the cancer is distal, pre-orificial, or responsible for stenosis.

For cancers of the rectum, surgical resections in older patients raise the specific issue of functional digestive disorders, especially relating to continence. The requirements of cancer treatment justify excision of the mesorectum 5 cm below the tumour. Although colo-anal anastomoses, even total or partial inter-sphincteric if necessary, can avoid abdominal perineal amputation and permanent colostomy, this type of anastomosis poses a problem in octogenarians. Recent recommendations in France's national digestive cancer thesaurus stipulate that in cases of sphincter incompetence with pre-operative anal continence issues that do not appear to be related to the size of the tumour, especially in older patients, colo-anal anastomosis is not recommended. Hartmann's procedure, in accordance with cancer treatment rules, can be an alternative to abdominal perineal amputation. Sphincter function must be assessed before any rectal surgery. Even though it is preferable to retain sphincter function to avoid any difficulties with clothing for a colostomy in patients with difficulties with movement or vision, post-surgery incontinence in octogenarians can be tolerated less well than a well-fitted stoma, especially if the patient is in an institution. This could avoid the need to wear permanent protection. Colo-anal anastomoses can therefore only be reserved for patients with good sphincter tonicity and normal pre-operative continence.

Extended lumpectomy

For stomach cancers, D2 lumpectomy is, after a 15-year follow-up, associated with a better cancer survival rate and a lower risk of locoregional recurrence[43]. This follow-up is not justified in octogenarians, especially because D2 lumpectomy carries a significantly increased risk of post-operative mortality and morbidity. The same authors had published the results of their study after a five-year follow-up, without showing any significant difference in survival. Seo *et al*. confirmed that in octogenarians, D2 lumpectomy was not justified because it did not improve survival[44]. The current recommendations are for a D2 lumpectomy without splenectomy, and a D1 lumpectomy for patients with a high surgical risk. For octogenarians, a D1 lumpectomy is sufficient without undertreating the patient from the oncological point of view.

For colorectal cancers, lumpectomies should be the same as for younger patients without any specific morbidity. However, it must always be borne in mind that older patients are poly-atheromatous and that vascular ligatures at the origin of the vessels for an adequate lumpectomy can be harmful. Hence for right-sided colon cancers, the superior right colic artery must not be cut until you have checked that the left colon has been vascularised correctly by the inferior mesenteric artery. A thrombosis, or history of aortic surgery, can mean that this does not exist in older patients. For cancers of the rectum, it is advisable to perform an inferior mesenteric lumpectomy by tying the inferior mesenteric artery 1 cm from the aorta to spare the nerves in the pelvic region that run alongside the aorta. However, from the oncological point of view, the level of proof of a ligature of the mesenteric artery almost at its origin is low. This procedure is also used for better mobility of the brought-down colon, allowing a tension-free low anastomosis. Making a cut just down from the superior left colic artery allows better vascularisation of the brought-down proximal segment. A recent meta-analysis of 8 randomised trials (n = 1 102) comparing superior and inferior ligature showed no significant difference for either the number of ganglions sampled or recurrence-free overall survival after five years[45].

Post-operative specificities

When an older person goes into hospital, this often represents disruption in their existence. One of the concerns of practitioners will be to reduce the risk of post-operative complications as much as possible and facilitate the patient recovering their independence, in order to allow them to return to their usual environment, with the minimum loss of function. It is therefore essential to know about their usual living conditions and their friends and family in order to achieve this objective

• *Rehabilitation*

As specified, this starts in the pre-operative phase and must be continued post-operatively. Bagnall *et al.* have published an exhaustive review of the literature on early rehabilitation after colorectal surgery in older patients. Both randomised prospective trials in this review suggest a reduction in post-operative morbidity, as well as a reduction in time spent in hospital ($p < 0.000$). None of the studies, including the non-randomised cohort studies, found any harmful effect, thus showing the safety of this protocol in older patients[46]. This rehabilitation includes:

- lack of a stomach tube (to be removed at the end of the intervention unless there are exceptional circumstances) or catheter
- early enteral feeding if possible 6 hours post-operatively without waiting for a bowel movement. Solid food is permitted, its texture must be adapted to the chewing and swallowing abilities of older patients. A nutritional substitute may be necessary if the daily oral food intake is below 60% of nutritional needs
- respiratory physiotherapy and early mobilisation. The patient is cared for by the whole team to get them mobile from the first day after the operation, so they can quickly regain their independence or get back to their pre-operative abilities
- rapid removal of drains and venous lines while avoiding them becoming too full. The bladder drain is not recommended or should be removed as soon as possible. It is however advisable to check for the absence of a distended bladder by doing an ultrasound at the patient's bedside
- opioid-sparing multimodal analgesia (locoregional anaesthesia and infiltration). The use of non-steroidal

anti-inflammatory drugs (NSAIDs) must take any comorbidities into account, especially renal function
- the oxygen supply should be adapted to the respiratory function. Good oxygenation reduces the risks of post-operative confusion. Saturation must be monitored for the first 48 hours
- glucose monitoring should be stepped up in order to detect hyperglycaemia before clinical signs appear.

In addition to rehabilitation, it is vital to, from before the operation or immediately post-operatively, anticipate the future on leaving the surgical department, "supervised" return home, appropriate follow-up care and rehabilitation.

• *Oncological monitoring after curative surgery*

No age limit is specified for oncological monitoring, but the recommendations emphasise that only patients able to withstand a reoperation and/or chemotherapy justify follow-up to screen for local or metastatic recurrence. This may involve screening for metastases in colorectal cancers. No study showed any impact on survival from a monitoring protocol for cancers of the oesophagus, stomach, or pancreas in older patients.

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■ Interventional imaging in the older person: example of colorectal cancer

Maxence Fermond, Badr Boutakioute, Rim Ouajdi, Tristan Cudennec, Mostafa El Hajjam

Introduction

An ageing population brings about an increase in health needs, given that over-75-year-olds represent around 10% of the French population[1]. In France, with 43,336 new cases and 17,117 deaths in 2018, colorectal cancer constitutes a public health problem. It is one of the most common cancers (ranked 3rd in men and 2nd in women) and represents the 2nd highest cause of death from cancer (2nd cause in men and 3rd in women). This cancer is rare in the under-50s and 8 deaths in 10 happen in the over-65s[2]. Older patients may not be eligible for a general anaesthetic and surgical treatment due to peri-operative complications that increase morbidity and mortality[3]. In addition, the disease has often progressed to an advanced stage by the time of diagnosis, which routinely limits the options for surgical treatment. Interventional radiology is currently a therapeutic tool that offers patients suffering from cancer a third option for localised treatment, as well as surgery and radiotherapy. The number of therapeutic interventions, such as percutaneous ablations and endovascular techniques, is also constantly rising. For this reason, since 2016 the guidelines of the European Society of Medical Oncology have included interventional radiology in the treatment algorithm[4].

- *Aims*

The aim of this update is to shed light on the various interventional procedures being carried out in older patients with colorectal cancer. These procedures can be divided into two groups: the first is diagnostic with the advantage of a biopsy of secondary lesions, especially in the liver; the second is therapeutic with drains, different types of embolisation (chemoembolisation, radioembolisation, haemostatic embolisation) and local or locoregional destruction of secondary lesions by physical processes, such as radiofrequency or cryotherapy.

• *Interventional imaging procedures*

Interventional radiology can treat certain diseases which previously could only be dealt with through surgery. It expands the diagnostic and therapeutic possibilities in oncogeriatrics, especially in colorectal cancer. However, there are very few studies on the applications and indications for interventional imaging in older people.

The Ambroise-Paré hospital is one of the centres where the age of hospitalised patients is among the highest in France. In 2017, people aged 75 and over represented 36% of adult hospitalisations. Half of interventions carried out in the interventional imaging unit are on patients aged over 70 and this growth has continued over the years.

Procedures are performed through the skin or through a natural orifice, usually under local anaesthetic or neuroleptic analgesia. It is rare to need to resort to a general anaesthetic with intubation. With guidance from the various imaging methods using ultrasound and X-rays, the radiologist can perform punctures, biopsies, insert equipment (bifurcated stents, glue, prosthesis, drain, etc.), or inject specific treatments into a particular tumour site.

• *A biopsy* using ultrasound or CT guidance is the most commonly performed procedure on the liver or lungs. When liver metastases are present, they are often easier to access than the primary colorectal tumour. A normal haemostatic balance is an essential prerequisite because the risk of haemorrhage increases with age (Figure 1). In one study, including 9,212 liver biopsies[5], mortality due to a haemorrhage was 0.11%, essentially in cases of tumour pathology (0.4% in cases of tumour pathology as opposed to 0.04% where there was no tumour).

The factors aggravating the risk of a haemorrhage were:
- old age
- the number of samples (> 3), a practice which has become essential because the multiplication of samples is useful for any type of analysis (standard histology, immunohistochemistry, molecular biology, cryopreservation, etc.)
- presence of cirrhosis, a cardiac or vascular liver.

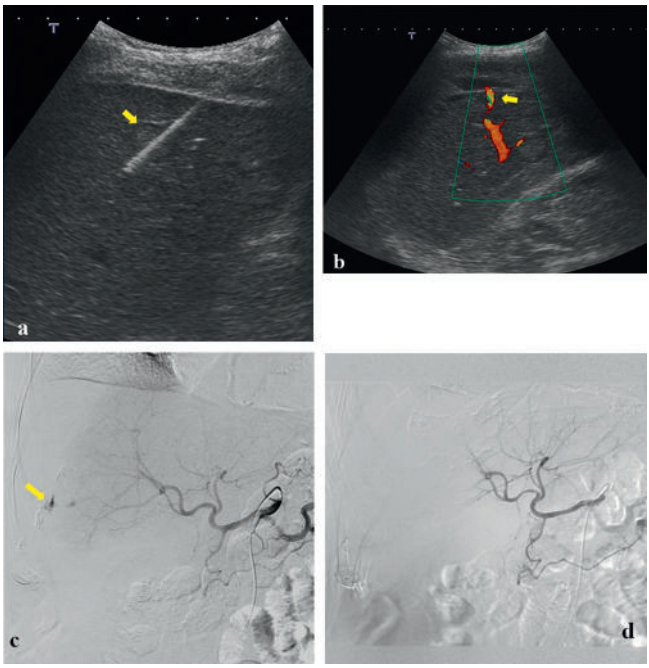

Figure 1: *91-year-old man with liver metastases. Normal haemostatic balance. Indication with an ultrasound biopsy. a: Biopsy needle in place in the liver nodule (arrow). b: Doppler ultrasound scan 5 minutes after end of the biopsy with intense pain, showing an active haemorrhage on the biopsy path, feeding into a peri-hepatic haemoperitoneum (arrow). The patient was taken to the angiography room for emergency embolisation to control the bleeding. c: Hepatic arteriogram showing a rupture in a subcapsular arteriole feeding into the haemoperitoneum (arrow). d: Angiographic check after embolisation showing the bleeding has stopped.*

In our experience, the rate of serious bleeding complications is extremely rare. One death has been recorded in 23 years of daily liver biopsies. Slight peri-hepatic bleeding occurs in 5% of cases and leads us to propose routine preventive embolisation of the puncture route after any liver biopsy in patients aged over 70. This is done using organic gelatin fragments to guard against the risk of a haemorrhage (Figure 2).

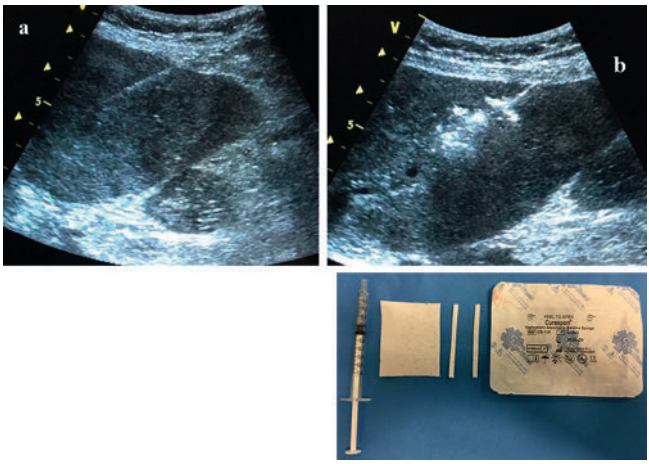

Figure 2: *Embolisation of the biopsy path. a: Ultrasound biopsy of a liver nodule. b, c: Embolisation at the end of a biopsy using gelatin fragments to obliterate the path and guard against the risk of a haemorrhage.*

• ***Drains***, guided by ultrasound or the scanner, for abscesses, excess bile or bleeding, are used routinely, especially post-operatively, thus reducing morbidity and mortality from corrective surgery (Figure 3). As an example, the amount of post-operative anastomotic fistulas secondary to surgery for cancer of the rectum is 2 to 3% after the age of 75, a little lower than in younger patients (5%), but the death rate is higher (3 to 4%), versus 0 to 1% in younger patients. This justifies the place of transgluteal drainage of pelvic abscesses using a scanner to prevent corrective surgery and removal of the anastomosis.

• ***Chemoembolisation*** is a technique consisting of catheterising the hepatic artery itself and injecting an emulsion into it or particles containing a cytotoxic agent (Figure 4). This allows dual action consisting of a tumour ischaemia associated with a high intra-tumoral concentration of the anti-tumour agent, thus reducing the systemic consequences[6].

There are numerous contra-indications, especially dilated bile ducts, portal vein thrombosis, biliary-enteric anastomosis, advanced cirrhosis, profound alteration of general health with malnutrition and significant spreading of the tumour outside the liver.

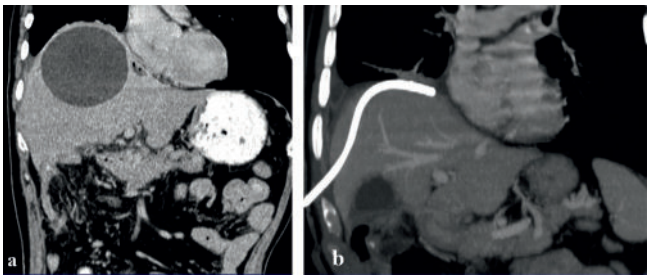

Figure 3: *76-year-old man with sepsis and pain due to a subphrenic abscess complicating a right colectomy. Indication with a percutaneous ultrasound drain. a: Frontal CT image showing a large suprahepatic abscess. b: Control scanner showing the drain in place and complete evacuation of the abscess.*

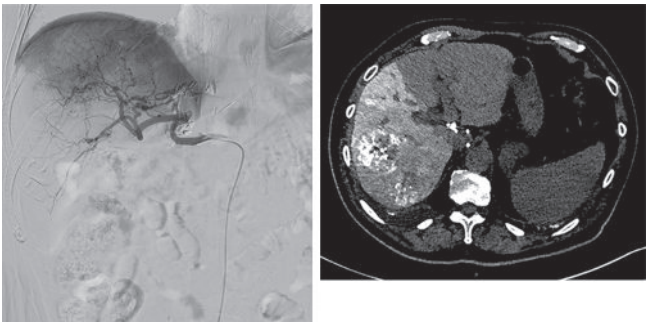

Figure 4: *75-year-old patient with colorectal cancer with multiple metastases in the liver. Hepatic arteriogram before chemoembolisation of the right branches. Non-injected CT scan performed the next day showing fixation of the treatment on the whole right liver, especially in the secondary lesions.*

• ***Radioembolisation*** consists of hepatic intra-arterial injection of microspheres containing Yttrium 90. Once injected, these particles will follow the tumour haemodiversion of arterial blood flow and end up in the tumour neo-vascularisation. β-radiation of the Yttrium 90 in the microspheres is therefore delivered directly to the centre of the tumour and is able to destroy it while preserving the healthy tissue. This technique requires a hepatic arteriogram to be performed first to assess the state of the hepatic and tumour vascularisation. Scintigraphy by intra-hepatic injection of Technetium-99 labelled albumin is performed to assess the hepatopulmonary shunts in order to modulate the radiation dose and an

MRI or a scan to calculate the doses to be delivered by assessing the healthy liver and the diseased liver.

• ***Portal vein embolisation*** consists of occluding part of the portal vein network in order to produce hypertrophy in any non-embolised hepatic segments (Figure 5). It is used pre-operatively before extended hepatic resection surgery when the future remaining liver is deemed to be insufficiently large, exposing the patient to a post-operative risk of liver failure, the main cause of death after major hepatectomy[7]. This method consists of liver tissue sampling of a portal tract and embolisation using an emulsion of cyanoacrylate glue and Lipiodol®, particles, bifurcated stents, plugs or a combination of these different processes.

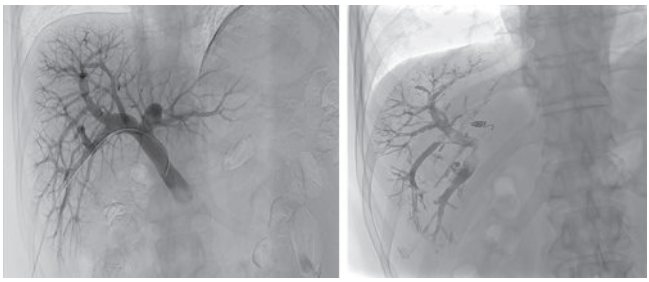

Figure 5: *Patient with multiple secondary hepatic lesions suitable for right hemi-hepatectomy with prior portal vein embolisation. Arteriogram before and after embolisation.*

• ***Thermal ablation*** is an increasingly common technique which destroys tumours and improves survival rates[8]. There are three types of thermal ablation: radiofrequency (RFA), cryotherapy and microwave. At present, radiofrequency is by far the most commonly used technique for percutaneous or peri-operative thermal coagulation of malign tumours in a solid organ with a very high success rate and manageable complications. Schullian *et al.*[9] reported on a set of 36 patients aged 80 to 90 who had been treated with radiofrequency for primary or secondary hepatic tumours. Comparison with a control group consisting of 36 younger patients showed no significant difference in terms of technical efficacy, local recurrence, major complications, overall survival and recurrence-free survival.

In our service, in 2016, out of 38 patients who benefited from liver RFA, 14 patients (37%) were aged over 70 and there were no complications in these patients.

The indications for thermal ablation at this age are:
- patients with between one and three liver metastases that can be accessed by percutaneous treatment, who are not eligible for complex surgery or who would not tolerate conventional chemotherapy
- achieving hepatic clearance, which therefore allows less aggressive chemotherapy (Figure 6).

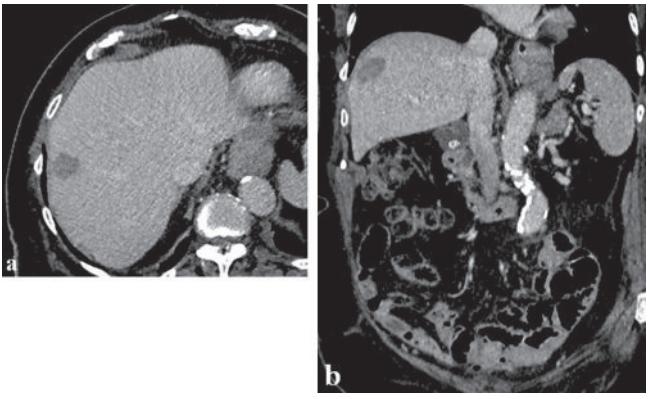

Figure 6: *93-year-old female patient with metachronous liver metastases from colon cancer. The scan (a, b) shows a lesion 2.5 cm in diameter in segment VIII which will be treated by ultrasound-guided percutaneous radiofrequency due to the impossibility of starting conventional chemotherapy as this was deemed to be too demanding for the patient. Achieving hepatic clearance on the control imaging can defer any further treatment.*

Problems encountered in interventional imaging

The indications for interventional radiology are yet to be defined, as this is technically more difficult in older people than in younger patients A state of agitation and potential confusion in patients complicates carrying out procedures, especially in an emergency. Positioning patients on X-ray examination tables (less comfortable than a bed) increases the likelihood of pain. The risk of bacteraemic discharge or even septicaemia, created for example by draining a collection of pus is not inconsiderable and may lead to the patient's death. Patients' understanding of instructions to lie still and apnoea

instructions is impaired due to hearing loss and the potential existence of neurocognitive disorders. All this affects acquisition of images and makes them more difficult to analyse.

We don't have enough hindsight concerning new oncological treatment methods such as targeted therapies and immunotherapy. But all the evidence suggests that interventional radiology will increasingly be the treatment of choice for iterative biopsies in order to find the various mutations that occur during the course of treatment for embolisations and vascular plasties, in order to improve the conditions in which treatments are administered. Radiology will increasingly be used for injections of particles charged with new therapeutic molecules, directly into tumours through the skin or by the endovascular route in order to concentrate their antitumour action and reduce systemic complications.

It must be remembered that older people are more frail and that these interventions should not be carried out routinely. They should not be considered harmless, as this risks them being viewed negatively - if the outcome is poor - by patients, their friends and family and attending physicians.

The need for anaesthetic care and a quasi-surgical environment may prove necessary, which is far from the norm in all centres. Learned societies (Société Française de Radiologie and Société Française de Gériatrie et Gérontologie) have adapted the good practice guide for diagnostic radiology to treating older people. Procedures specific to geriatric interventional radiology are increasingly common thanks to collaborative working between oncologists, geriatricians, radiologists and anaesthetists.

In practice, the physiological age should be the basis for deciding whether or not to treat patients with interventional imaging where the geriatrician and interventional radiologist play a leading role (diagram 1).

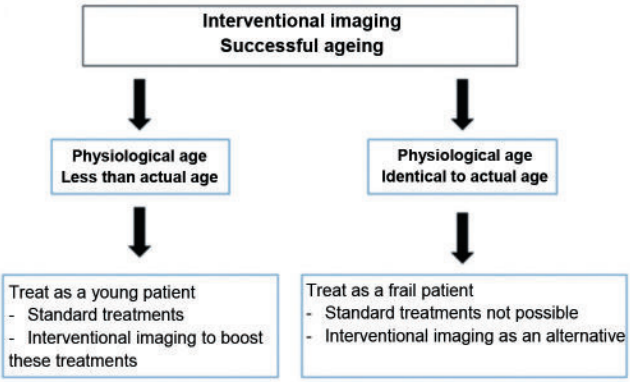

Diagram 1: *Treatment of older patients with interventional imaging.*

Conclusion

Colorectal cancer is a public health problem in the face of which interventional imaging has a rightful place at all treatment stages, especially for older patients. It can be included in the care pathway in perfect synergy with other diagnostic and therapeutic methods and contributes to better disease prognosis. The bonus of its minimally invasive nature should not overshadow the need for an anaesthetic environment and vigilance to prevent over or under-treatment.

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PERI-OPERATIVE CARE

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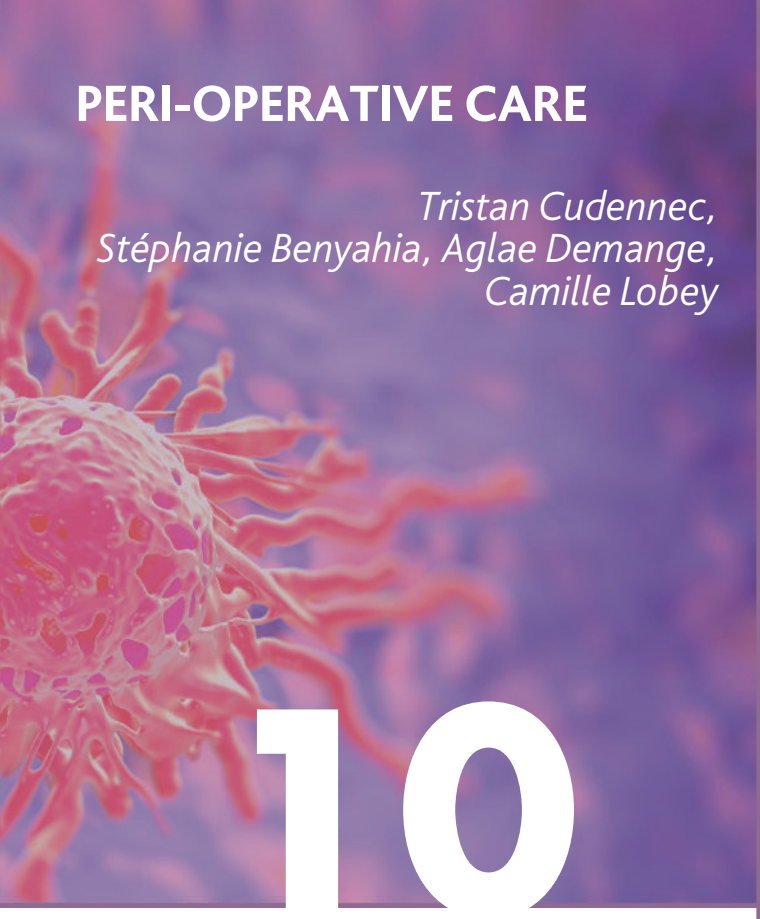

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Peri-operative care of older patients with cancer can be broken down into 3 stages: the pre-operative phase during which risk factors for complications during hospitalisation should be looked for and the patient's health should be optimised via prehabilitation; the operative phase which will be discussed in the relevant chapter; and the post-operative phase during which early rehabilitation should be encouraged and plans made for further treatment.

The pre-operative phase

The best way to improve the quality of oncology care for older patients is to bring together the different specialties: surgery, anaesthesia and geriatrics. The geriatric assessment should be part of the decision-making process in geriatric oncology, including in a surgical context, in order to identify those patients most at risk of post-operative complications and assess the best possible benefit/risk balance of treatment. Anticipation of preventive care is essential in order to reduce post-operative morbidity and mortality in frail older patients. Everyone should be familiar with the risk factors for onset of delirium, the main complication observed in the post-operative period. Other parameters in the geriatric

assessment, such as for example the patient's nutritional status, their functional independence, or even the existence of thymus disorders or cognitive impairment must be documented if we wish to limit morbidity and mortality made more likely by this care[1].

• *Geriatric assessment*

The geriatric assessment should look for signs of frailty[2], whether medical, psychological or social. The standardised geriatric assessment can reduce mortality within 1 year and the number of unscheduled readmissions to hospital. It also has a favourable impact on the mood, nutritional status and independence of patients who benefit from it. In an oncological context, it was demonstrated that the geriatric assessment helped increase survival rates in patients who had benefited from it, regardless of the nature of subsequent care, such as a specific cancer treatment or palliative care[3].

The purpose of this assessment is to maintain independence and the best possible quality of life. Familiarity with functional independence and comorbidities represents the main challenge for assessment in a cancer context. Independence for everyday activities will be estimated best by Katz's *Activities of Daily Living* (ADL) and Lawton's *Instrumental Activities of Daily Living* (IADL)[4,5]. Familiarity with this independence is not sufficient to optimise the choice of therapeutic treatment.

• *Comorbidities*

Several scales can be used to assess these. The Charlson score has the advantage of being easy to use[6]. It has already been used to estimate the risk of occurrence of post-operative complications, the length of hospital stay or even the risk of entering an institution. The score obtained using this scale can be used to estimate the risk of mortality within 1 year and that of death linked to comorbidities (Appendix 1).

The American Society of Anesthesiology (ASA) score is not strictly speaking a comorbidity assessment score[7]. It is conducted by anaesthetists prior to any operation to estimate the risk of peri-operative mortality. A French study looked at the mortality rate directly or partly attributable to an anaesthetic procedure. This risk is 5.20/100,000 anaesthetic procedures when the person

Appendix 1: *Risk of mortality within 1 year and risk of death linked to comorbidities using the Charlson scale*

Charlson score	Mortality within 1 year (%)
0	12
1-2	26
3-4	52
≥ 5	85
	Death linked to comorbidities (%)
0	8
1-2	25
3-4	48
≥ 5	59

is aged 40 to 74. It increases fourfold (risk of 21.0) if the patient is aged 75 or older. Moreover, this study also showed that when the ASA score was 2, the risk of mortality per 100,000 anaesthetic procedures was 5, as opposed to 27 and 55 when the ASA score was 3 or 4[8].

An American single-centre prospective study set itself two objectives: assessing the correlation between the ASA classification and the geriatric assessment data; determining any association between these two determinants and 6-month survival[9]. Between January 2015 and April 2018, 980 people aged over 75 who had benefited from a CGA and surgical treatment for cancer were included. They had benefited post-operatively from co-management by a surgeon and geriatrician. 81 patients (8.3%) included in the study cohort died within 6 months following surgery. In 85.4% of cases, they had an ASA score of 3. The average number of deteriorated geriatric assessment parameters (13 parameters in total) in patients was 4 for ASA scores of 2, 5 for ASA scores of 3 and 7 for ASA scores of 4. The results show that the ASA score is not effective in identifying patients who have falls, are losing weight and those with neurocognitive disorders. Moreover, in terms of mortality within 6 months, the associated factors in a multivariate analysis are geriatric syndromes (OR 1.14 for every deteriorated area), admission to ICU within 30 days, average length of stay and albumin level prior to operation. The

ASA score was not associated with mortality within 6 months.

The International Society of Geriatric Oncology (SIOG) Surgical Task Force looked into surgeons' attitudes to assessment and care of older patients with cancer[8]. The results of this survey, to which 251 surgeons responded, showed that there was no age limit on proposing elective surgery for cancer in 80.9% of cases. For 4.4% and 13.1% of them respectively, the ages of 80 and over or 90 and over were the criteria associated with a decision not to operate. In just 48% of cases, surgeons deemed it essential to be able to assess the patient's frailty during the pre-operative period. The tools used most regularly were, in descending order the ASA score (76%), the *Performance Status* (50%), nutritional status (42%) or POSSUM score (*Physiological and Operative Severity Score for the enumeration of mortality and Morbidity*)[10] (14%).

The burden of geriatric events in older adults who have benefited from major surgery to treat cancer was studied. A retrospective study conducted over the period 2009-2011 in more than 900,000 older patients aged over 65 provided some brief replies[11]. The most frequently observed complications were onset of delirium, dehydration, falls, fractures or bed sores. At least one of these complications was observed in 9.2% of cases. They occurred more frequently after the age of 75, when the Charlson score was 2 or higher and for certain tumour locations (bladder, ovary, colon-rectum, pancreas and stomach). When a patient had a complication, their risk of presenting with others was multiplied by 3.73.

It is rarely possible to conduct a geriatric assessment in an emergency context. It is nonetheless desirable that the surgeon and anaesthetist treating the patient should be aware of certain frailty markers and able to identify the risk factors for onset of delirium, which often complicates the peri-operative period.

- *Delirium*

This syndrome is associated with:
- altered consciousness with reduced capacity to focus, sustain or shift attention
- cognitive deterioration unprovoked by pre-existing established dementia or progressive dementia

- and evolution over a short period of time with quick appearance of symptoms and fluctuation of these during the day.

Its incidence, how it evolves (nearly 20% of confusional states persist for more than 6 months after first becoming apparent), and its potential seriousness (excess deaths, extension of the SMD, unscheduled early readmissions to hospital, early admission to an institution), are all good reasons for taking a particular interest in this issue[12,13]. Its prevalence on admission is 10 to 20% in older patients admitted to hospital. It can be as high as 65% during the post-operative period[14].

Delirium was defined as a predictive factor of mortality in the 12 months following hospitalisation[15]. There has been shown to be a correlation between advancing age and incidence of delirium post-operatively in instances of major surgery [6].

Some predictive factors for onset of this syndrome are well known[17,18]:

- on patient admission to hospital:
  - impaired visual acuity (RR 3.5)
  - severe illness (myocardial infarction, septicaemia, acute respiratory insufficiency, diabetic ketoacidosis, etc.) (RR 3.5)
  - previous impairment of higher functions (RR 2.8)
  - dehydration (RR 2.0)
  - deteriorated functional state (RR 1.7)
- during hospitalisation:
  - use of restraint
  - existence of malnutrition (albuminemia < 30 g/l)
  - addition of more than 3 new drugs in less than 24 hours
  - insertion of a urinary catheter
- other recognised factors in surgical oncology:
  - pain and how it is managed post-operatively (injectable opioids more harmful than those administered orally)[19]
  - ADL and IADL pre-operative scores[20,21]
  - polypharmacy[22]
  - ASA score[23].

In 2016, a Korean team proposed a prediction score that could be used to identify people at serious risk of developing delirium in a surgical context[24]. This score, called the DELPHI score, contains 9 items that are simple

to enter: the patient's age, their functional independence, consumption of alcohol, existence of hearing loss, a history of delirium, emergency surgery, open surgery, admission required to intensive care and the CRP rate. These items can be used to obtain a score of up to 15 points. When the score obtained is 7/15 or more, the risk for the patient of being confused is 81%. The sensitivity and specificity of this score are 80.8% and 92.5% respectively.

• *Nutrition*

Malnutrition is a frequent complication as cancers evolve, linked to an imbalance between needs that may have increased and inputs which have often reduced[25]. Malnutrition represents a separate mortality risk factor during specific cancer treatment[26]. Another study, which included 317 patients with an unknown primary carcinoma, showed that the two main risk factors for death were the existence of hypoalbuminemia (RR 2.7) and metastases in the liver (RR 2.27). A number of teams interested in treating cancers in older patients included nutritional status in the vulnerability criteria which need to be taken into account before envisaging any decision on specific oncological treatment[27,28]. Whatever tool is used to detect malnutrition, it is clear that identifying it should be an integral part of the initial review when cancer is discovered in a patient, all the more so when they are aged over 75. The aims when treating it are to correct a nutritional status which is often impaired before starting cancer treatment and to combat any potential undesirable effects of these specific treatments. Recourse to enteral feeding should be envisaged. In addition, in older patients, it is always useful to eliminate unnecessary diets (no sugar, no salt, no fat, etc.), and to sift through any medication they are taking (analgesic, psychotropic, anorectic drugs, etc.). Finally, when renutrition is started, it is necessary to assess its efficacy so it can be adapted.

• *Surgical risk calculator*

In all situations, the risk-benefits balance when performing a surgical procedure must be discussed:
- expected benefits
- risk of excess deaths
- risk of post-operative complications.

A tool proposed by the American College of Surgeons is available online, called the *Surgical Risk Calculator* (*www.riskcalculator.facs.org*). It is designed to provide practitioners with information about the specific risks to each patient for a given surgical procedure. It thus allows the patient to give informed consent. This database was built up from 5 million surgical procedures carried out between 2016-2020 in the 874 hospitals participating in the ACS NSQIP. Once certain information concerning the surgical procedure and patient-specific data (age, sex, functional status, emergency situation, ASA score, taking corticosteroids, diabetes, high blood pressure, respiratory insufficiency, weight and size) has been entered, the calculator suggests an estimate of the following risks:
- serious complication
- complications
- pneumonia
- cardiac complication
- operating site infection
- urinary tract infection
- deep vein thrombosis
- renal insufficiency
- death
- foreseeable use of aftercare and rehabilitation
- average time in surgery.

Information is given for the patient and compared with the average data for the population entered in the database. In addition, since not all the patient comorbidities could be entered initially, it is possible for the practitioner to increase the risk.

More recently, when the patient is aged over 65, it has been made possible to enter 6 additional items:
- the need for the patient to have help moving around
- the place where the patient lives
- a history of falls
- existence of neurocognitive problems
- a palliative clinical situation
- the patient's capacity to give their consent.

Thus, with the help of the risk calculator, data is available on 4 other risks:
- onset of post-operative delirium
- risk of functional decline
- risk of loss of mobility
- risk of developing bed sores.

The question of how relevant these predictions are for the French population is a valid one (different patient profiles, especially in terms of comorbidities). The surgical team at the Ambroise Paré hospital in Boulogne-Billancourt tried to find out whether it was possible to predict the post-operative morbidity and mortality after emergency surgery for obstruction due to colon cancer using this digital risk calculator. The results confirm its reliability in this context for predicting overall morbidity, severe morbidity and mortality (*M. Collard, 12e Congrès Francophone de Chirurgie Digestive et Hépato-bilio-pancréatique, December 2016*).

Post-operative period

Peri-operative care of older patients with cancer includes specific actions which will be described in the relevant chapter. However, it is worth stressing that low blood pressure should be managed during the procedure, early analgesia put in place, transfusions used and even possibly that oxygenation, temperature and glycaemia should be monitored. The choice of anaesthetic and its duration should also be taken into consideration.

During the post-operative phase, several aspects should be taken into consideration, such as:
- management of cognitive impairment
- the need for early rehabilitation
- pain relief
- or even any care the patient is receiving from geriatrics.

A study showed that the pre-operative cancer assessment of an older patient was a predictive factor of morbidity and mortality within 30 days. It can also predict the length of hospital stay. Using the PACE tool, impaired functional independence, state of fatigue and the score obtained in the *Performance Status* were predictive factors of post-operative complications[29].

A study showed that the two factors correlated with higher post-operative mortality are being aged over 85 (RR 2.65) and having emergency surgery (RR 3.42)[30].

- *Cognitive impairment*

As stated for the pre-operative period, the search for the existence of cognitive disorders or factors that might

make the onset of delirium more likely should be looked for during this period. A French prospective study (118 patients with an average age of 81 who had benefited from non-emergency major digestive surgery) showed that 24% of patients had delirium. For 43% of patients, the ASA score was 3 or 4. In a multivariate analysis, 3 factors were correlated with observation of post-operative delirium: existence of a risk of falling as identified by the *Timed Get up and go test* (p = 0.009) (OR 4.8; CI 95%: 1.5-15.6), an ASA score of 3 or 4 ($p = 0.02$) (OR 3.3; CI 95%: 1.2-9.0) and use of tramadol derivatives during the post-operative period ($p = 0.0009$) (RR 7.1; CI 95%: 2.2-22.5). The mortality rate was 14% in those with confusion as opposed to 3.3% in patients without confusion ($p = 0.051$). In addition, the average length of stay was 19 ± 11 days in patients who had presented with delirium as opposed to 14 ± 8 in other patients ($p = 0.01$). Finally, the onset of this complication was not associated with the onset of a complication linked to the surgical procedure[31]. These results underline the importance of the geriatric assessment and the need to have simple tools that can be used to identify the largest number of at-risk patients. Preventive actions can be taken.

Management of delirium is based on:

- searching for and managing the causal factor(s) (repeated clinical examination, exhaustive initial biological assessment)
- the causes to be searched for as a priority due to their frequency in older patients:
  - distended bladder, faecal impaction
  - sepsis
  - metabolic disorder
  - withdrawal (long course of benzodiazepines) or poor drug tolerance (in particular, be wary of nefopam, tramadol and hydroxyzine)[32]
  - myocardial or cerebral damage
  - pulmonary embolism
- always cite the iatrogenic condition (sedatives, psychotropic drugs, drugs with high anticholinergic activity)
- non-pharmacological interventions:
  - reframing in time and space
  - calm and reassuring attitude
  - encouraging wearing of devices to correct sensory deficits (hearing aids, prescription lenses)

  - as far as possible, not resorting to physical restraint which reinforces the symptoms
  - getting the patient back on their feet and functionally independent as soon as possible, ideally with the help of physical therapy
- medicinal interventions:
  - may at times become necessary if certain symptoms occur (anxiety, agitation)
  - use of a benzodiazepine with short half-life and rapid elimination, such as oxazepam or alprazolam
  - use of neuroleptics which are sometimes used in cases of acute confusion associated with productive mental disorders (hallucinations, delirium), however the literature shows little evidence of efficacy in this indication and these molecules are associated with the onset of numerous undesirable effects
  - depending on the HAS recommendations, giving the patient the benefit of a geriatric opinion as quickly as possible[33].

- *Improved prehabilitation and rehabilitation after surgery*

Prehabilitation is based on a pre-operative routine to enhance general health and wellbeing[34]. It combines nutritional care (high-protein diet), physical activity (muscle strengthening) and psychological support. It is particularly justified in geriatric oncology because of post-operative complications, whether specific to the procedure or in association with geriatric comorbidities (falls, malnutrition, dehydration, confusion, bed sores, fractures, etc.). Prehabilitation essentially means customising the individual care pathway to deal with specific problems (comorbidities, competing causes of death, malnutrition, psycho-cognitive disorders, sarcopenia, etc.), a request for therapy, and need to stick to the care plan. Its aim is to avoid functional decompensation due to the stress of surgery!

Rehabilitation is based on motivating a multi-professional healthcare team (surgeon, anaesthetist, nurses, auxiliary nurses, physical therapist) to improve the quality and speed of post-operative recovery. This collaboration begins with the patient being admitted, and its aim is to reduce post-operative morbidity and length of hospital stay[35,36]. It includes the choice of surgical technique, types of anaesthetic and intra-operative monitoring, peri-operative pain management, as well as

reintroduction of oral food intake and getting patients back on their feet as soon as possible.

The aim of Enhanced Recovery After Surgery (ERAS) is to reduce the extent of physical and nutritional deconditioning after surgery. It is based on reducing the extent and duration of peri-operative stress by limiting the fasting period, installing the patient in a chair quickly, while minimising invasive treatment (drains, catheters, etc.) and improving pain management.

- *Care pathway*

Oncogeriatric collaboration also allows the patient concerned to be in the right care structure at the right time. It is important to anticipate in advance where the patient's place should be in the care pathway and in the geriatric sector. In this way, patients identified as the most frail and the most at risk of post-operative complications will derive a clear benefit when it comes to the peri-operative geriatric assessment and could benefit subsequently from customised care (resuscitation, geriatric aftercare and rehabilitation, home care, hospitalisation at home).

Conclusion

Good practice for managing cancer surgery of an older patient involves:

- conducting an appropriate geriatric assessment
- improving the decision-making process and the quality of care
- identifying frailty factors and patients most at risk of post-operative complications
- choice of operating technique and types of anaesthetic
- optimising prehabilitation and rehabilitation
- essential rapprochement between surgeon, anaesthetist and geriatrician.

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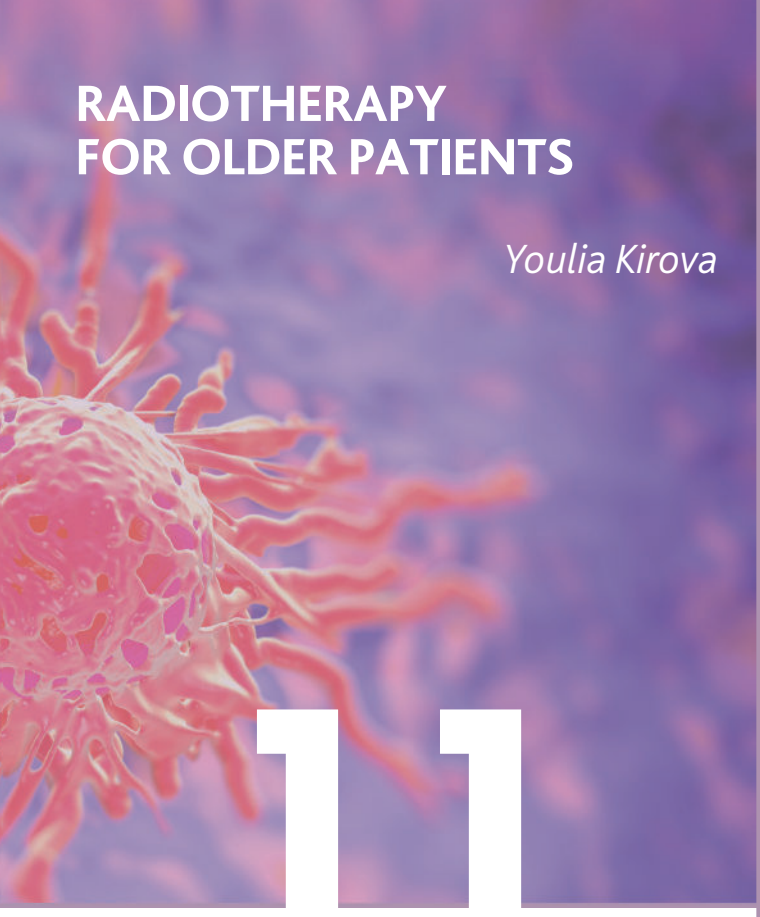
RADIOTHERAPY FOR OLDER PATIENTS

Youlia Kirova



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The history of radiotherapy began with the discovery of X-rays by the German physicist Röntgen in 1895. The first attempts to find medical applications in July 1896 in the field of radioscopy and radiography then opened up new opportunities in the diagnostics field.

The destructive properties of the rays were then exploited for therapeutic purposes, and radiotherapy was born. Its main application is dealing with cancerous tumours. Between 4 and 23 July 1896, Victor Despeignes used radiotherapy to treat cancer for the first time, validated by publications and indisputable practical evidence.

A. Béclère declared in 1904: "Röntgen's rays are like Achilles' spear, they hurt and they heal".

Work on radioactivity by Henri Becquerel and Pierre and Marie Curie then expanded knowledge and provided new therapeutic weapons. All three received their first Nobel Prize for Physics in 1903 for their work on radioactivity. Pierre and Marie Curie announced the discovery of two radioactive elements: radium (Ra) and polonium (in homage to Marie Curie's country of birth). Madame Curie received a second Nobel Prize for Chemistry in 1911 for her work on radium. Radioactivity is the

property which possesses certain elements that can transform spontaneously into another element through decay of the atomic nucleus with emission of alpha or beta particles or electromagnetic rays called X-rays and gamma rays[1].

From 1896, Henri Becquerel described the effects on his skin of a tube containing radioactive material, which had been left in a jacket pocket. He had just discovered a powerful but equally dangerous weapon: this was the birth of radiobiology.

In March 1887, Béclère set up nationwide teaching of therapeutic radiology and created, in 1897, the first radiology laboratory in Tenon where he had just been appointed the head of department.

Due to a lack of satisfactory facilities, he left Tenon to join the Saint-Antoine hospital in 1898 and created the first French radiology centre there; he worked as its head until he retired. There he combined clinical practice and laboratory research, especially in measuring new types of radiation, their intensity and their penetration in the body.

An individual is said to have been irradiated when they have been exposed to radioactive radiation. Irradiation can be internal or external depending on the location of the radioactive source.

Radioactive rays release energy when they travel through our body tissue. They cause cell ionisation, which damages their different components, especially DNA, genetic information support, by two action mechanisms:

- direct effect: interaction of the DNA molecule and an electron that start to move following absorption of a photon
- indirect effect: interaction of an electron with a water molecule. Production of a free radical which in turn causes a lesion in the DNA. Single or double-strand DNA breaks will cause some cells to die, others to mutate and others will survive because they have the ability to repair themselves.

The radiotherapy dose is given in grays = a unit named after the English physicist Stephen Gray (1670-1736) to measure the energy provided by ionising radiation and absorbed by matter, in a tumour or tissue. One gray

(Gy) corresponds to 1 joule of energy per 1 kg of irradiated matter. The gray replaced the rad (1 Gy = 100 rads).

The dose needed to control each type of tumour is calculated using the linear-quadratic model according to the equation: $S = e^{-(aD + bD^2)}$.

There is some variability depending on the biological system and the nature of the radiation which needs to be taken into account when calculating doses not to be exceeded on organs at risk (OARs).

Prescription of personalised radiotherapy for every patient depending on their type of cancer, age and comorbidities, involves choosing a number of parameters such as definition of volumes and total doses:
- target volumes/total dose
- structures at risk/dosage constraints.

• *Fractionation (number of sessions) and spread (duration of RT)*

- conventional fractionation/spread: 1.8-2 Gy/fraction and per day, 5 times per week (9-10 Gy/week)
- hyperfractionation: increase the protection of healthy tissue 1 Gy/fr, 2 fractions/d, 5 days per week. Requires increasing the total dose, similar spread to conventional treatment
- accelerated radiotherapy: for fast-growing tumours. By increasing the number of fractions/day, of a size similar to conventional fractions: shortens the spread considerably
- hypofractionation: often used in older people because you reduce the number of fractions per week, increase the dose per fraction and reduce the total dose to avoid difficulty in moving and ensure good tolerance with an optimal therapeutic effect.

• *Type of radiation and energy*

Several types of radiation: X-ray photons, electrons, protons. A choice is made depending on the tumoral lesion or the treated region using depth performance curves.

• The main types of RT are:

- external radiotherapy: (irradiation source placed outside the patient). Essentially X-rays and electrons are used, which are easy to produce, better radioprotection (linear particle accelerator)
- radionuclide therapy: sealed radioactive sources are placed in the tumour or a natural cavity (for example: gynaecological tumours, prostate cancer, etc.)
- metabolic radiotherapy: unsealed sources, often injectable (such as Iodine-131 treatment for thyroid cancer).

At present, along with surgery, radiotherapy is the most common treatment for cancer. It improves overall survival in several diseases thanks to therapeutic advances and can prevent late-onset complications. The development of new radiation techniques and machines makes it possible to perform targeted radiation around the tumour and/or lymphatic drainage and to offer this treatment to all patients with cancer, including older people with a number of comorbidities and frailties[2].

A number of factors should be taken into account (Figure 1):
- choosing the volume
- choosing the fractionation
- new treatment molecules with a toxicity profile that is as yet unknown, their combination with RT
- preserving quality of life for the older person.

One example of a treatment adapted to the patient's age and the risk of toxicity is shown in Figure 1.

In conclusion, the radiotherapy proposed to every older person must be suitable for their physiological age, general health and type of tumour.

During repeated crises due to COVID, specific protocols have been put in place by several learned societies in order to reduce the duration of radiotherapy[2,4].

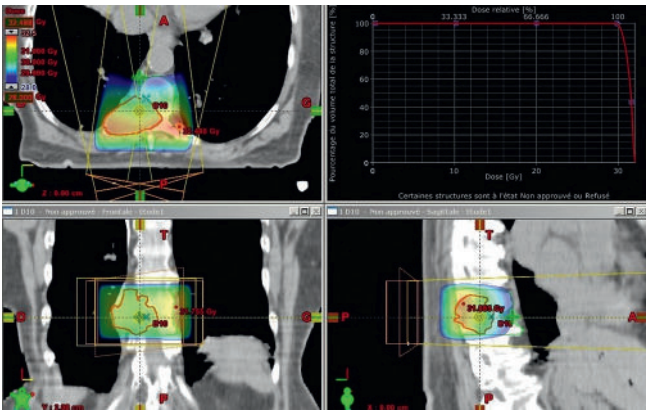

Figure 1: *80-year-old female patient with metastatic thyroid carcinoma in the lung and bones, metastatic since 2006, and several comorbidities. Lesion located opposite the heart and lungs, infiltrating the spinal cord. Localised IMRT (Intensity Modulated Radiation Therapy = sculpting isodoses around the tumour mass while avoiding the OARs) hypofractionated (30 Gy/ 10 fractions and 2 weeks). This personalised irradiation has allowed doctors to control the disease with perfect tolerance, no toxicity and a better quality of life because signs of pressure and pain disappeared following radiation treatment.*

Several radiotherapy protocols with extreme fractionation have been adopted very quickly in the older person for both breast cancer (treatment over the course of a single week in 5 sessions), prostate cancer and malignant blood diseases[2,3].

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PRECAUTIONARY PRINCIPLES WHEN USING SPECIFIC TREATMENTS

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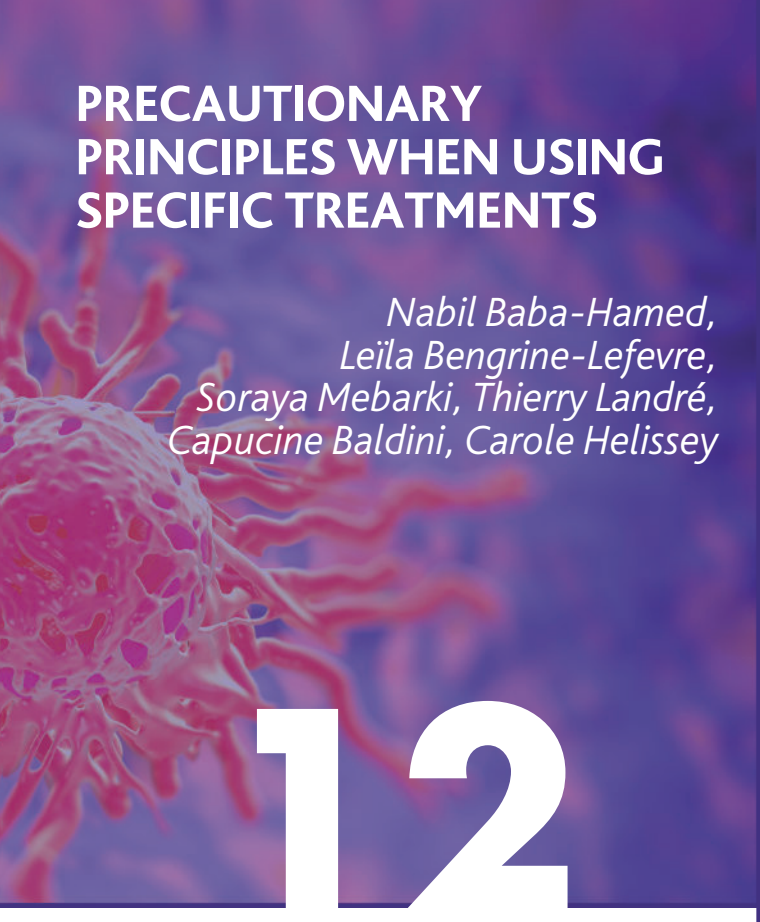

12

■ Hormone therapy

Nabil Baba-Hamed

Hormone therapy (HT) plays a key role in treating so-called hormone-dependent/hormone-sensitive cancers, as they progress and at every stage. These tumours, essentially represented by prostate cancers, breast cancers and to a lesser degree endometrial cancers, have a high incidence and prevalence in older patients, which is why this chapter is devoted to the principles for using hormone therapy.

Prostate cancer (PC)

Around 40% of patients with PC receive HT in the six months following diagnosis[1]. It may continue to be used for a number of years. The aim is to block androgen synthesis or action. This essentially happens thanks to LHRH antagonists (triptorelin, leuprorelin) or LHRH antagonists such as degarelix acetate, anti-androgens such as bicalutamide or more recently enzalutamide, apalutamide and darolutamide or other molecules such as abiraterone acetate which inhibit biosynthesis of androgens in the testicles, suprarenals and prostate tumour tissue. These molecules are prescribed as a

single-agent therapy or combined with one another or other chemotherapy molecules such as docetaxel. Although indispensable, they are not without adverse events, which will need to be minimised and treated.

- *LHRH agonists/antagonists: used at different stages of the disease, they can be responsible for:*

- **hot flushes** due to disordered hypothalamic thermoregulation[2]. Some drugs proved beneficial such as medroxyprogesterone[3], certain antidepressants such as venlafaxine at a dose of 37.5 mg/d, paroxetine at a dose of 10 mg/d[4,5] and certain anticonvulsants such as gabapentin[6]
- **sexual problems:** diminished libido and erectile dysfunction are directly related to low androgen levels; these result in lowered self-esteem and withdrawal, causing patients to stop treatment. Two predictive factors are being aged > 70 and diabetes[7]. Phosphodiesterase inhibitors such as sildenafil and tadalafil can improve these problems, taking account of the usual precautions in older patients. An alternative is intracavernous self-injection of prostaglandin
- **musculoskeletal effects:** fatigue, sarcopenia, osteopenia and osteoporosis. The risk of pathologic fracture is multiplied by 6[8,9], and the risk factors are androgen blockade lasting > 3 years, advanced age, smoking, Caucasian body type, pre-existing reduction in bone density and corticosteroid therapy[10,11]. Prevention includes taking physical exercise to avoid being overweight, quitting smoking, taking calcium and vitamin D supplements. A bone density test should be performed before treatment, and monitored subsequently, a practice which is unfortunately still very rare[12,13]. A T-score of < -2.5 should trigger treatment for osteoporosis. In the absence of bone metastases and resistance to castration, this treatment relies on oral or conventional IV biphosphonates such as zoledronic acid, or more recently denosumab, a RANK ligand inhibitor, which inhibits the destructive activity of osteoclasts. This delays the appearance of bone metastases, and was the subject of a randomised phase III study versus placebo[14,15]. In CRPCs (castration-resistant PCs) with bone metastases, it has a better effect than zoledronic acid
- **cardiac toxicity** causing an increase in the rate of myocardial infarction which is often fatal in patients aged

> 65 was noted, with complete androgen blockade (CAB)[17]. This toxicity can be explained by modification of the lipoprotein metabolism, vascular stiffening or long QT[18]. Physical exercise is recommended, as well as correction of risk factors such as diabetes

- **cognitive disorders and depression** with failing memory, difficulty concentrating, anxiety and disturbed sleep[19]. Studies on this topic are sometimes contradictory, but physical activity seems to have a positive effect[20]
- **gynecomastia** most commonly observed with anti-androgens and estrogenics, which are used less and less. A meta-analysis showed that tamoxifen given preventively at a dose of 20 mg/d and therapeutic radiotherapy could reduce gynecomastia induced by anti-androgens[21].

• *Anti-androgens*

These may be traditional (cyproterone acetate, bicalutamide) or new-generation (enzalutamide, apalutamide, darolutamide). The latter work by inhibiting the androgen from binding to its receptor, nuclear translocation of the active receptor and its binding to the DNA. They are used in combination with LHRH analogues. Enzalutamide is used in metastatic chemo-naive CRPCs[22] or after failure of chemotherapy[23], and more recently in metastatic castration-sensitive PCs (mCSPCs)[24]. Since apalutamide and darolutamide are indicated in non-metastatic CRPCs[25,26], recent data have demonstrated its action in mCSPCs[27]. Adverse events are dominated by hot flushes, headaches, gynecomastia and certain cognitive disorders. Since anti-androgens are powerful CYP3A4 inducers, take care if combining them with substrates of this cytochrome such as midazolam, warfarin or omeprazole.

• *Abiraterone acetate*

A suprarenal and testicular androgen biosynthesis inhibitor which works by inhibiting the CYP17 enzymatic complex, this is indicated in the mCRPC[28] and more recently in the mCSPC[29]. Adverse events include high blood pressure, digestive disorders and less frequently haematotoxicity. It should be taken on an empty stomach, in order to avoid increased bioavailability due to a hypercaloric meal[30]. This concept is difficult to reproduce in older

patients, due to cognitive disorders and a pillbox which is already very full, a potential source of confusion.

Breast cancer

The vast majority of breast cancers after 70 overexpress hormone receptors (ER+ and/or PR+), leading to hormone therapy irrespective of the stage of the disease. Aromatase inhibitors are the most commonly used in older patients due to their superiority to tamoxifen in an adjuvant situation[31,32]. Their adverse events are not insignificant, and they must be prevented, sought out and treated.

- *Aromatase inhibitors (AIs)*

Oestrogens in post-menopausal situations essentially come from suprarenal transformation of androgens - thanks to an enzyme called aromatase - into oestrone and oestradiol. AIs can be steroidal, such as exemestane or non-steroidal, such as letrozole or anastrozole.

The worst side effects induced by AIs are:

- **hot flushes**, less frequent than with tamoxifen, but occur in 33 to 36% of cases according to studies[33,34]. Antidepressants such as selective serotonin reuptake inhibitors have shown some benefit, such as venlafaxine[35], but also acupuncture, hypnosis and physical exercise
- **osteoarticular effects**, indeed oestrogen suppression promotes osteoclastic activity and bone demineralisation, which increases the risk of fracture, already existing in menopausal women. The effect of steroidal AIs would be less unfavourable on bone density, probably due to greater androgenic activity than their non-steroidal equivalents[36]. A bone density test with risk of fracture calculation: FRAX®[37] score and a dose of vitamin D are recommended before AIs are initiated; the majority of learned societies recommend treatment with biphosphonates in cases of T-scores $\leq$ 2.5, or in cases of osteopenia, with a high risk of fractures[38]. The bone density test should be repeated every 1 to 2 years. Taking calcium and vitamin D supplements, physical activity and prevention of falls are necessary[39]. Arthralgia and joint stiffness respond conventionally to simple analgesics or even NSAIDs, and also to acupuncture[40]. If symptoms persist, replacement with

another AI, steroidal for example, or tamoxifen is recommended. Hypnosis, which is increasingly common, can also improve patient comfort, by relieving pain intensity and hot flushes[41]

- **cardiac toxicity:** AIs increase the risk of cardiovascular toxicity (chronic heart failure, ischaemic heart disease) compared to tamoxifen, but this is still rare. This effect has been associated with hypercholesterolaemia, noted with non-steroidal AIs in the ATAC and BIG studies[41,33]. There are no specific recommendations concerning cardiac monitoring or cholesterolaemia, but caution is needed in patients with a history of heart disease and in combination with anti-HER2s
- **genito-urinary side effects** are rare, oestrogen suppression causes a change in the vaginal epithelium, and can exacerbate urinary tract problems such as pollakiuria, incontinence or even urinary infections[42]
- **cognitive side effects** are often reported with chemotherapy, but oestrogen receptors have been identified in several areas of the brain and must play a role in cognition[43]. The medical literature is sparse on this topic, only one small study showed a rise in memory impairment with anastrozole compared to tamoxifen[44]
- **alopecia** is a little-known effect with this therapeutic class, it happens rarely and with minimal intensity. One hypothesis would be 5a-reductase stimulation, which increases testosterone levels, mimicking male androgenetic alopecia[45]. Reversible effect, but which compromises observance.

• *Anti-oestrogens*

Two main families:

- SERM *(Selective estrogen receptor modulator)* **tamoxifen**: used in early or late stages. In addition to hot flushes and alopecia, it increases the risk of thrombo-embolic events[46]. No specific preventive recommendations, apart from probably regular physical activity. It also encourages the occurrence of uterine myomas or even more rarely endometrial cancer, which is closely related to the period of exposure[47]. A pelvic and/or endovaginal ultrasound every 6 to 12 months is a good idea with a more in-depth gynaecological examination in cases of menstrual bleeding. Finally, use in combination with certain SSRI-type antidepressants such as paroxetine or fluoxetine is prohibited due to the powerful inhibitory effect of

CYP2D6, an enzyme which is involved in converting tamoxifen into its active metabolite, endoxifen[48,49].

- SERD *(Selective estrogen receptor degradation)* **fulvestrant**: pure oestrogen receptor antagonist, administered by a monthly intra-muscular injection, at a dose of 500 mg. Used at an advanced or metastatic stage after failure of an AI[50] or as a first-line treatment[51]. Acceptable toxicity profile with some hot flushes and pain at the injection sites. Particular caution is recommended in patients on anticoagulants or anti-aggregants.
- Elacestrant: first oral SERD that has showed efficacy in advanced breast cancer as a 2nd or 3rd line treatment compared with standard hormone therapy[52], currently undergoing approval in the United States, and not yet available in France.

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■ Chemotherapy

Leïla Bengrine-Lefevre, Soraya Mebarki

Chemotherapy is commonly applicable provided that precautions are taken to account for physiological changes due to age (loss of functional reserve).

This means actively searching for factors predictive of toxicity[1].

There are some class-specific factors.

Pharmacokinetic changes

A number of changes are observed as people age:
- absorption may be reduced, especially in cases of atrophic gastritis
- volumes of distribution are also altered by changes in body composition: increased weight of body fat and Athanasios reduction of intracellular water[2]
- physiological sarcopenia and hypoprotidemia linked to malnutrition are a source of increased toxicity due to an increase in the active unbound fraction of the therapies
- modification of the hepatic metabolism; modification of cytochromes, fibrotic phenomena and reduced hepatic vascularisation
- reduced renal clearance due to nephron loss leading to decreased functional reserve: possibility of acute renal insufficiency on the "healthy" kidney in stress situations due to opposition to secondary renal insufficiency with a given disease
- the role of polypharmacy
- watch out for salt and water retention linked to repeated corticosteroid therapy
- routine checks for dihydropyrimidine deshydrogenase deficiency (DPD) by measuring the level of uracil before starting fluoropyrimidine-based chemotherapy (5-fluorouracil or capecitabine) are now mandatory in France; although this deficiency is rare, its presence can cause severe toxicity[3,4].

Haematological toxicity

There is increased toxicity, irrespective of the medication. This means following the recommendations of the ASCO: EPO if anaemia[5] is present after routine correction of associated vitamin deficiencies and G-CSF[6]. The

dose usually needs to be adapted[7] and the dosage regimens adjusted to improve tolerance (for example: weekly regimen for paclitaxel).

Cardiac toxicity

Numerous molecules are implicated:
- "historic" molecules: anthracyclines (dose-dependent systolic heart failure, myocardial ischaemia, arrhythmia), 5FU - capecitabine (coronary artery spasms), taxanes (salt and water retention)
- anti-HER2 therapies: trastuzumab, pertuzumab, TDM1
- anti-VEGF or VEGF-R therapies: heart failure (bevacizumab, trastuzumab)
- anti-CD20 and CD52 antibody: postural hypotension.

There is a very clear increase in potential unfavourable events, especially in combination with cardiotoxic drugs (for example: herceptin and anthracyclines).

If cardiotoxic agents are proposed, conduct a routine heart check-up (TTE to assess systolic function and look for signs of diastolic dysfunction (prolonged relaxation time, altered E/A, increased filling pressure, fractional shortening), or else an exercise tolerance test, myocardial scintigraphy).

Balancing the specific treatment prior to administration[8].

Schedule close monitoring: clinical (increase in blood pressure), ECG (non-specific but predictive changes) and biological (troponine, BNP).

Consider liposomal anthracyclines, which are available and included in breast cancer adjuvants[9].

Close cardiovascular monitoring should be envisaged in cases of corticosteroid therapy.

Neurotoxicity

This is more likely with use of the following molecules: paclitaxel, vincristine, vinorelbine, cisplatin, oxaliplatin, docetaxel, bortezomib.

There is greater sensitivity due to the history and an increased risk of loss of independence.

Account must be taken of any history, especially diabetic, or any diseases that cause peripheral neuropathy.

Monitoring symptoms at every session to determine reasons for early termination: question-and-answer session, ROT, tuning fork.

No protective element exists, irrespective of age[10].

Renal toxicity

There are problems with assessing kidney function.

Creatinine clearance according to MDRD is probably closer to clinical reality, but drugs are assessed according to the Cockcroft formula.

Currently, results reporting is assessed according to the CKD-EPI formula.

The increased risk of cumulative toxicity must be considered if patients are being treated with polychemotherapy.

Cisplatin is contraindicated for clearance below 60 ml/min. It must only be used in a very select population, without renal insufficiency or severe heart disease due to hyperhydration. The expected benefit must be weighed up against the risks, especially in chemoradiotherapy combinations used to treat locally-advanced diseases (cervical cancer, lung cancer).

Capecitabine, methotrexate, raltitrexed (alternative to 5FU) need the dose to be adjusted. Only carboplatin is immediately at a dose adjusted to renal function (AUC).

Worsening of kidney disease must be monitored due to cumulative toxicity of some lesser-known drugs (pemetrexed)[11].

If in doubt: go to the siteGPR website (*www.sitegpr.com*).

Hepatotoxicity

The dose needs to be adjusted when using doxorubicin, epirubicin, taxanes[12] and irinotecan.

Cognitive disorders

Chemo-induced cognitive disorders are often underestimated.

They are reversible but can reveal underlying frailty: this is the advantage of the geriatric assessment++++[13].

Hormone therapy can make things worse. Advantage of follow-up+++.

• *Common administration protocols*

- folfox for "older patients"[14], 400 mg/m^2 of folinic acid, 2,400 mg/m^2 continuous infusion of 5FU, 85 mg/m^2 of oxaliplatin
- folfiri[15]: 400 mg/m^2 of folinic acid, 180 mg/m^2 of irinotecan, 2,400 mg/m^2 continuous infusion of 5FU
- paclitaxel weekly for breast cancer[12]: 80 mg/m^2
- paclitaxel 60 mg/m^2
- carboplatin (AUC 2)[16] 3 weeks of 4 +/- paclitaxel 60 mg/m^2
- simplified LV5FU2 D1 = D14
- R miniCHOP
- carboplatin AUC4, J1, J21 (J28), paclitaxel 80 mg/m^2 weekly D1 = D21 or D1 = D28
- gemzar 1000 mg/m^2 weekly D1, D8, D15, D1 = D28.

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■ Targeted therapies

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Available in numerous pathologies, here are some specific data. This chapter focuses primarily on medical oncology therapies outside the scope of haematology, without claiming to be completely exhaustive in terms of current developments. Practitioners need to monitor early access regularly and with a view to the benefits of proposing molecular research, including for older patients, even though specific data do not yet exist for the majority of molecules.

Monoclonal antibodies

Few drug interactions, often prescribed in combination with conventional chemotherapy.

- ***Anti-HER2 antibodies***: trastuzumab, pertuzumab, T-DM1

Trastuzumab MA: breast cancer in older women[1], HER2-overexpression in metastatic gastric cancer. Little cardiac toxicity as an adjuvant[2], more in older female patients with risk factors of age, a history of heart disease[3,4] and combination with chemotherapy[5]. A subcutaneous form is available in an adjuvant situation.

Pertuzumab MA: 1st-line treatment for breast cancer, in combination with trastuzumab and docetaxel but limited in the subgroup of over-75s, probably due to the small number of people[6].

Also authorised in locally-advanced, inflammatory breast cancers or those with a high risk of relapse, as a neoadjuvant and as an adjuvant in breast cancers with a high risk of relapse.

In a metastatic situation, a new subcutaneous formulation combining trastuzumab and pertuzumab is available.

Trastuzumab-emtansine (T-DM1) MA: after failure of trastuzumab and taxanes in a metastatic situation, no specific data. New authorisation as an adjuvant in breast cancers with a high risk of relapse.

Cardiac monitoring required using scintigraphy or preferably an echocardiogram+++.

- *Anti-VEGF/VEGF-R antibody*: bevacizumab, aflibercept, ramucirumab

Bevacizumab MA: metastatic colorectal cancer[7], metastatic lung adenocarcinoma in combination with a platinum salt, triple-negative breast cancer. No difference in terms of toxicity nor in terms of efficacy[8,9] in colorectal tumours. Increased toxicity, risk of thrombo-embolic events multiplied by 7.5 when there is a history of thrombosis and age ≥ 65 years[10]. Not recommended in older patients with lung cancer due to increased toxicity.

MA in FIGO stage IIIc and IV ovarian cancer in an "adjuvant" situation. Efficacy data in older female patients are available, showing no increase in side effects[11].

Aflibercept MA: as a 2nd-line treatment for metastatic colon cancer in combination with FOLFIRI. Similar efficacy and tolerance compared to younger patients[12].

Ramucirumab MA: as a 2nd-line treatment for gastric cancer in combination with paclitaxel[13]. Not reimbursed in France. No specific data for older patients.

Monitoring of high blood pressure+++: investment in a home blood pressure monitor. Antihypertensives used as a first-line treatment are converting enzyme inhibitors (CEIs), angiotensin-II receptor blocker (ARBs) and calcium channel blockers.

Screening for proteinuria required before each treatment. Published treatment recommendation not specific to the older population. Permanent discontinuation is recommended in the event of rapid worsening of renal function, severe nephrotic syndrome or thrombotic microangiopathy[14]. Arterial thromboses are a contraindication.

New molecule: sacituzumab govitecan. Antibody-drug conjugate targeting TROP-2 and incorporating a topoisomerase inhibitor. Indicated in triple-negative breast cancer after two failed treatment cycles.

Enfortumab vedotin access for bladder cancers after progression with immunotherapy. Watch out for skin toxicity.

- *Anti-EGFR*: cetuximab and panitumumab

MA: RAS wild-type metastatic colorectal cancer.

Efficacy and toxicity of cetuximab identical in older and younger patients[15,16].

Efficacy of panitumumab is comparable to that of cetuximab[17]. The PANDA study demonstrated its usefulness as a first-line treatment in older patients with RAS wild-type cancer in combination with chemotherapy such as FOLFOX[18].

Patients should be warned of their common toxicity, which mainly affects the skin (rash, folliculitis, xerosis, paronychia)[19]. Watch out for diarrhoea and hypomagnesemia+++.

Cetuximab is also authorised in combination with radiotherapy in ENT cancers in cases of locally-advanced disease or in combination with platinum-based chemotherapy in cases of recurrent and/or metastatic disease[20].

Checkpoint inhibitors (see the chapter on immunotherapy)

- *Anti-CTL4 antibody:* ipilimumab
- *Anti-PD-1 antibody:* nivolumab, pembrolizumab<
- *Anti-PDL-1 antibody:* avelumab, atezolizumab, durvalumab

Protein kinase inhibitors

Small molecules administered orally, mostly metabolised by the CYP3A4 cytochrome. Problem of interaction and observance.

- *VEGFR inhibitors:* sunitinib, pazopanib, axitinib

These are indicated in advanced or metastatic kidney cancer (also for pazopanib in soft tissue sarcomas). Sunitinib retains identical efficacy in older patients suffering from metastatic kidney cancer, but has greater toxicity[21].

An optimal continuous dose of 37.5 mg/d seems to be better tolerated and is therefore more suitable[22].

Sorafenib is indicated in advanced kidney cancer and hepatocellular carcinoma. Same efficacy and tolerance in hepatocellular carcinoma above and below 80 years of age[23].

Regorafenib, indicated in advanced metastatic colorectal cancer, after failure of other treatments[24]. Regold study showing increased toxicity for older age brackets. Take care with the dose, which can be reduced without decreasing efficacy. MA also in hepatocellular carcinoma as a second-line treatment. MA in gastrointestinal tumours that have progressed after a first-line treatment.

No specific data available for pazopanib and axitinib. However, pazopanib, which is as effective as sunitinib in kidney cancer, has a better tolerance profile[25], being preferred to sunitinib by patients[26].

Vandetanib is indicated in advanced medullary thyroid cancer. No specific data for older patients. Risk of long QT syndrome.

Lenvatinib is indicated in hepatocellular carcinoma as a first-line treatment (not reimbursed) or in iodine-refractory progressive, locally-advanced or metastatic, differentiated thyroid cancer in the SELECT[27] and REFLECT[28] studies. The over-75 patient population tolerated the treatment less well, mainly because of the risk of high blood pressure and long QT syndrome.

New early access authorised since March 2022 in combination with pembrolizumab in endometrial cancer that has progressed after a platinum cycle.

RET inhibitors

Selpercatinib (conditional MA) is a selective RET inhibitor. Its most common toxicities are high blood pressure (14%), increased transaminases (10%) and hyponatremia (6%).

Pralsetinib (early access) is also used as a single-agent therapy in patients with RET fusion-positive NSCLC, as a second-line treatment. It is tolerated relatively well, with haematological (18% neutropenia) and vascular (11% high blood pressure) toxicity.

Ras mutation

Sotorasib is the first G12C inhibitor with access in lung cancer with this mutation.

Toxicity marked by: high blood pressure and proteinuria, haemorrhage, asthenia, hand-foot syndrome and diarrhoea.

- *EGFR inhibitors:* erlotinib, gefitinib, afatinib and osimertinib, 3rd-generation inhibitor (FLAURA study[29]) in advanced non-small cell lung cancer (NSCLC), with activating mutation of the EGFR. Erlotinib can be prescribed as a second-line treatment independently of its mutational status. Toxicity dominated by skin rashes, asthenia and diarrhoea. Tolerance and efficacy identical to that in young people for erlotinib in NSCLCs[30]. Good tolerance was noted in a retrospective study of 55 EGFR-mutated patients with a median age of 81, treated with gefitinib as a first-line treatment, with a control rate of 92.7%[31]. Osimertinib is used in patients who have the EGFR T790M mutation.

- *EGFR exon 20 insertion*

Mobocertinib has benefited from compassionate access since August 2021. It is proposed after progression of an initial round of chemotherapy in patients with mutation by exon 20 insertion on the EGFR gene. The main adverse events are diarrhoea (85%), nausea (43%) and skin rash (36%).

Poziotinib (compassionate access) is also a TKI that targets EGFR exon 20 insertions. The main side effects are skin rash (90%), diarrhoea (82%) and mucositis (70%).

Amivantamab is also available as early access in patients suffering from non-small cell lung cancer who carry an activating mutation of EGFR by exon 20 insertion.

- *C-MET exon 14 skipping mutation*

Capmatinib (early access in 2021) is used as a single-agent therapy at a dose of 400 mg x 2/day per os, in previously-treated metastatic NSCLC patients who present with mutation of the c-MET exon 14. The main toxicities are peripheral oedema as well as low-grade nausea and vomiting.

Tepotinib (early access in 2020) is also indicated for this c-MET mutation. Peripheral oedemas are the main side effects.

- *Her2 inhibitor:* lapatinib

In a small set, in combination with capecitabine, in HER2+ breast cancer, after failure of one treatment with trastuzumab, it showed similar efficacy and a similar profile to younger people[32].

Toxicity includes asthenia, skin rash, diarrhoea and heart attack in rare instances.

Tucatinib has just obtained authorisation for female patients suffering from Her 2+ breast cancer after failure of two rounds of anti-Her2 treatment. No data.

- *mTOR inhibitor:* everolimus, temsirolimus

Everolimus is indicated in advanced kidney cancer, hormone-sensitive breast cancer in combination with exemestane after failure of an initial round of hormone therapy and advanced pancreatic neuroendocrine carcinoma. The tolerance profile of the latter drug is identical to that of younger people with identical or even better efficacy[33].

Temsirolimus is indicated in advanced kidney cancer with a poor prognosis and mantle cell lymphoma. No specific data.

The toxicity of this therapeutic class is dominated clinically by mucositis and interstitial lung diseases, biologically by hyperglycaemia and hypercholesterolaemia.

- *Kit/PDGF inhibitor*: imatinib

No specific data in stromal tumours. A study of chronic myeloid leukaemia in older patients showed satisfactory tumour control, but treatment was stopped prematurely in 36.6% of patients[34]. Cases of cardiac decompensation in older patients have been reported[35].

- *EML4-Alk translocation inhibitor*: crizotinib, brigatinib, alectinib (new first-line standard following the ALEX study)[36], ceritinib

Indicated in advanced NSCLCs with rearrangement of the ALK fusion gene, which represents approximately 5% of NSCLCs, but patients are often young and light- or non-smokers[37], so there is no specific data for older

patients. Alectinib also appears to be associated with a better tolerance profile[38].

- *BRaf inhibitor*: vemurafenib, dabrafenib, encorafenib

Indicated in advanced malign melanoma with BRAF V600E mutation, no data available concerning tolerance and efficacy in older patients, but the pivotal study with vemurafenib included patients of up to 86 years old[39]. One clinical case was reported with dabrafenib in a patient aged 80[40].

Data from sub-groups is in favour of use, with the drawbacks concerning lack of specific data from geriatric assessments[41].

Also authorised is a combination of encorafenib and cetuximab as a 2nd-line treatment for colon cancer with a BRaf mutation.

Dabrafenib also benefits from early access for low-grade gliomas with a relapsed or refractory BRafV600E mutation.

Enfortumab vedotin benefits from early access for patients suffering from urothelial cancer who have received a PDL1 or PD1 inhibitor.

- *MEK inhibitor*: cobimetinib, trametinib, binimetinib

In combination with anti-BRafs. Little specific data.

- *CD4-6 kinase inhibitor*: palbociclib, abemaciclib, ribociclib

Indicated in locally-advanced or metastatic RH+/HER2- breast cancer in women who have previously been treated with hormone therapy. Efficacy appears to be identical irrespective of age[42,43]. The main toxicity is neutropenia which leads in rare cases to febrile neutropenia; an alert has been issued concerning the risk of interstitial lung disease (www.Fda.gov)[44]. Watch out for fatigue, which is a common factor with all molecules. The PALOMAGE study looked specifically at tolerance of palbociclib in older female patients. Authorisation for abemaciclib as an adjuvant is imminent. Watch out for fatigue, which is a common factor with all molecules, and diarrhoea with abemaciclib. Toxicities appear to be somewhat more marked in older female patients with ribociclib[45]. Caution: ribociclib can lead to long QT syndrome.

- *PARP inhibitor*: olaparib, niraparib, talazoparib, rucaparib

Olaparib MA: indicated in platinum-sensitive relapsed ovarian cancer by BRCA 1/2 mutation. Indicated in an adjuvant situation in BRCA-mutated ovarian cancer. Indicated in combination with bevacizumab in female patients with an HRD profile. Indicated in BRCA-mutated breast cancer previously treated with anthracycline and taxane[46]. New access in BRCA-mutated breast cancer. Taken twice a day.

MA for niraparib on platinum-sensitive relapse with similar efficacy[47]. MA in adjuvant situation in female patients who have responded to first-line treatment. Taken once a day.

MA for rucaparib on platinum-sensitive relapse of ovarian cancer. Biological liver toxicity. Taken twice a day with dose adjustment at different levels as there are several dosages available.

Special study showing similar efficacy profiles[46] (SIOG) and for olaparib[48,49].

End of EAP for talazoparib in breast cancer. No specific data available for older patients.

- *NTRK inhibitor*: larotrectinib, selitrectinib after failure of an initial therapy targeting NTRKs. No specific data. Rare mutations (fewer than 1% of cancers)
- *idh1 inhibitor*: ivosidenib

New early access in bile duct cancer after failure of initial treatment.

- *FGFR inhibitor*: erdafitinib: stage IV urothelial cancers progressing after chemotherapy and immunotherapy

Lurbinectinib after failure of platinum-based chemo for small cell lung cancers.

Vectorised internal radiotherapy

Lutathera is the first treatment to be authorised as a first-line treatment of well-differentiated neuroendocrine tumours.

We are seeing the arrival of PMSA radiotherapy for patients suffering from prostate cancer with bone metastases when hormone therapies have failed. This technique is currently being implemented in France.

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■ Immunotherapy

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Introduction

Immune checkpoint inhibitors (ICIs) are a game-changer in the treatment of numerous cancers. Different molecules in this class have obtained marketing authorisation as a single-agent therapy in non-small cell lung cancer, melanoma, squamous cell carcinoma of the head and neck, and kidney cancer[1-6]. And their benefit in terms of overall survival has also been demonstrated in combination with chemotherapy, targeted therapies, or radiotherapy[4-8].

However, there has been less consideration of their efficacy and their tolerance in older patients, since this population is under-represented in clinical trials.

Older patients do however have certain specific characteristics, such as the presence of comorbidities and frailties, and their immune system may be impaired, which could have an impact on the efficacy and tolerance of these innovative therapies. And the emergence of combinations leads to different tolerance profiles, depending on the associated mechanisms.

In this chapter, we will first present the rationale for inhibition of immune checkpoints, then the concept of immunosenescence and its involvement in the anti-tumour response. Then we will present the efficacy of ICIs. Finally, we will stress the specific toxicities of ICIs and how they are managed in older patients.

Rationale for inhibition of immune checkpoints (ICs)

ICs are receptors and ligands involved in modulating the immune response. Recognition of the antigen by the receptor present on the T lymphocyte activates the latter. But this step is regulated by the balance between the co-activation or inhibition signals, represented by the IC. This allows tolerance of the self and modulation of the intensity of the immune response[9].

One of the properties of the tumour cell is that it can escape immune surveillance via the IC. Hence, the development of ICIs made it possible to re-establish this immune surveillance and induce a prolonged anti-tumour response[10].

Different ICs have been identified and are targeted by different antibodies. The anti-CTLA-4s or anti-PD-1s or PD-L1s were the first to be put forward for clinical development.

- *Cytotoxic T-Lymphocyte antigen 4 (CTLA-4)*[10.11]

CTLA-4 is the first co-inhibitor to have been studied.

It is expressed by the activated T CD4+ and CD8+ lymphocytes, and is permanently expressed by the regulatory T lymphocytes (Tregs).

It acts as a counterbalance to the activity of CD28, a costimulatory receptor present on T lymphocytes.

CD28 and CTAL-4 present the same ligands CD80 (or B7.1) and CD86 (or B7.2). CTLA-4 has a stronger affinity for these ligands.

When activated it increases the suppressive function of Tregs and inhibits IL2 production and expression of the IL2 receptors.

The anti-tumour effect of CTLA-4 inhibitors is mediated by Treg inhibition and an increase in the activity of cytotoxic lymphocytes.

- *The PD1/PDL1 signalling pathway*[10-12]

Programmed cell death 1 (PD-1) is another key point in controlling the immune system. It involves a T cell co-inhibitory receptor activated in the peripheral tissues.

The PD-1 ligands are PD-L1 (B7-H1) and PD-L2 (B7-DC) which are expressed in the antigen-presenting cells, the tumour cell and also in the tumour microenvironment.

PD-L1 causes immunosuppression in the tumour microenvironment.

The expression of PD-L1 is found in numerous tumour models. Blocking the PD-1/PD-L1 interaction re-establishes immune surveillance and results in a prolonged anti-tumour effect.

Immunosenescence and its involvement in tumorigenesis[13-18]

Senescence is a physiological process which leads to slow deterioration of organic functions due to ageing.

Cellular senescence is associated with modifications to the structure of chromatin, loss of growth factor response capacity, accumulation of damage to DNA, brain activation, metabolic modification and mitochondrial disorders.

Unlike dormant cells, senescent cells still have some activity and secrete factors in their environment which modulate signalling pathways in neighbouring cells; this is associated with inflammation and malignant tumours.

Senescence also leads to chronic low-grade inflammation due to secretion, by immune cells, of several proinflammatory cytokines (interleukin-1b [IL-1b], IL-18 and tumour necrosis factor-a [TNF-a]13. This uncontrolled chronic inflammation is responsible for the damage caused by age-related illnesses (cardiovascular diseases, cancer and dementia), and is defined as "inflammaging".

Immunosenescence refers to continuous remodelling of the lymphoid organs, leading to a reduction in immune function in older people.

We therefore see ageing of the haematopoietic stem cell compartment, reduced release of tumour antigen, impairment of the antigen-presenting cells, reduced activation of T cells with senescent T cells, and with a reduced capacity to get rid of the tumour cells.

This progressive deterioration in protective immunity leads to a reduction in overall immune surveillance which increases the incidence of infection and cancer.

Efficacy of ICIs in older patients

- *Anti-CTLA-4 Ipilimumab*

Ipilimumab is a fully-humanised monoclonal antibody directed against CTLA-4. It is the first immune checkpoint inhibitor to be approved by the FDA for treatment of patients with unresectable or metastatic melanoma.

Hodi *et al.* reported a phase III study, assessing ipilimumab, which may or may not be combined with glycoprotein 100 (gp100), compared to gp100 only in patients with previously-treated metastatic melanoma[19]. Six hundred and sixty-seven patients were included in this study; 403 received a combination of gp100 and ipilimumab at a dose of 3 mg/kg, 137 patients only received

ipilimumab and 136 patients only received gp100. Ipilimumab was administered once every 3 weeks. The median overall survival (OS) was 10.0 months in patients receiving ipilimumab plus gp100, compared to 6.4 months in patients receiving gp 100 only (HR = 0.68; $p < 0.001$). The median OS with ipilimumab only was 10.1 months (HR = 0.66; $p = 0.003$). No difference in overall survival was detected between the ipilimumab groups (HR = 1.04; $p = 0.76$). Of these 676 patients, 196 (29%) were aged over 65. One hundred and twelve patients were randomised into the group with ipilimumab and gp 100, 42 into the group with gp100 only and 42 into the group with ipilimumab only. The OS analyses in these sub-groups showed that the effect of ipilimumab was independent of age. In the older population, a reduction of 31% in the risk of death was observed with ipilimumab plus gp100, compared to gp100 only (HR = 0.69 (0.47-1.01)), and a reduction of 39% in the risk of death was observed with ipilimumab only compared to gp100 only (HR = 0.61 (0.38-0.99)).

Sileni *et al.* assessed the efficacy and safety of ipilimumab at its approved dose of 3 mg/kg in older patients in the framework of an expanded access programme[20]. One hundred and ninety-three patients aged over 70 were included and of these patients, 27 were aged over 80. The disease control rate related to immunity was 38%, with 2% producing a full response, 13% a partial response and 23% with a stable illness. The median disease control duration was 11.5 months (CI 95% 9.3-13.7). There was no difference between patients aged over 70 years (8.9 months (CI 95% 7.2-10.6)) and under 70 years (7.0 months (CI 95% 6.1-7.9)) $p = .17$.

Robert *et al.* reported, in a phase III study, a benefit in overall survival in patients with metastatic melanoma from the ipilimumab + dacarbazine combination as a 1st-line treatment compared to dacarbazine only, 11.2 months vs 9.1 months (HR = 0.72; $p < 0.001$)[21]. But this clinical benefit is not demonstrated statistically in patients aged over 65 (160 patients were included).

In a meta-analysis including patients treated for melanoma, non-small cell lung cancer or kidney cancer, the benefit of anti-CTLA-4s was identical regardless of age compared to the control arm (HR = 0.73; CI 95% 0.62-0.87; $p < 0.001$)[22].

Tremelimumab

Tremelimumab is a fully-humanised IgG2 monoclonal antibody directed against CTLA-4.

Ribas *et al.* assessed the efficacy of tremelimumab (15 mg/kg once every 90 days) compared to chemotherapy in patients with unresectable melanoma at stage IIIc or IV, as a 1st-line treatment, in a phase III study[23]. Six hundred and fifty-five patients were included, 328 in the tremelimumab group and 327 in the chemotherapy group. Unfortunately, there was no difference in overall survival between the two groups: 12.6 months (CI 95%, 10.8 to 14.3) for the tremelimumab group and 10.7 months (CI 95%, 9.36 to 11.96) for the chemotherapy group (HR = 0.88; $p = 0.127$). In this study, 200 patients (31%) were aged over 65, 110 in the tremelimumab group and 90 in the chemotherapy group. There was no difference in overall survival between these groups in the older population (HR = 0.87; $p = 0.384$).

• *Anti-PD1 Nivolumab*

Nivolumab (BMS 936558, MDX 1106, ONO-4538) is a fully-humanised IgG4 monoclonal antibody directed against PD-1, which blocks its connection with its ligands (PD-L1 and PD-L2).

In a phase III study, Borghaei *et al.* assessed the efficacy and tolerance of nivolumab in patients with non-small cell lung cancer (NSCLC), as a second-line treatment after platinum-based doublet chemotherapy[24]. Five hundred and eighty-two patients were included, 287 in the nivolumab arm (3 mg/kg every 2 weeks) and 268 in the docetaxel arm (50 mg/m^2 every 3 weeks). Nivolumab showed an improvement in OS compared to docetaxel with a median OS at 12.2 months (CI 95%, 9.7 to 15.0) in the nivolumab group *versus* 9.4 months (CI 95%, 8.1 to 10.7) in the docetaxel group (HR = 0.73; CI 96%, 0.59 to 0.89; $p = 0.002$). In this study, 200 patients (34%) were aged 65 to 75 and 43 patients (7%) were aged over 75. A reduction of 37% in the risk of death was observed in the nivolumab group compared to that of docetaxel (HR = 0.63 (0.45-0.89)) in the > 65 to < 75 group. A reduction of 10% in the risk of death was noted with nivolumab compared to docetaxel (HR = 0.90 (0.43-1.87)) in the ≥ 75 group.

Motzer *et al.* in a phase III randomised trial, in advanced renal cell carcinoma (RCC), reported a reduction in the risk of death of 27% with nivolumab compared to everolimus[25]. In this study, 324 patients (39%) were over 65. This advantage was demonstrated in patients aged 65 to 75 with a reduction in the risk of death of 36% in the nivolumab group compared to the everolimus group (HR = 0.64 (0.45-0.91)). However, this advantage was not observed in the over-75 group (HR = 1.23 (0.66-2.31)), due to the low number of patients in this sub-group.

Nivolumab showed an overall survival benefit as a second-line treatment in patients with metastatic relapse of a tumour of the head and neck in the 6 months following platinum-based chemotherapy compared to chemotherapy only (methotrexate, docetaxel, cetuximab) (HR = 0.70; CI 97.73%, 0.51-0.96; p = 0.01)[26]. But this benefit is not found in the sub-group aged between 65 and 75 (HR = 0.93 (0.56-1.54)). It should be noted that only 113 patients were aged over 65.

Pembrolizumab

Pembrolizumab is a humanised IgG4 antibody against PD-1.

In a phase III study, Robert *et al.* compared pembrolizumab (10 mg/kg, every 2 weeks or every 3 weeks) with 4 doses of ipilimumab (3 mg/kg every 3 weeks) in patients with advanced melanoma[27]. Eight hundred and thirty-four patients were included, 279 in the pembrolizumab arm every 2 weeks, 277 in the pembrolizumab arm every 3 weeks and 278 in the ipilimumab arm. 1-year overall survival was 74.1% for the patients receiving pembrolizumab every 2 weeks (HR = 0.63; CI 95%, 0.47-0.83; $p < 0.0005$) compared to the ipilimumab group, 68.4% for the pembrolizumab group every 3 weeks (HR = 0.69; CI 95%, 0.52-0.90; $p = 0.004$) and 58.2% for the ipilimumab group. In this study, 238 patients (29%) were aged over 65, with the same clinical benefit (HR = 0.56, CI 95% (0.36-0.87)) in the pembrolizumab group every 2 weeks.

Reck *et al.* assessed the efficacy of pembrolizumab as a 1st-line treatment in patients with metastatic NSCLC with an expression of plus 50% of PD-L1 in the tumour cells compared to chemotherapy[28]. Progression-free survival was 10.3 months in the pembrolizumab group *versus* 6.0 months in the chemotherapy group

(HR = 0.50; CI 95% (0.37-0.68); $p < 0.001$). 6-month overall survival was 80.2% in the pembrolizumab group *versus* 72.4% in the chemotherapy group (HR = 0.60; CI 95% (0.41-0.89); $p = 0.005$). One hundred and sixty-four patients aged over 65 were included with an improvement in progression-free survival and overall survival in the pembrolizumab group (HR = 0.45 (0.29-0.70)), in this sub-group.

- *Anti-PDL1 Atezolizumab*

Atezolizumab (MPDL3280A, humanised IgG4) is a humanised IgG4 antibody targeting PD-L1.

Rittmeyer *et al*. assessed the efficacy of atezolizumab compared to chemotherapy in patients with metastatic NSCLC as a 2nd or 3rd line treatment[29]. Overall survival improved in the atezolizumab group vs docetaxel (13.8 months vs 9.6 months) (HR = 0.73; CI 95% [0.62-0.87], $p = 0.0003$). The sub-group of patients aged over 65 represented 47% of the patients included (n = 397). In this sub-group, the median overall survival was 14.1 months in the atezolizumab group vs 9.2 months in the docetaxel group (HR = 0.66; CI 95% [0.52-0.83], p = 0.0003).

Durvalumab

Durvalumab (MEDI 4736, fully human IgG1) is a humanised IgG1 antibody targeting PD-L1.

Maintenance durvalumab showed an improvement in progression-free survival in patients with stage III NSCLC after chemoradiotherapy compared to the placebo (the median progression-free survival was 16.8 months in the durvalumab arm *versus* 5.6 months in the placebo arm (HR = 0.52; CI 95% [0.42-0.65]; $p < 0.001$)[30]. Three hundred and eighty-two patients aged over 65 were included. This benefit was found but was not significant (HR = 0.74 (0.54-1.01).

What is the tolerance profile of ICIs?

Immune inhibitors demonstrated better tolerance than cytotoxic chemotherapy. However, the downside of these drugs was inducing immune-related adverse events (irAE) and every organ could develop an AE.

Immune-related adverse events can be more serious in older patients due to the reduction in functional reserve

and comorbidities associated with age[31.32]. In addition, the phenomenon of "immunosenescence"[14] could affect both the efficacy and tolerance of these new molecules. With, as emphasised earlier, the models of expression of co-stimulatory or co-inhibiting proteins of T cells which change considerably the expression of inhibitory receptors such as PD-1 or LAG-3 which are improved and associated with a reduction in co-stimulatory molecules. Paradoxically, immunosenescence is also associated with higher concentrations of inflammatory cytokines. Finally, older patients are known to have higher prevalence of autoantibodies, which may lead to an increase in auto-immune diseases with use of ICIs in this population.

Sileni *et al.* described the toxicity of ipilimumab in patients aged over 70 compared to younger patients[20]. The specific AEs were 36% and 33% respectively for older people and young people. Pruritis, skin rash, diarrhoea, nausea and hepatotoxicity were the most specific AEs in the older population. The frequency of these toxicities was similar between both age groups, with a slight increase in dermal toxicity in older people (10% as opposed to 7%). Serious AEs (6%) and the median time for resolution of reported AEs were similar between both groups.

Excess toxicity can be observed among the youngest and oldest patients receiving an anti-PD-1 or an anti-PD-L1, and not in an immediate way as seen with chemotherapies, but later, after several injections.

Singh *et al*. reported AEs depending on age for patients treated with nivolumab regardless of the type of tumour[33]. No difference in terms of incidence of grade III-V AEs between patients aged under 65 and patients aged over 65. However, patients aged over 70 had more grade III-V AEs than the under-65s with 71.7% as opposed to 58.4%. In addition, it was noted that AEs which led to discontinuation of treatment, or requiring introduction of concomitant treatment to modulate immunity, were more frequent for patients over 70 compared to those aged under 65 (with 19.8% and 51.9% for older people as opposed to 14.4% and 41.5% for younger patients).

In the pooled analysis of KEYNOTE trials with pembrolizumab via different types of tumour in 3991 patients,

46% of whom were 65 and over and 16% were 75 and over, there was no significant difference according to age. These data were updated in 2019 and confirmed similar tolerance with a threshold of 75[34].

Cohort studies reported excess toxicity of grade ≥ 2 in 191 patients aged 70 and over, with one treatment per anti PD-(L)1 (33% as opposed to 25%; $p = 0.035$)[35]. Dermal toxicity was more common in older people (49% as opposed to 28%, $p = 0.007$).

Other cohort studies did not reveal a difference in terms of incidence or severity, but the numbers were smaller[36.37].

These results should be treated with caution due to the small sample size of the older groups. AEs requiring drugs to modulate immunity were similar depending on the different organs in each age group, except for diarrhoea/colitis and skin rash, found more in older people with 5.2% and 10.4% as opposed to 2.4% and 7.6%. Because of the increase in diarrhoea, special supervision was necessary for older people with a risk of dehydration and renal insufficiency.

Special attention should be given to combinations in this population of older people. The initial data show similar efficacy compared to young patients[5-8], the cut-off in the majority of studies being 65 years old. But we have little data in terms of tolerance in this population.

Management of immune AEs in older patients[38]

Although there do not appear to be more immune AEs in older patients, special supervision is important, especially when the majority of available data comes from trials in which older patients are under-represented.

Here are some recommendations for managing these innovative treatments which require us to change our usual practice.

- *Prevent*

Before starting immunotherapy, it is advisable to detect any personal or family history of auto-immune disease or chronic viral infection whose pathogenesis could be potentialised by ICI treatment. However, a controlled auto-immune disease is not deemed to be a contra-indication

for the currently approved ICIs. But in this situation, the risk-benefit ratio needs to be assessed.

To facilitate early identification of the symptoms associated with immune AEs, it is essential to inform the patient, their family and carers about the nature and specificity of immune AEs. It is important to ask the patient to report very promptly any new symptom or aggravation of pre-existing symptoms to allow correct assessment without delay. Patients must also be informed that immune reactions may occur at any time: at the start, during or after stopping treatment.

- *Anticipate*

Our patients may retain toxicity from previous treatments. The physical examination, lab tests and scans done when introducing immunotherapy should be used as a benchmark for any new anomaly that occurs during treatment. Any standard comorbidity should be correctly assessed before starting and during ICI treatment. It is advisable to involve the geriatrician if frailty is detected by the G8 tool. The minimum tests should include FBC, renal function, serum electrolytes, hepatic function and regular thyroid assessment (TSH). A chest scan should be done routinely when introducing immunotherapy in cases where pulmonary toxicity might occur.

- *Detect*

New symptoms or an increase in pre-existing symptoms should routinely be suspected to be an immune AE. However, the frequency of an immune AE is relatively low compared to other causes such as progression of the disease or intercurrent infection, and this must first be excluded.

Nonetheless, immune toxicity should always be considered and lead to appropriate investigations. Standard assessment is then essential as it will provide a benchmark.

In clinical practice, particular attention should be paid to the appearance of respiratory (cough, shortness of breath), gastro-intestinal (diarrhoea) or cutaneous symptoms (skin rash). The non-specific general signs should suggest endocrine toxicity (especially a thyroid disorder). In older patients, frustrating symptoms such as

confusion should be explored, because they are potentially linked to the treatment.

The lab tests should look in particular at haematological toxicity (anaemia, thrombocytopenia), hepatotoxicity (elevated transaminases) and renal toxicity (increase in creatinine). TSH should be checked regularly (every 2 to 3 months). Given that immune AEs can be delayed, clinical and biological supervision of patients should be maintained after stopping treatment (every 3-6 months).

• *Treat*

If an immune AE has been diagnosed, several items need to be discussed:
- informing the patient about elements they can watch out for
- symptomatic treatment
- suspension or cessation of the immunotherapy agent; corticosteroid therapy (be more vigilant with older patients because there is an increased risk of side effects)
- specialist advice on the affected organ to assess the advantage of other immunosuppressive agents (such as anti-TNF for severe colitis), especially for severe, persistent or recurrent toxicity.

It is important to note that corticosteroid therapy is not routinely used to treat immune AEs: the majority of grade I immune AEs can be managed with symptomatic treatment alone. In addition, reduction in ICI dose is not currently recommended for the 3 approved ICIs.

• *Supervision*

Resolution of immune AEs can vary considerably depending on the different types of toxicity: gastro-intestinal, hepatic and renal toxicity usually improve rapidly on starting immunosuppressants, whereas skin and endocrine toxicity are more chronic.

Endocrine deficiencies often require long-term hormone replacement therapy (HRT).

If starting corticosteroid therapy, HRT should be cut down gradually (usually over a period ≥ 1 month) to avoid a relapse or aggravation of the immune AE.

Finally, the use of prolonged immunosuppressive treatments requires supervision and appropriate prophylactic treatment to prevent potentially fatal opportunist infections.

in older people, tolerance of immune AEs must be monitored carefully because the associated comorbidities may decompensate more easily. In addition, the use of certain symptomatic treatments (such as antihistamine for pruritis) or corticosteroids may expose older patients to iatrogenic events such as aggravation of diabetes, impaired mental health, high blood pressure, etc.

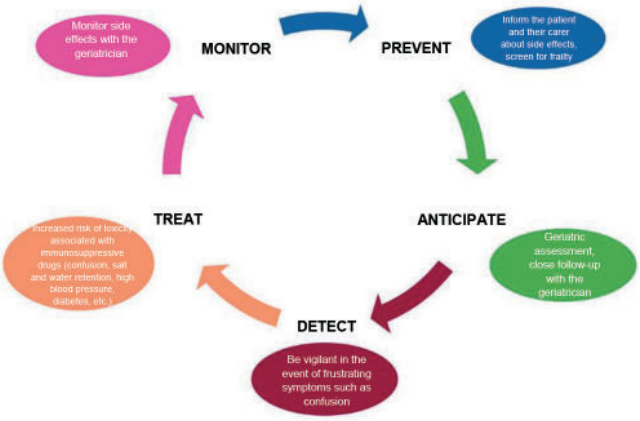

Figure 1: *Major treatment principles - adapted from "O'Donovan, A., Baldini, C, Battisti, N.M.L. (2022). Radiotherapy and Systemic Anti-Cancer Treatment in Older Adults with Cancer and Frailty. In: Gomes, F. (eds) Frailty in Older Adults with Cancer. Springer, Cham. https://doi.org/10.1007/978-3-030-89162-6_14".*

Conclusion

ICIs are promising innovative therapies, especially with the rise in combinations, but their tolerance profile differs from that of chemotherapies or other targeted therapies, necessitating careful supervision.

Like the majority of studies assessing ICIs and involving a low number of older patients, it remains difficult to confirm the impact of these new treatments on older people. It could well be expected that the clinical specificity of older patients (comorbidities, concomitant treatment, reduction in functional reserve, frailties) and immunosenescence might affect the efficacy and

tolerance of ICIs in this population. However, the data suggest that older patients are benefiting from the revolution of ICIs in oncology, but that older patients should be followed up more closely in collaboration with the geriatrician. Dedicated prospective studies are ongoing to assess the efficacy and tolerance of ICIs in this population.

Combinations bring new challenges. Identifying which older patients would be likely to benefit most from these combinations without excess toxicity will be of capital importance in the years to come.

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SUPPORTIVE CARE

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13

Supportive care is defined as all care and support needed by patients throughout their cancer journey, together with specific treatments for blood cancer, when applicable[1].

This approach is perfectly consistent and even complementary to geriatric oncology, which could be defined as "a multidimensional, multidisciplinary approach using the most ethically-appropriate ways to care for older patients with cancer at the various stages of their illness"[2].

Supportive care is based around a multi-professional, multidisciplinary approach in order to take an overall view of the patient and their friends and family. This involves assessing the patient and their next of kin, then ensuring coordination between the various players involved in treating both the cancer and any symptoms.

■ Complications of chemotherapy

Digestive toxicity[3,4]

Nausea and vomiting are among the most common side effects of chemotherapy (CINV). There is no particular specificity for treating these in older people and they

are treated in exactly the same way as in young adults. However, their consequences, like those of diarrhoea, can rapidly become more serious and lead to weight loss and/or dehydration which may potentially result in hospitalisation. Prevention is therefore of the utmost importance in this patient population.

The AFSOS recommendations updated in 2017 classify nausea/vomiting in four groups: anticipatory (occurring before treatment is administered), acute (appearing in the first 24 hours after treatment) and delayed (occurring more than 24 hours post-treatment), and finally refractory nausea which resists first-line, properly conducted medical treatment.

Several therapeutic classes are involved in treating it, with no dose adjustment nor particular precautions on the basis of the patient's age.

Chemotherapies are classified in 4 classes, according to their emetogenic potential (Appendix 1).

Appendix 1[11]:

Very low	Low	Average	High
Risk of CINV < 10%	Risk of CINV between 10 and 30%	Risk of CINV between 31 and 90%	Risk of CINV > 90%
Bevacizumab		ACVBP	5-FU-streptozotocine
Cetuximab	Pemetrexed	Standard & intensified AI	ABVD
Bleomycin	CYTA-BOM	Pemetrexed-eloxatin	API-AI
Melphalan-prednisone	Topotecan	Irinotecan	BEACOPP
Vinorelbine IV	Fotemustine	Irinotecan-eloxatin	BEAM
Sorafenib	Mitoxantrone	CAPOX-Cetuximab	BEP
Sunitinib	Paclitaxel	Carboplatin AUC6&7	BEP-paclitaxel

Temsirolimus	Paclitaxel-Bevacizumab	Carboplatin-etoposide	CBV
Panitumumab	Docetaxel	Carboplatin-gemcitabine	Cisplatin regimens
	Docetaxel-Vinorelbine	Carboplatin-LV5FU2	Cisplatin-etoposide
	Every 7 or 14 days	Carboplatin-Vinorelbine	Carboplatin-gemcitabine
	5-FU regimens	Carboplatin-paclitaxel	Cisplatin-LV5FU2
	5-FU-Vinorelbine	Carboplatin-Docetaxel	Cisplatin-5-FU-Docetaxel
	Trastuzumab	CHOP or R-CHOP	Cisplatin-Vinorelbine
	Gemcitabine	CMF	Cisplatin-pemetrexed
	Gemcitabine - Vinorelbine	COP	Cisplatin-paclitaxel
	Gemcitabine - Docetaxel	COPADEM	Cisplatin-Docetaxel
	LV5FU2	EC or AC	Cisplatin-Capecitabine
	LV5FU2-Vinorelbine	Oxaliplatin-Cyclophosphamide	Dacarbazine
	Methotrexate	Oxaliplatin-paclitaxel	DHAP

	Vinorelbine - Capecita-bine	EOX	High doses of doxorubicin
	Weekly paclitaxel	Etoposide-Ifosfamide	Doxorubi-cin-strepto-zotocin
	Weekly docetaxel	FEC or FAC	ECF
	Capecita-bine	FOLFIRI	ECX
	Capecita-bine-Bevaci-zumab	FOLFIRI-NOX	EP
		FOLFOX	High doses of ifosfamide
		GEMOX	ICE
		Ifosfamide	IVAP-IVA
		Metho-trexate	High doses of metho-trexate
		Vinorelbine-doxorubicin	VIP
		NAVOX	
		Docetaxel-doxorubicin	
		TEC or TAC	
		TOPOX	
		VAD	
		XELOX	

The treatment recommendations are as follows:

- *highly emetogenic chemotherapy:* 3 possible regimens:
  - aprepitant 125 mg + setron (granisetron or ondansetron or palonosetron) + corticosteroids on D1 then continue aprepitant 80 mg and corticosteroids on the following 2 days
  - rolapitant 180 mg + setron (granisetron or ondansetron or palonosetron) + corticosteroids on D1 then continue corticosteroids on the following 2 days
  - NEPA (netupitant 300 mg + palonosetron) + corticosteroids on D1 then continue the corticosteroids on the following 2 days. If this treatment is insufficient, add a benzodiazepine or an anti-D2 during chemotherapy on the following 3 days during the next treatment
- *averagely emetogenic chemotherapy*: combine aprepitant 125 mg with a setron and corticosteroids on D1, then continue aprepitant 80 mg only on D2 and D3. Another possible regimen with rolapitant 180 mg + setron + corticosteroids on D1 only. If this treatment is insufficient, add a benzodiazepine 1 hr before chemotherapy or an anti-D2 in the acute phase, and continue corticosteroid therapy on the 2 days following chemotherapy during the next treatments
- *slightly-emetogenic chemotherapy*: corticosteroid therapy only or anti-D2 on the day of chemotherapy. Addition of a setron to the corticosteroid or a corticosteroid to the anti-D2 if needed as secondary prophylaxis
- *minimally-emetogenic chemotherapy*: no recommended premedication; addition of an anti-D2 in the event of vomiting
- *anticipatory CINV can be treated with Alprazolam*
- *refractory CINV: for a little more than a year it has been possible to offer Olanzapine at minimum dose (5 mg), which has demonstrated excellent efficacy. However, it will be necessary to ensure that this is tolerated well in older patients since it is an antipsychotic.*

Mucitis can be induced by some chemotherapies and radiotherapy. It is a common complication which is often underestimated since it is low grade. It can have serious consequences as it encourages superinfections, and makes malnutrition and dehydration worse, especially in older patients.

There is no cure for mucitis that has demonstrated real efficacy. Preventive measures must therefore be taken. They include good oral hygiene and the use of bicarbonate-based mouthwashes (+/- an antiseptic). Antifungal treatments must not be used preventively, except in special cases. The pain associated with grade III/IV mucitis is severe and requires the use of systemic opiates.

New techniques using local low-intensity laser treatment do however appear to be promising for treating mucitis both preventively and curatively. These techniques are not yet widely available and are still mostly found in hospital environments.

Diarrhoea is a common side effect of some cytotoxic chemotherapies (irinotecan, capecitabine) and targeted therapies (cetuximab, everolimus), as well as of external radiotherapy on organs where the radiation field encircles the digestive tube (rectum, anus, prostate, bladder); symptomatic treatment is the rule after eliminating diarrhoea caused by an infection, especially if the patient has a fever, or after antibiotic treatment (look for diarrhoea with *Clostridium* difficile). There is no particular way to treat diarrhoea in older patients, apart from the need to take greater care to avoid rapid, potentially severe dehydration (difficulty of hydrating older patients via the oral route, less marked feeling of thirst, vomiting, etc.). Treatment consists of using diosmectite, racecadotril, +/- loperamide, combined with an anti-diarrhoea diet and adequate hydration.

Older patients are more prone to constipation, sometimes a side effect of treatment (setrons, level II and III analgesics), which may be made worse due to a reduction in physical activity, poor hydration or unvaried diet. Treatment primarily consists of giving hygiene and dietary advice; osmotic laxatives are recommended as a first-line treatment, but in older patients stimulant laxatives can be useful. With distal constipation, laxative suppositories are recommended.

Anaemia[5]

In older patients, the causes of anaemia are numerous and often interlinked: deficiencies, inflammatory syndrome, bleeding, renal insufficiency. The cancer itself, and chemotherapies in particular, can make patients' anaemia worse, and have a significant impact on their quality of life. The consequences of anaemia in the older population are a public health issue since its onset is

associated with increased risks of cardiac complications, cognitive disorders, as well as falls, hospitalisation, iatrogenic accidents and a doubling of the risk of death. It would appear vital to correct other causes of anaemia than cancer and chemotherapies (in cases of iron deficiency, supplements should be given intravenously). For patients treated with chemotherapy with Hb < 10 g/dL, treatment with EPO should be envisaged. There is no difference between the different EPOs in terms of efficacy and safety of use. The dose used in cancer treatment is stronger than that used in renal insufficiency; there is no particular recommendation for older patients. The target Hb level in cancer treatment is 12 g/dL and the EPO should be stopped once this is reached. The main objective of treatment in older patients is to improve quality of life and prevent, reduce or eliminate the need for blood transfusions.

Febrile neutropenia[6]

The consequences of febrile neutropenia (FN) are considerable since the onset of infections against a background of severe immunodepression leads to increased mortality. Being aged > 65 is the factor most often associated with an increased risk of FN. Malnutrition, being female, a haemoglobin level < 12 g/dL, hepatic or cardiovascular kidney disease are also risk factors of FN. GCS-F should be used systematically if the risk of FN linked to chemotherapy is > 20% or between 10 and 20% in patients presenting with individual risk factors (especially age and a history of FN).

The usual doses to prevent chemo-induced FN are 500 IU/kg/d or 5 µg/kg/d for filgrastim and lenogratsim or 6 mg for pegfilgrastim. The first injection must be no earlier than 24 hours and no later than 72 hours after the end of chemotherapy. The most common adverse effects of G-CSF are bone pain, which can usually be controlled by level 1 analgesics.

Skin toxicity from chemotherapies and targeted therapies[7]

Aseptic folliculitis (skin rash), xeroderma and paronychia represent very common side effects of anti-EGFRs (cetuximab, panitumumab, and tyrosine kinase inhibitors such as erlotinib and gefitinib). Treatment of skin rash

consists of using emollients, local antibiotics and dermocorticosteroids in cases of grade I toxicity; the use of systemic antibiotics (cyclines) is recommended in cases of grade II toxicity; a reduction in dose or temporary discontinuation of the anti-EGFR is the rule in cases of grade III toxicity. This side effect does not last, and will correct itself on discontinuation of the specific treatment; resuming this treatment will not always result in recurrence of skin toxicity.

Hand-foot syndrome is found with sunitinib, sorafenib and docetaxel. The clinical symptoms are erythema, hyperkeratosis, vesicles and blisters, dysaesthesia; the presence of pain classifies the hand-foot syndrome as grade II or III depending on the functional impairment. Treatment consists of administering emollients, healing salves, wearing soft shoes with soles to even out the pressure zones. Grade I toxicity often requires doses of medication to be reduced; grade III toxicity leads to stopping the implicated molecule (temporarily or permanently).

Alopecia is frequently observed during administration of conventional cytotoxic chemotherapies. It is not however one of the side effects of targeted therapies. The efficacy of wearing a cold cap has not been proved, and is very poorly tolerated by patients. Early prescription of a wig for women before their hair starts to fall out is often necessary, and ensures better tolerance.

Note that in older people who already have a weakened scalp and naturally-occurring hair loss, all cancer treatments are likely to increase this phenomenon, with frequent grade I alopecia.

■ Nutritional management[8]

There is a greater risk of malnutrition in older patients with cancer than in younger ones. 30 to 50% of patients suffering from cancer are malnourished. The risk of malnutrition is greater in the older population due to their social situation (isolation, solitude), loss of independence (shopping, meal preparation), dental problems, altered taste and smell, appetite and satiety problems, to the extent that 4 to 10% of older people at home are malnourished, and nearly one in two older people is malnourished when they go into hospital. This malnutrition is likely to get worse throughout the specific

treatments due to the side effects of these treatments (asthenia, mucitis, digestive problems, anorexia, etc.).

The new 2021 SFNCM recommendations propose a new definition of malnutrition in older patients aged over 70 (ref. SFNCM).

Malnutrition in adults aged over 70 is defined by:
- 1 causative criterion from the following list:
  - reduced food intake, by 50% for more than 1 week, or any reduction for more than 2 weeks
  - decreased digestive absorption
  - worsening situations (acute, chronic progressive or malignant progressive pathologies).

Associated with at least one phenotypic criterion for severity from the following list:
- Mild malnutrition:
  - weight loss ≥ 5% and < 10% in 1 month or ≥ 10% and < 15% in 6 months or ≥ 10% and < 15% compared to their usual weight before the illness began
  - 20 ≤ BMI < 22 kg/m^2
  - albuminemia > 30 g/L.
- Severe malnutrition:
  - weight loss ≥ 10% in 1 month or ≥ 15% in 6 months or ≥ 15% compared to their usual weight before the illness began
  - BMI < 20 kg/m^2
  - albuminemia < 30 g/L.

Screening for malnutrition should be performed routinely from the first consultation and during each consultation. This involves weighing, calculating the BMI and weight loss, assessment of ingested food and MNA *(mini nutritional assessment)* (Appendix 2). It should be combined with a standard geriatric assessment (higher functions, comorbidities, mobility and loss of independence, pain, social situation).

Weight loss of more than 5% increases the risk of postoperative complications and toxicity from the chemotherapy and radiotherapy. It also adversely affects quality of life and reduces survival.

Nutritional management includes a personalised consultation with a dietitian which should be routine in cases of malnutrition, or when a treatment likely to promote weight loss is envisaged (radiotherapy or

concomitant chemoradiotherapy in the ENT or upper digestive tract). It must happen when treatment begins, then regularly throughout follow-up. This consultation may result in the prescription of food supplements and/or advice to enrich the diet, adapting the tastes and texture to patients' likes and dislikes and what their food intake options are. Dietary advice must be explained to the person who prepares the meals (patient or carer).

In some cases, artificial feeding is necessary. This can be administered using the enteral route, via a nasogastric tube or gastrostomy tube, or parenteral route, via a central or peripheral line. The enteral route should always be preferred to the parenteral route because it is more efficient, better tolerated and has fewer side effects. Parenteral feeding should preferably be administered via a dedicated central line.

The SFNEP recommendations stipulate that in cases of curative radiotherapy or chemoradiotherapy in the ENT or mouth area, enteral feeding using a gastrostomy tube should be set up routinely at the start of treatment, regardless of the patient's nutritional status. If the oropharyngeal area is not included in the radiation field, a gastrostomy tube for enteral feeding should only be inserted in cases of malnutrition. In the absence of malnutrition at the start of treatment and reduced oral calorie intake during treatment, enteral feeding via a nasogastric tube is recommended.

In cases of curative chemotherapy, artificial feeding has not been studied much. If the patient is not malnourished and their oral intake remains correct, it is not recommended. Conversely, enteral feeding should be preferred in the opposite case. Parenteral feeding is only indicated if the digestive tube is unusable or inaccessible.

In a palliative situation, nutritional support is recommended when the limiting factor is not the tumour growing but the lack of nutrient intake. Starting artificial feeding is not recommended if the patient's life expectancy is less than 3 months and functional impairment is permanent and severe (PS $\geq$ 3).

Appendix 2: *Mini Nutritional Assessment Status*

Answer the first part of the questionnaire by indicating the appropriate score for each question. Add up the points in this part.

Screening

A/ Is the patient experiencing loss of appetite? Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = Severe anorexia
1 = Moderate anorexia
2 = No anorexia
B/ Weight loss during the last 3 months
0 = Weight loss > 3 kg
1 = Does not know
2 = Weight loss between 1 and 3 kg
3 = No weight loss
C/ Mobility
0 = Bed or chair bound
1 = Able to get out of bed/chair but does not go out
2 = Goes out
D/ Acute illness or psychological stress in the past 3 months?
0 = Yes
2 = No
E/ Neuropsychological problems
0 = Severe dementia or depression
1 = Mild dementia or depression
2 = No psychological problems
F/ Body Mass Index (BMI = weight in kg/height in me/(size)^2 in kg/m^2)
0 = BMI < 19
1=19 ≤ BMI < 21
2 = 21 ≤ BMI < 23
3 = BMI ≥ 23
Screening, if the result is 11 or less, fill in the questionnaire to get an accurate assessment of nutritional status.

Global assessment

G/ Does the patient live independently at home?
0 = No 1 = Yes
H/ Do they take more than 3 medications per day
0 = Yes 1 = No

I/ Do they have bedsores or skin wounds?
0 = Yes 1 = No
J/ How many proper meals does the patient have a day?
0 = 1 meal
1 = 2 meals
2 = 3 meals
K/ Do they eat?
- Dairy products at least once a day? Yes/No
- Eggs or vegetables once or twice a week? Yes/No
- Meat, fish or poultry daily? Yes/No

0.0 = if 0 or 1 Yes
0.5 = if 2 Yes
1.0 = if 3 Yes
L/ Do they eat fruit or vegetables at least twice a day?
0 = No 1 = Yes
M/ How much do they drink a day? (water, juice, coffee, tea, milk, wine, beer, etc.)
0.0 = Less than 3 glasses
0.5 = 3 to 5 glasses
1.0 = More than 5 glasses,
N/ Ways of feeding
0 = Needs help
1 = Can feed themselves with difficulty
2 = Can feed themselves without difficulty
O/ Does the patient think that they are well fed? (nutritional problems)
0 = Severe malnutrition
1 = Doesn't know or mild malnutrition
2 = No nutritional problems
P/ Does the patient feel that they are in better or worse health than the majority of people of their age?
0.0 = Worse
0.5 = Does not know
1.0 = As good
2.0 = Better
Q/ Brachial circumference (BC in cm)
0.0 = BC < 21
0.5 = BC ≤ 21 BC ≤ 22
1.0 = BC >22
R/ Calf circumference (CC in cm)
0 = CC < 31 1 = CC ≥ 31
Comprehensive assessment (max. 16 points)
+ Screening score = Total score (max. 30 points)

Assessment of nutritional status
From 17 to 23.5 points risk of malnutrition
Less than 17 points poor nutritional status

■ Treatment of thromboembolic disease

Unfractionated Heparins (UFH) at curative doses

- IV pump: Heparin sodium or SC in 2 or 3 inj°/d: Calciparine 0.1 ml = 2500 U.
- Heparin sodium via IV pump should be preferred as a first-line treatment to heparin calcium SC.
  - Initial dose: 500 IU/kg/d, lower dose if high risk of haemorrhage (300 to 400 IU/kg/d)
  - Routine biological monitoring via anti-FXa (aFXa) UFH activity
- IV pump: 4-6 hrs after start of infusion or dose modification
- SC: mid-way between 2 injections (after at least 2 injections)

- Routine platelet monitoring: 2x/wk for 1 month then 1x/wk until treatment discontinuation
- Target: 0.3 < aFXa UFH < 0.7 IU/ml
- If aFXa < 0.3 IU/ml: + 2000 IU/d
  - If aFXa > 0.7 IU/ml: check that there is no bleeding 1 hr after stopping (or even later depending on the clinical situation), resume with a reduction of at least 2000 IU/d

Low Molecular Weight Heparins (LMWH) at curative doses

- Tinzaparin: 175 IU/kg 1x/d SC
- Enoxaparin: 100 IU/kg 2x/d SC
- Dalteparin: 100 IU/kg 2x/d SC
- Routine biological monitoring (older patient) via LMWH aFXa activity:
  - 4-5 hrs after inj° (LMWH in 1 inj°/d) or 3-4 hrs after inj° (LMWH in 2 inj°/d), after at least 3 inj°
  - variable therapeutic area with LMWH
  - modification of +/- 2,000 IU/d (LMWH in 1 inj°/d) or 1,000 UIX2/d (LMWH in 2 inj°/d).
- Contraindicated if CrCl < 20 ml/min. Tinzaparin or dalteparin can be used with caution if 20 < CrCl < 50 ml/min.
- *VTEs and progressive cancer:* LMWH 6 months minimum for DVTs then discuss the risk-benefit ratio and acceptability, 3 months' treatment for SVTs.

- *Non-routine platelet monitoring*: 2x/wk for 3 wks then 1x/wk until treatment stops; recommended in cases of: surgery or trauma < 3 months, administration of LMWH/UFH < 6 months, comorbidities at risk if onset of HIT.

New recommendations (2021) now permit the use of oral anticoagulants from the time of diagnosis:
- treatment with apixaban1 (Grade 1 +)
- as an alternative, except for digestive or bladder cancer, treatment is proposed with edoxaban2 (Grade 2 +)
- as an alternative, except for digestive or bladder cancer, treatment is proposed with rivaroxaban (Grade 2 +).

In cases of severe renal insufficiency (GFR 15 to 30 mL/min), use LMWH, due to lower efficacy of VKA (Grade 2 +).

■ Pain relief[9,10]

Pain is the symptom most feared by patients and their loved ones. It is more than a symptom when physical pain and mental anguish are linked. In spite of various recommendations issued since those of the WHO in 1986, cancer pain is still underestimated and undertreated. Self-assessment of pain is a priority for older patients, who must remain involved in their own care. If self-assessment is impossible, hetero-assessment tools (for example the Algoplus® scale for acute pain) should be used.

As concerns therapeutic drug management of older patients:

Level 1: non-opioid analgesics. The preference should be for paracetamol rather than NSAIDs or aspirin, because of the risk of gastrointestinal bleeding and the risk of acute renal insufficiency.

Level 2: combines non-opioid analgesics and weak opioid analgesics. Potentiation of the effects of these molecules has an important role in geriatrics.

Level 3: strong opioid analgesics. Strong opioids are not contraindicated in older patients but should be started at lower doses. They should be carefully titrated to arrive at the optimum pain relief with the fewest side effects possible. Constipation problems should be

prevented (a laxative should be prescribed routinely, especially Naloxegol which is specifically indicated in opiate-induced constipation), or treated as soon as they appear to avoid having to stop the treatment suddenly. It is currently available on the French market in a form combining prolonged-release Oxycodone with Naloxone which is a morphine receptor antagonist and can minimise the effect of constipation in particular.

Other treatments

The combination of different approaches (pharmacological and non-pharmacological) appears to be more effective than one or other in isolation. Non-pharmacological approaches include a programme of physical activity, physiotherapy (warm/cold compresses, TENS, ultrasound, massages), occupational therapy. Acupuncture, chiropractic, music therapy, osteopathy and therapeutic touch can also be useful in some older patients and are safe if used appropriately.

■ Psycho-social treatment

Psycho-oncology treatment

Depression is more common but more difficult to detect in older people than in young adults. Cancer, like other somatic diseases which adversely affect the patient's independence, especially dementia (such as Alzheimer's, etc.) or Parkinson's disease, are an added factor for the risk of depression.

The prevalence of major depressive disorder is 5 to 9% in the over-75s. Five to 30% of this population present with sub-clinical symptoms. In the institutionalised population, the prevalence of major depressive disorder is 15 to 20%. There is a high risk of older people with depression going on to commit suicide.

Depression has a pejorative impact on quality of life, increases the risk of loss of independence, impedes recovery from organ damage and increases the risk of death. Coexistence of depressive syndrome and a somatic disease such as cancer is a sign of a poor prognosis in terms of length of treatment and functional recovery.

Specific symptoms of depression linked to older people are irritability, anger, aggression, frequent unexplained symptoms, lack of motivation, boredom, feeling useless, withdrawal, isolation, anxiety, confusion, dependence, memory loss, etc.

The picture of depressive syndrome is often deceptive, as it evolves slowly and is often masked by other symptoms. Sometimes symptoms can be attributed to ageing or comorbidities, which results in under-diagnosis and hence less frequent use of appropriate treatments than in young adults.

Several diagnostic tools have been approved to establish a diagnosis of depression in older people, such as the DSM-IV scale or the geriatric depression scale (Appendix 3). This *Geriatric Depression Scale* (GDS) consists of 30, 15 or 4 items, and has been specially developed and approved for old age. Its sensitivity is 80%, with specificity of 93%.

The most active drugs are tricyclics, serotonin reuptake inhibitors or a mixture. As concerns therapeutic drug management, caution doesn't mean under-treatment, and the effective dose needs to be reached, which is *a priori* identical to that for young adults.

Appendix 3: *Geriatric Depression Scale*

Value of answers	1	0
1. Are you satisfied with your life?	Yes	No
2. Have you given up many of your activities?	Yes	No
3. Do you feel that your life is empty?	Yes	No
4. Do you often get bored?	Yes	No
5. Are you in a good mood most of the time?	No	Yes
6. Are you afraid that something bad will happen to you?	Yes	No
7. Do you feel happy most of the time?	No	Yes
8. Do you often feel helpless?	Yes	No

9. Do you prefer to stay at home, rather than go out and do new things?	Yes	No
10. Do you think your memory is worse than that of other people?	Yes	No
11. Do you think it is marvellous to live in current times?	No	Yes
12. Do you feel worthless nowadays?	Yes	No
13. Do you have a lot of energy?	No	Yes
14. Do you feel your current situation is hopeless?	Yes	No
15. Do you think that others are in a better situation than you?	Yes	No
Calculate the score:_____/15 **Results:** **The normal score is below 5.** **From 5 upwards there is a risk of depression.** **A total of more than 12 suggests severe depression.**		

Social care

This is of prime importance in older patients, and relies on an assessment of medical/financial needs and the patient's level of independence. It should also include an assessment of the needs of carers who are themselves often old and infirm.

Conclusion

The oncogeriatric assessment is vital in order to put in place the best supportive care. This ensures physical and psychological tolerance, and helps maintain social resources in older patients with cancer. During treatment, it is important to preserve the patient's functional independence, by warding off acute complications which could harm their quality of life. Setting up supportive care should be a multidisciplinary effort and involve an identified sector with dedicated staff trained in geriatric oncology. They can provide information, support carers and ensure the older person is supported and able to socialise. Finally, they help prepare the patient's return home and then monitor their family and social life.

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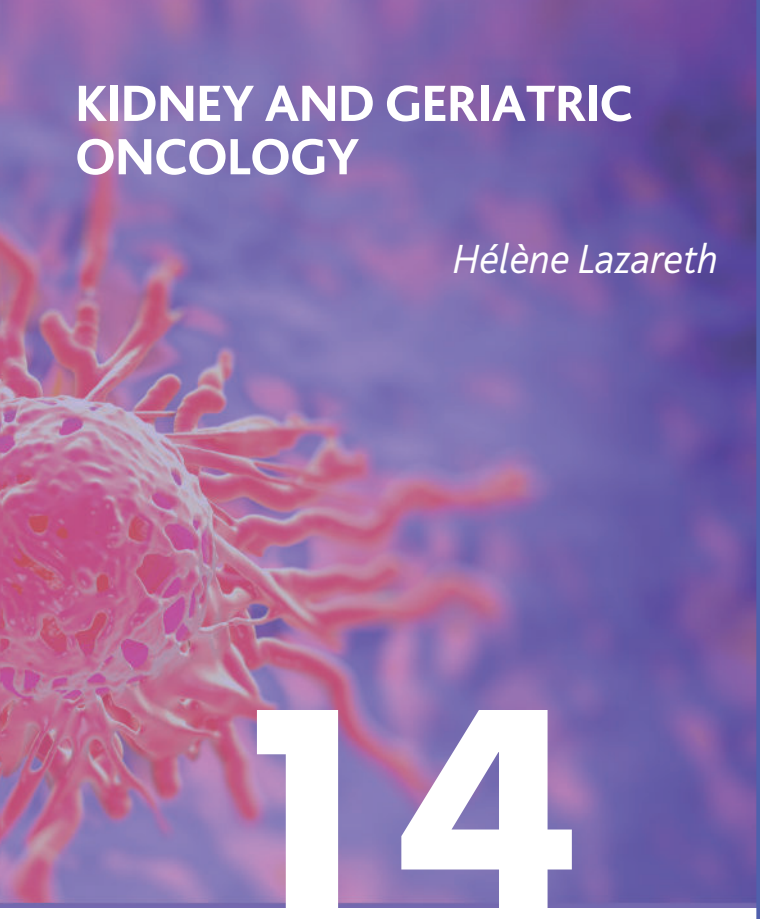
KIDNEY AND GERIATRIC ONCOLOGY

Hélène Lazareth



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Introduction

Geriatric oncology is used to treat increasingly old patients with an increasing number of comorbidities[1,2]. Ageing is characterised by a physiological decline in kidney function[3] and chronic renal failure is a comorbidity frequently found in older patients. It is estimated that almost one older patient in five, treated in oncology, has a glomerular filtration rate (GFR) less than 60 ml/min/m^2 [4].

Moreover, conventional chemotherapies as well as new therapeutic treatments (targeted therapies, immunotherapy) can be associated with multiple renal toxicities[5]. The main renal side effects encountered include: high blood pressure, proteinuria, episodes of acute renal failure, thrombotic microangiopathy, immunological damage or development of chronic renal failure. Onset of renal toxicity may force doctors to suspend a treatment or even contra-indicate it or reduce the dosage, despite its oncological efficacy.

Assessing kidney function is essential throughout the patient's treatment in order to screen early for renal toxicity and allows the patient to be sent to the nephrologist

so they can be offered customised multidisciplinary treatment.

Assessing kidney function

It is essential to assess kidney function at all times when caring for patients in oncogeriatrics: before starting any treatment and before every treatment cycle.

The level of kidney function is an important element in the therapeutic decision and for dose adjustments. The treatments used often involve renal excretion and a narrow therapeutic index[6]. Hence, overestimating kidney function exposes patients to risks of toxicity, whereas underestimating kidney function exposes patients to lack of therapeutic efficacy.

The reference method used to assess kidney function is precise measurement of the glomerular filtration rate by urinary or plasma clearance of a radiolabelled exogenous tracer ([^{99m}Tc]-DTPA, [^{125} I]-iothalamate or [^{51} Cr]-EDTA). Indication of a GFR measurement is posed on a case-by-case basis when a very precise GFR value is needed or the expected precision of estimators is deemed inadequate for the patient's care[7].

Estimating kidney function in older patients often poses problems, as these patients are under-represented in studies aiming to develop equations for estimating the GFR[8]. In addition, formulas for estimating the GFR use creatinine, which varies according to several factors such as muscle mass, which we know varies with age. The Cockcroft and Gault formula, the first equation proposed and developed historically in 1976[9], is still very often used to estimate kidney function in oncology patients, despite its inaccuracy. It should no longer be the preferred option for estimating kidney function. This formula, established on a small, almost exclusively male cohort, uses a dose of serum creatinine calculated using Jaffé's colorimetric method, a method which has since been abandoned and replaced by standard spectrometric tools. The Cockcroft formula has not been re-evaluated since dosage techniques have evolved[7].

The formula for estimating the GFR according to MDRD (modification of diet in renal disease), developed in 1999[10,11], has been validated in patients aged over 65[12,13] and is widely used in oncology[6,14].

More recently, the formula for estimating the GFR according to CKD-EPI (chronic kidney disease epidemiology) has been developed[15]. This has also been approved in patients aged over 65[16]. It is used in oncology, where the non-indexed formula on the body surface appears to be the most reliable[17]. It was recently proposed that ethnicity be removed when calculating the CKD-EPI formula[18]. In a 2021 study, Casal *et al*. showed that omitting ethnicity from the GFR calculation using CKD-EPI reduced the GFR values in Afro-Americans. These patients were therefore exposed to a risk of undertreatment that could affect their prognosis[19]. It was recently proposed that cystatine C be added to creatinine in the CKD-EPI formula for estimating the GFR in older patients[13].

It is important to monitor kidney function closely in patients receiving oncogeriatric care, and repeatedly, in order to detect any kidney disorder early, so they can be treated and their anti-cancer treatments can be adapted.

Conventional chemotherapies

A number of so-called "conventional" chemotherapies are associated with renal toxicity. These are always used in combination with other drugs, which are also potentially nephrotoxic.

- *Platinum salts*

Of all the platinum salts, cisplatine is the most nephrotoxic. It is still widely used to treat ENT, bladder, testicular, ovarian or pulmonary neoplasia[20]. Renal toxicity is dose-dependent and represents the main downside of using cisplatine. in older patients in particular, renal toxicity is one of the main causes of stopping cisplatine and represents 25 to 30% of all interruptions in treatment due to related side effects[21]. It is estimated that the overall incidence of nephrotoxicity from cisplatine is higher in older patients (10.06% *versus* 6.51% in young patients)[22]. The main factors likely to explain this increased risk of nephrotoxicity in older patients are: the existence of chronic renal failure, presence of comorbidities, especially cardio-vascular, the combination of nephrotoxic drugs (such as AINS or IEC/ARA2) or increase of the free fraction of cisplatine (non-albumin bound). Patients

usually have renal failure alone, which has sometimes gone unrecognised. This dose-dependent toxicity causes acute tubular necroses or interstitial nephritis. Reduction of the glomerular filtration rate persists remotely and it is estimated that nearly 30% of patients have impaired kidney function after 2 years of treatment[23]. Hypomagnesemia related to renal magnesium loss is frequently associated (42 to 100% of patients, depending on duration of exposure and the total cumulative dose of cisplatine) and may persist remotely[24].

- *Ifosfamide*

Ifosfamide is an alkylating agent in the oxazaphosphorine family. This molecule is used to treat sarcomas, some lymphomas and ovarian cancers. Its nephrotoxicity is well known in children, of whom approximately 30% will develop chronic renal failure. The main renal symptoms from ifosfamide are: acute renal failure, a Fanconi syndrome or in rare cases distal tubular acidosis or nephrogenic diabetes insipidus. In adults, the use of ifosfamide is accompanied by episodes of acute renal failure (ARF) which may or may not be associated with a Fanconi syndrome. In these patients with ARF, in a retrospective French cohort, it was necessary to resort to dialysis in 17.6% of them[25]. No specific study has yet been conducted in older patients.

- *Antifolates*

Methotrexate is the frontrunner in this family. Renal toxicity only occurs when used in high doses (> 1 g/m^2), especially during treatment of blood diseases. Tubular crystallisation of methotrexate can occur, especially if the urine pH is acid. Preventive alkalinisation of urine combined with the use of folic acid can avoid this toxicity. In rare cases, the use of glucarpidase and resorting to haemodialysis is necessary temporarily. For most patients, the use of folic acid is sufficient and allows renal recovery, without contraindication for readministration of methotrexate[20].

Pemetrexed is a new antifolate used to treat mesotheliomas and some lung cancers. It is contraindicated in cases of serum creatinine clearance < 45 ml/min. Cases of acute tubular necrosis, interstitial nephritis with fibrosis and diabetes insipidus were described with the use

of this molecule. Kidney function is impaired in the long term[26].

• *Gemcitabine*

Gemcitabine is a pyrimidine nucleoside analogue used to treat lung, pancreatic, bladder and breast cancers. Gemcitabine is responsible for dose-dependent renal toxicity. In a set of 29 patients with nephrotoxicity to gemcitabine, all were in acute renal failure and 90% had high blood pressure[27]. Gemcitabine can also cause thrombotic microangiopathy[28].

Anti-angiogenics

The development of anti-angiogenics marked a therapeutic revolution in cancer care and improved patient prognosis. Since the advent of trastuzumab, a humanised antibody targeting HER2, authorised in 1998 for treatment of breast cancer, then imatinib, a multiple tyrosine kinase inhibitor in chronic myeloid leukaemia, authorised in 2001, numerous molecules targeting one or more angiogenesis pathways have been marketed.

Anti-angiogenics targeting VEGF/VEGFR are directed against circulating VEGF (bevacizumab, aflibercept) or against its receptor (sunitinib, sorafenib, pazopanib, axitinib, etc.). This last case involves tyrosine kinase inhibitors, which are usually multiple: they are then called multikinase inhibitors.

The most common renal symptoms caused by anti-angiogenics are proteinuria (sometimes nephrotic) and high blood pressure. The frequency of occurrence varies according to the type of cancer: between 12.9 and 20% of patients had high blood pressure and 15 to 72% of patients developed proteinuria in the MARS study[14]. In the ROSiA international study comparing patients aged over 70 with younger patients receiving bevacizumab, it was demonstrated that the occurrence of grade 3 hypertension was more common in older patients (41% *versus* 22%)[29]. The occurrence of proteinuria is more common in cases of renal neoplasia, especially after uninephrectomy (21 to 63% of patients). With bevacizumab, the level of proteinuria appears to be dose-dependent and its risk of occurrence is increased when combined with other chemotherapies[28]. Renal tolerance of bevacizumab (hypertension, proteinuria) appears to be similar

in older patients compared to younger patients (under 65)[30]. Cases of thrombotic microangiopathy may occur, especially with bevacizumab and aflibercept[31]. Renal progression is favourable in 50% of cases after discontinuation of treatment[32]. Specific glomerular disorders, such as focal and segmental hyalinosis and minimal change kidney disease, were described with tyrosine kinase inhibitors, meaning that the pathophysiological mechanisms underlying the kidney disorder differ between VEGF direct inhibitors and tyrosine kinase inhibitors[33].

Other targeted therapies

Among the multiplicity of other targeted therapies that have been developed, which cause renal toxicity, EGFR pathway inhibitors are worthy of mention. Both cetuximab and panitumumab, monoclonal antibodies targeting EGFR induce hypomagnesemia in almost a third of patients[34].

BRAF inhibitors (vemurafenib, dabrafenib, encorafenib), an MAP kinase pathway oncogene, were developed primarily to treat metastatic melanoma. Their use is associated with the occurrence of reversible acute renal failure such as immunoallergic tubulointerstitial nephropathy, acute tubular necrosis or even Fanconi syndrome[35,36]. PARP inhibitors (olaparib, niraparib, rucaparib) are associated with an elevated serum creatinine level, reversible when discontinued. This is secondary either to an interaction with the tubular transporters of creatinine, or intra-renal haemodynamic phenomena[37].

Immunotherapy

Immunotherapy now occupies a central position in cancer care. It relies on the use of immune checkpoint inhibitors (ICIs). These treatments have revolutionised the prognosis for numerous tumours, especially at a metastatic stage, and they are increasingly widely indicated. The aim of immunotherapy is to restore the anti-tumour immune response in the host. ICIs target CTLA4 molecules on the lymphocyte surface and PD1/PDL1 molecules in the tumour microenvironment.

By inhibiting CTLA4 (ipilimumab, tremelimumab), PD1 (nivolumab, pembrolizumab, pidilizumab) or PDL1 (atezolizumab, durvalumab, avelumab), ICIs are able to

destroy the tumour cell with the T lymphocyte. The main side effects of ICIs are symptoms of autoimmune disease, which can affect all the organs, with variable severity. These are common, around 60 to 85% with variable incidence[38]. Although skin (vitiligo), digestive (colitis) or liver (hepatitis) problems are by far the most common, kidney disorders are still rare, at around 3%. Recent studies have shown higher incidence of nephrotoxicity (around 9.9 to 29%)[39]. The main risk factors of developing kidney disorder from immunotherapy are:
- existence of underlying chronic renal failure
- use of proton pump inhibitors
- combination of two immunotherapies.

The most common type of renal failure is acute tubulointerstitial nephritis (more than 90% of cases), occurring in a median of 14 weeks after introducing the treatment. The rate of proteinuria is low (< 1 g/g) combined with leukocyturia in 50% of cases. The response to corticosteroid therapy is good in 85% of patients with a risk of relapse on restarting treatment of around 25%. Lack of renal recovery after stopping treatment was associated with higher mortality[40]. It appears that older patients are no more likely to present with grade 3 toxicity linked to use of ICIs than younger patients[41]. Some authors have even suggested that ICIs are better tolerated in older patients[42].

Conclusion

Nephrological care of older patients in oncology is more and more commonly needed and more complex, due to the use of innovative therapies with new toxicity, which call their use into question and can jeopardise the oncological survival of patients. Knowing how to assess kidney function repeatedly and screen for kidney disorder, referring the patient to the nephrologist, while being sure to protect the kidneys on a daily basis, is one of the challenges of providing optimum oncological care of patients.

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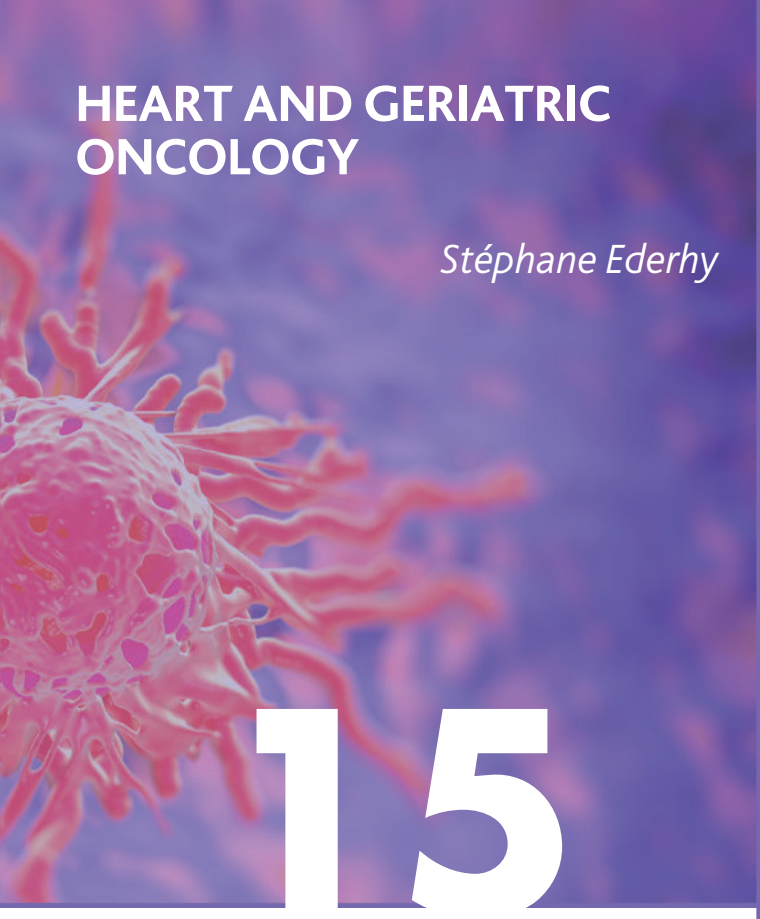
HEART AND GERIATRIC ONCOLOGY

Stéphane Ederhy



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Introduction

Anthracyclines (ATCs), targeted molecular therapies (TMTs), and immunotherapies (IMTs) have transformed the care and prognosis of patients with cancer. Their administration can however be complicated by cardiac toxicity, whose spectrum depends on the molecule administered[1]. The 2 main secondary complications with administration of ATCs are left ventricular systolic dysfunction (LVSD) and acute heart failure (AHF). Targeted therapies can lead to an increased risk of LVSD, AHF, acute coronary syndrome (ACS), high blood pressure and long QT syndrome[1]. Immunotherapies are the source of acute and sometimes fulminant myocarditis, the incidence of which is low (< 1%) but which have a significant risk of being fatal, in an estimated 40 to 50% of cases. Cardiovascular assessment upstream of prescription depends both on the molecule administered and the risk of suspected cardiac complications. Currently the most successful strategy is represented by prevention of risk of acute heart failure linked to administration of ATCs and trastuzumab[1].

Pre-chemotherapy cardiovascular assessment

Initiation of a potentially cardiotoxic treatment must be preceded by a cardiovascular assessment consisting of a list of current treatments, cardiovascular risk factors, questioning to seek out functional signs suggestive of cardiovascular disease (shortness of breath, angina, palpitations, syncope), a physical examination with measurement of heart rate and blood pressure. Performing an electrocardiogram, especially for treatments likely to result in long QT syndrome, should be encouraged[1].

Dosage with troponin and natriuretic peptides (BNP or NT pro BNP) is encouraged by the 2022 ESC guidelines on cardio-oncology and can be offered to patients treated by ATC, ATC and TZM, in order to identify those at risk of developing LVSD or those treated by immunotherapy in the context of early screening for myocarditis[1].

Measuring left ventricular ejection fraction (LVEF) and assessment of myocardial strain parameters (global longitudinal strain) are suggested for early screening of cardiac toxicity in oncology plans containing ATCs or a combination of ATC + TZM[1].

This initial assessment conducted by the oncologist in charge of the patient should be obtained for all patients who could benefit from being administered anthracyclines or targeted molecular therapies[1].

Anthracyclines

Cardiotoxicity secondary to administration of anthracyclines most commonly manifests as LVSD, with or without symptoms. It occurs early on, in the year following administration in 1.6 to 2.1% and can complicate care in 5% of patients after the 1st year. This toxicity is generally dependent on the dose administered, and is deemed to be irreversible in the absence of any prevention strategy.

The aim of preventing cardiotoxicity brought on by anthracyclines is to minimise the risk of LVSD, but without compromising the efficacy of the cancer treatment. This is primarily achieved by early screening for cardiac toxicity by imaging tools (GLS), and/or biomarkers (troponin, natriuretic peptides), before irreversible myocardial damage sets in[2,3].

Dosage with troponin proved its worth in early screening for cardiotoxicity induced by ATCs[2]. Measuring LVEF using echocardiography (2D or 3D when available) and GLS are suggested in early screening for anthracycline-induced cardiac toxicity[2]. When one of these parameters is abnormal, a specialised cardiology consultation is needed to assess, in collaboration with the oncologist, the risk-benefit ratio of administering treatment.

Targeted therapies: trastuzumab

Trastuzumab-induced cardiotoxicity does not appear to depend on the dose administered and is, as a general rule, reversible on discontinuation of treatment or after starting ACE-adapted or beta-blocking cardioprotective treatment[4]. It can potentially manifest itself as LVSD, the incidence of which can vary from 8% if trastuzumab is prescribed as a single-agent therapy, to more than 30% in cases of concomitant administration of anthracyclines[4].

Dosage with troponin was also studied in this context and proved its worth in early detection of *myocardial* lesions, in patients who had benefited from being administered trastuzumab[3]. Monitoring patients treated with TZM is based on regular clinical assessment in combination with measuring LVEF, GLS and dosage with troponin and natriuretic peptides[2]. Assessment of these parameters should be repeated every three months, throughout the duration of treatment. A cardiology consultation is required when an anomaly is noticed, to decide in collaboration with the oncologist after analysis of the risk-benefit ratio, whether to discontinue or continue treatment, under cover of a suitable cardioprotective treatment.

Anti-angiogenics (sunitinib, sorafenib)

Anti-angiogenic targeted molecular therapies, such as sunitinib or sorafenib (VEGF inhibitors/VEGF receptors), may be behind cardiac toxicity that is less well identified and documented[1].

Sunitinib may cause LVSD with generally favourable progression after halting treatment temporarily or permanently, and/or reduction in the dose of the TMT, and starting a suitable treatment for heart failure[1]. The

prevalence of LVSD caused by this treatment varies considerably in the literature, ranging from 2.7% to more than 10%[1].

Elevated troponin was recorded during administration of these therapies in a number of recent studies[3]. But no statistically significant link could be clearly established between this and later occurrence of left ventricular dysfunction or cardiovascular events. Hence, in the absence of robust validated data in the literature concerning its dosage, and by extension to the recommendations applied in the context of administering trastuzumab, only an initial echocardiographic assessment, repeated every three months throughout the duration of therapy (measuring LVEF, GLS), is required in the context of treatment using VEGF inhibitors/VEGF receptors[1]. Additional studies are needed to explain the place of the dose of troponin in this precise context.

Cardiac toxicity of immunotherapies

The main complications and cardiological manifestations associated with the prescription of immunotherapies (IMT) include acute/fulminant myocarditis, complete heart block and pericarditis. Secondary myocarditis from immunotherapies is linked to lymphocytic infiltrate in the heart muscle by activated CD8 lymphocytes[5].

Myocarditis is the main cardiac complication of immunotherapies though its incidence is low, estimated at 0.19% in a review of the literature of all phase III studies, and 0.27% in the pharmaceutical industry's pharmacovigilance databases. Cases of acute myocarditis are usually seen in the first 3 months of administering immunotherapy, produce atypical non-specific symptoms, and can rapidly progress to cardiogenic shock and death in 25 to 50% of cases[5].

Diagnosis relies on early identification of patients, quickly performing an echocardiograph and a cardiac MRI which can highlight an aspect suggestive of myocarditis in the form of subepicardial delayed enhancement. Endomyocardial biopsies still have an important role to play in diagnosing this complication, especially when it has not been possible to establish the definitive diagnosis by the cardiac MRI, and also in serious or corticosteroid-resistant forms[5].

Rapid emergency administration of a corticosteroid bolus as soon as there is clinical suspicion, sometimes in fulminant forms with cardiogenic shock on implementation of circulatory support, constitutes the essential care component[5].

Suspected myocarditis while under IMT then deserves to be mentioned in broad terms if there are non-specific clinical signs (shortness of breath, chest pains, palpitations, faintness, syncope), or signs and symptoms that can immediately cause complicated heart failure *de novo* (acute pulmonary oedema, cardiogenic shock status, haemodynamic instability, atrioventricular conduction disorder, ventricular arrhythmia)[6].

For patients benefiting from routine monitoring (clinical examination, troponin (I or T) and ECG) before and during administration of an IMT, the diagnosis of acute myocarditis must be mentioned in symptomatic patients and also in patients without cardiac symptoms and with elevated troponin (I or T) and/or modifications of the ECG[6].

Regardless of the situation that led to a confirmed or suspected diagnosis, the diagnostic process for a patient suspected of presenting with myocarditis should lead without delay to an ECG and dosing with troponin I or T[6].

Any clinical suspicion of myocarditis under IMT and/or elevated troponin I or T and/or changes on the ECG must lead to rapid hospitalisation in a cardiac unit. Patients presenting with suspected acute myocarditis on the basis of clinical and/or biological data (troponin I or T) and/or ECG must be admitted initially to cardiac intensive care so their haemodynamic status in particular can be closely monitored, as well as any arrhythmia, and action can be taken as quickly as possible in the event of haemodynamic and/or rhythmic deterioration[6].

The diagnosis relies on performing a coronary angiograph, a transthoracic echocardiogram (TTE) with the aim of measuring the LV ejection fraction, analysing the segmental kinetics, suggesting a differential diagnosis (CPA, cardiac metastasis) when performing a cardiac MRI (T1, T2 signal, delayed enhancement) and/or in some cases of endomyocardial biopsy. A myocardial or peripheral skeletal muscle biopsy is often necessary to establish the diagnosis, given the sensitivity and

imperfect specificity of the cardiac MRI in these forms of myocarditis or Takotsubo syndrome[1].

Strategy for assessing at-risk patients before introducing chemotherapy (Figure 1)

The main aim is therefore to be able to differentiate, very quickly and using simple parameters, patients who are able to receive potentially cardiotoxic chemotherapy without a prior cardiologist's opinion from the small majority of patients who ultimately need to be assessed by the cardiologist.

It is then useful to distinguish 3 main clinical situations: the asymptomatic patient with high cardiovascular risk defined by the existence of two cardiovascular risk factors or presenting with cardiovascular history, the patient who has presented with a recent cardiovascular event in the 3 to 6 months preceding administration of chemotherapy, and finally the symptomatic patient.

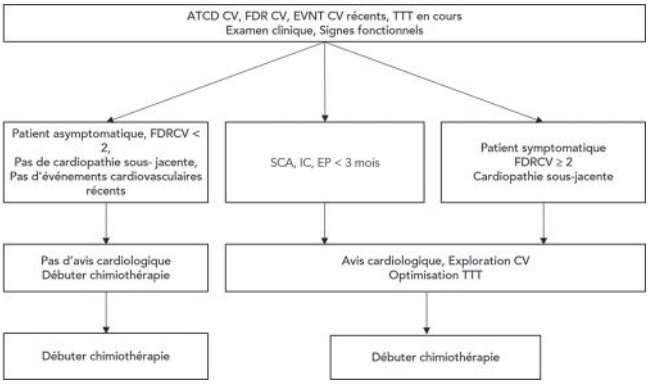

Figure 1: *Cardiovascular assessment before chemotherapy.*

Patient is symptomatic before starting chemotherapy

When a patient presents before administration of chemotherapy (anthracycline or targeted therapies) with symptoms suggestive of cardiovascular disease, such as chest pain, shortness of breath, palpitations, onset of dizziness/syncope, or a change in their ECG (abnormal conduction or repolarisation), the planned chemotherapy cannot be administered straight away and a cardiologist's opinion should be sought.

This is a situation where the cardiologist needs to, within a reasonable period, conduct a full exploration which,

depending on the initial symptom, will always consist of an ECG, an echocardiogram and sometimes a coronary angiograph. Depending on the results of this review, after optimising the medical treatment and controlling symptoms, chemotherapy can usually be started.

Patient has presented with a recent cardiovascular event

There are no specific recommendations for patients who should be contra-indicated before administration of a targeted therapy or defining explorations to be made before administration of a targeted therapy.

Part of the answer to this difficult question is given, both by the inclusion or exclusion criteria of phase III studies that have evaluated the targeted therapies, and by the register published by Schmidinger[7] evaluating cardiovascular complications in a population of unselected at-risk patients who need to receive sunitinib or sorafenib. This study demonstrated that the number of cardiovascular events in an unselected patient population could be as high as 33%. These events are usually reversible on discontinuation of the targeted therapy and are sensitive to cardioprotective medical treatment.

In brief, the main thing to remember is that patients who presented with acute coronary syndrome, an episode of heart failure, or a recent pulmonary embolism were excluded from most of the phase III trials evaluating the targeted therapies. By extension, it seemed prudent to conform to this proposal and wait for such events to be at a distance before introducing a targeted therapy, having taken care to check that patients are once again asymptomatic and that cardioprotective treatment has been started following a cardiologist's opinion.

Patient with high cardiovascular risk

Patients deemed to be "at risk" are defined arbitrarily by the presence of at least 2 authenticated risk factors, underlying heart disease, or have already presented with likely symptoms or documented cardiovascular events[1]. There is no formal contra-indication for prescription of a cardiotoxic molecule. However, this must not happen until after a specialist consultation with a cardiologist and further tests (ECG, troponin dose, TTE with measurement of LVEF and global longitudinal

strain), and starting cardioprotective therapy in some cases.

Conclusion

Conventional chemotherapies and targeted molecular therapies may be at the origin of cardiotoxicity, of which the main manifestation is left ventricular systolic dysfunction, with or without symptoms. This cardiac toxicity has a certain impact on morbidity and mortality of patients needing to receive these treatments. It is therefore necessary to identify it early on, so that cardioprotective treatment can be started quickly in order to prevent its progression. The dose of troponin, LVEF measurement and assessment of global longitudinal strain are the three parameters currently recommended for early detection of this toxicity. A cardiologist's opinion is needed before starting cardiotoxic chemotherapy for symptomatic patients, with high cardiovascular risk or who have experienced a recent cardiovascular event. After obtaining the cardiologist's opinion, starting or optimising cardioprotective treatment, it is usually possible to start chemotherapy under the cover of close monitoring.

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MANAGEMENT OF THROMBOSIS

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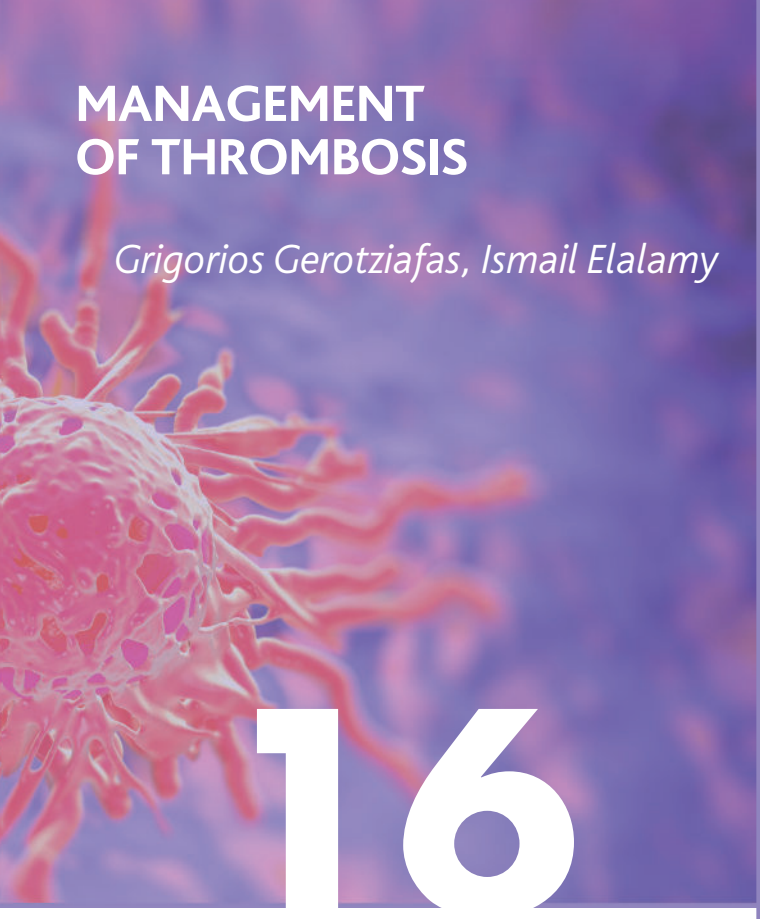

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Introduction

Antithrombotics play an essential role in the prevention and treatment of venous and arterial thromboses, which are frequently encountered in oncology. Of all the cardiovascular diseases, venous thromboembolism (VTE) is still a major health problem, especially when it occurs in patients with cancer. Cancer itself is a major thrombotic risk factor[1]. Thrombosis in patients with cancer is described by the term "cancer-associated thrombosis" (CAT) and represents the second-highest cause of death after cancer itself. The incidence of symptomatic VTE in patients with an active cancer is around 10%, with approximately 544,000 deaths linked to VTE every year in Europe[2-5]. The risk of recurrence of VTE, including when treated correctly with anticoagulants, is 3 to 5 times higher in patients with an active cancer compared patients not suffering from cancer[6,7].

In addition, non-valvular atrial fibrillation (NVAF) is a common comorbidity in patients with cancer. The presence of NVAF may be associated with an occult cancer and a newly-appeared NVAF at the same time as cancer may be an indicator of an advanced stage of cancer[8-10]. A Danish study analysed the incidence of NVAF in a

cohort of 316,040 patients with a cancer identified in a register of the general population containing 4,324,545 individuals. The incidence of NVAF was increased in all cancer sub-types. For all cancers, the incidence of NVAF was 17.4 per 1000 person-years (PY) as opposed to 3.7 per 1000 PY in the general population, and the difference increased with age. The covariate-adjusted IRR for NVAF in all cancers was 1.46 (confidence interval 95%; 1.44-1.48). The strength of the association decreased over time from the cancer diagnosis[11].

Adequate anticoagulation is the cornerstone of CAT treatment. The recommended antithrombotics in prevention and treatment of venous thrombosis and stroke prevention in patients with atrial fibrillation are: low molecular weight heparins (LMWHs) and unfractionated heparins (UFHs), vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs).

However, optimising anticoagulant treatment for patients with CAT is a challenge due to a high risk of haemorrhage, especially in patients with gastro-intestinal (GI) and genito-urinary (GU) cancers in which the primary tumours are intact. The frequent presence of severe chemotherapy-induced thrombocytopenia, lower GI absorption of oral anticoagulants due to vomiting, diarrhoea or mucositis and the potential multiple interactions between DOACs with several drugs, chemotherapy and other treatments form an overarching problem to be taken into consideration.

CAT has a high risk of relapse in spite of anticoagulant treatment. Patients with a malign tumour have a risk of relapse of VTE three times higher than patients without cancer on anticoagulant treatment[12-14]. The frequency of major haemorrhagic complications in patients with cancer receiving anticoagulant treatment is in the order of 10%, or around five times higher than patients without cancer[15]. Renal insufficiency and being aged over 65 are among the most important haemorrhagic risk factors during anticoagulant treatment[16]. Renal insufficiency is very common, especially in patients with solid tumours.

Knowledge of the pharmacological and pharmacokinetic properties of antithrombotic agents and when they should be prescribed are key steps in controlling the risk of haemorrhage associated with their use in oncology.

Definitions of renal insufficiency

Chronic renal insufficiency (CRI) is defined by a permanent decrease in the glomerular filtration rate (GFR) and for its first-line diagnosis. This is done by measuring serum creatinine (SCR) and formulas for estimating renal function such as Cockcroft-Gault's, which takes account of the patient's age, sex and weight, or the abbreviated MDRD formula (aMDRD - *abbreviated Modification of Diet in Renal Disease formula).* A GFR below 60 mL/min/1.73 m^2 signals renal insufficiency, whether or not the reduction in GFR is accompanied by other clinical or biological signs. Renal insufficiency is said to be chronic when it has been present for at least three months and is irreversible. Severe or terminal renal insufficiency is characterised by a GFR below 15 mL/min/1.73 m^2. Table 1 shows the classification of renal insufficiency depending on the stage of severity.

- ***Brief summary of the frequency of renal insufficiency in oncology***

The IRMA-1 and IRMA-2 studies *(Renal Insufficiency and Anticancer Medications)* demonstrated the strong prevalence of chronic renal insufficiency in two populations of almost 5000 adult patients not on dialysis who have solid tumours[17,18]. Few patients had elevated serum creatinine levels (7.2% in both cohorts). Conversely, an appropriate assessment of renal function in these patients using the MDRD formula reported a high prevalence of chronic renal insufficiency; approximately 50% of patients presented with a GFR below 90 mL/min/1.73 m^2 and 12% a GFR below 60 mL/min/1.73 m^2[19].

The BIRMA study *(Belgian Renal Insufficiency and Anticancer Medications)* analysed the prevalence of renal insufficiency in 1218 patients with cancer as well as the profile and dosage of prescribed anticancer medication. According to the MDRD formula, 29.4% presented with a GFR higher than 90 mL/min, 48% a GFR of 89-60 mL/min, 15% a GFR of 59-30 mL per minute, 0.9% a GFR of 29-15 mL and 0.3% below 15 mL/min[20].

This study showed that chemotherapy is the main factor leading to deterioration of renal function; 40% of chemotherapy-naive patients had normal renal function (GFR > 90 mL/min) as opposed to just 25% after chemotherapy. Age was revealed to be the second-most

important factor affecting renal function; approximately 30% of patients aged over 60 had a GFR < 30 mL/min[21].

Table 1: *Definition and stratification of chronic renal disease according to Launay-Vacher V*[36]

Stage	Description	GFR (mL/min/ 1.73 m^2)
High risk	Existence of risk factors for renal disease (diabetes, high blood pressure, family history, older patient, etc.)	≥ 90
1	Signs of kidney disorder (proteinuria, kidney size, etc.) and normal GFR	≥ 90
2	Kidney disorder and "slight" reduction of GFR	60 to 89
3	"Moderate" reduction of GFR	30 to 59
4	Severe reduction of GFR	15 to 29
5	Terminal renal insufficiency (dialysis or transplant needed)	< 15

The prevalence of renal insufficiency was also high in patients with haematological malignancy and more specifically multiple myeloma with a level of 20% on diagnosis and reaching 40% to 50% as the disease progresses[22].

Antithrombotic agents and renal function

- *Vitamin K antagonists*

VKAs inhibit y-carboxylation of vitamin-K dependent coagulation factors (factors II, VII, IX and X) and natural coagulation inhibitors: proteins C and S, leading to production of inactive factors called PIVKA (*Protein induced by vitamin K antagonist*). On initiating treatment, VKAs have a discreet pro-coagulant effect due mainly to the very rapid reduction in protein C, which is a natural coagulation inhibitor with a very short half-life.

VKAs are the primary cause of serious adverse events and the primary cause of hospitalisation for documented adverse events, with approximately 17,000 hospitalisations and 5000 deaths per year[23].

The three main risk factors for haemorrhage in patients on VKAs are:
- alcohol abuse
- a history of gastro-intestinal bleeding
- renal failure[24].

Managing treatment with VKAs is made difficult by a narrow therapeutic window, variable individual sensitivity, numerous metabolic drug-drug interactions (extrinsic vitamin K intake in food, modification of endogenous vitamin K production by intestinal bacteria, alcohol intake). For all these reasons, regular INR monitoring is essential. In an oncological context, the individual variability of the anticoagulant effect combined with possible interactions between the VKA and chemotherapy require close INR monitoring. VKAs are highly bound to plasma proteins, mainly to albumin, are metabolised in the liver and excreted in inactive form in stools and urine. There is no need to adjust the dose in cases of renal insufficiency. Nonetheless, hypoalbuminemia during CRI leads to a higher free fraction and hence a more marked anticoagulant effect in these patients. Although VKAs are catabolised in the liver, renal insufficiency can adversely affect their metabolism by reducing activity of liver enzymes[25]. Hence, patients on VKAs with renal insufficiency may require more frequent INR monitoring to maintain stable anticoagulation in the therapeutic area (INR = 2-3)[26]. Therefore, in patients on VKAs with renal insufficiency, the frequency of adjusting the dose is twice as high as in people with normal renal function. The risk of overdose (INR > 4) and hence the risk of major haemorrhage is four times higher in patients with renal insufficiency and this risk is particularly high in patients with severe renal insufficiency (GFR < 30 mL/min) compared to patients with moderate renal insufficiency (GFR 30-59 mL/min)[27].

• *Heparins*

*Unfractionated heparin*UFH is a very heterogeneous mixture of sulphated polysaccharide chains with a wide variety of molecular weights, extracted from pig intestines. It exerts its anticoagulant activity by binding to

antithrombin (AT) via the pentasaccharide domain, which multiplies by around 10,000 times the inhibitory effect of the AT on thrombin (FIIa) and activated factor X (FXa). UFH has non-specific binding with plasma proteins, some of which neutralise its anticoagulant effect (i.e. platelet factor 4). These bonds are the reason for poor predictability of the anticoagulant effect and as a consequence, the need for close biological monitoring of the level of anti-Xa concentration in the plasma and frequent adjustment of the dose. These procedures are particularly important in patients with renal insufficiency as well as cancer patients.

UFH is essentially metabolised by the reticuloendothelial system and the inactive metabolites are eliminated via the kidneys. The endothelium has a strong affinity for long chains which it fixes, internalises and degrades. Metabolism happens according to a saturable mechanism, involving binding to plasma proteins (vitronectin, a histidine-rich glycoprotein) or to the endothelial cells, with elimination by the reticuloendothelial system then, according to a non-saturable mechanism, via renal clearance, a particularly predominant mechanism in heparin chains with a molecular weight below 5,000 Da.

Apart from the risk of haemorrhage associated with its use, UFH can cause osteopenia and immuno-allergic thrombocytopenia (heparin-induced thrombocytopenia or HIT) due to the presence of antibodies which recognise platelet factor 4 bound to heparin, leading to platelet activation and coagulation, and which may result in venous and/or arterial thromboses. HIT can occur in 1 to 3% of patients on UFH, and heparin must then be discontinued and another immediate-action antithrombotic introduced[28].

Low molecular weight heparins

LMWHs are obtained by the chemical or enzymatic depolymerisation of UFH and are also very heterogeneous mixtures of sulphated polysaccharide chains. LMWHs are characterised by a molecular weight below 8,000 Da (2,000 to 8,000). Each LMWH may therefore appear to be unique, given the variations in its oligosaccharide composition and its different pharmacological properties which are the subject of discussion on LMWH interchangeability and resistance to the potential development of generics or biosimilars.

The bioavailability of LMWHs after subcutaneous injection is higher than 90%. LMWHs present a significantly lower degree of non-specific binding with plasma proteins compared to UFH and thus have predictable and stable anticoagulant activity during the daily therapeutic cycle as well as a decreased risk of heparin-induced thrombocytopenia. Hence there is no need for biological monitoring and dose adjustment, in the majority of patients, in the context of prevention and treatment of VTE and in the context of atrial fibrillation. The pharmacological properties of LMWH make them easier to handle than UFH or VKAs in cancer patients who need to receive anticoagulant treatment.

The anticoagulant activity of LMWHs is determined like that of UFH, by presence of the pentasaccharide structure in approximately 30% of heparin chains. Chains with a molecular weight of 5,400 Da or more can inhibit both thrombin and FXa, whereas chains with a molecular weight below 5,400 Da inhibit FXa.

The half-life of chains which only have anti-Xa activity is around 4 to 8 hours whereas elimination of chains with a molecular weight above 5,400 Da (which therefore have anti-Xa and anti-IIa activity) is significantly faster. These chains therefore have a pharmacokinetic profile similar to UFH and are eliminated by the reticuloendothelial system, whereas chains with a molecular weight below 5,400 Da are eliminated by the kidneys.

LMWHs are characterised by an anti-Xa/anti-IIa activity ratio which is always higher than 1. A lower ratio reflects a higher capacity to inhibit thrombin and is evidence of a larger proportion of material with a molecular weight above 5,400 Da.

LMWHs such as dalteparin and tinzaparin, with an anti-Xa/anti-IIa activity ratio close to 2, can be used in patients with renal insufficiency. The IRIS multicentre study (*Innohep in Renal Insufficiency Study*) conducted in 87 older patients with moderate or severe renal insufficiency treated with tinzaparin at curative doses (175 IU anti-Xa/kg per day subcutaneously for 8 days) did not reveal any significant accumulation of anti-Xa activity[29]. In patients with moderate or severe renal insufficiency who are receiving curative doses of tinzaparin, an empirical reduction in the dose led to a significant decrease in concentration of anti-Xa activity in plasma and,

as a consequence, sub-optimal anticoagulation[30]. Conversely, in patients with renal insufficiency, the use of enoxaparin, which has an anti-Xa/anti-IIa activity ratio at 3.6 is associated with a tendency to accumulation of anti-Xa activity; this contraindicates this treatment in patients with severe renal insufficiency, and calls for close monitoring of plasma anti-Xa activity and dose adjustment in patients with minor or moderate renal insufficiency[31-33].

• *Fondaparinux*

Fondaparinux sodium (molecular weight 1,728 daltons) is the first indirect selective inhibitor of factor Xa obtained by chemical synthesis and thus presenting no risk of biological contamination. The lack of non-specific binding with plasma proteins and especially with PF4 is the reason for predictability of the anticoagulant effect and the lack of risk of HIT during treatment with fondaparinux.

After subcutaneous injection, bioavailability is 100% and elimination is exclusively via the kidneys. Since the half-life of pentasaccharide is longer (17 hours), increases with age and impairs renal function, fondaparinux should not be used in patients with severe CRI. In cases of moderate or minor renal insufficiency, fondaparinux should be used very cautiously with close monitoring of its plasma concentration and dose adjustment so that its plasma concentration remains below 1 µg/mL[34].

• *Direct oral anticoagulants*

DOACs are synthetic molecules with a molecular weight of around 500 daltons which target the active site of serine proteases for coagulation directly and specifically (i.e. factor Xa or thrombin). Their absorption, plasma distribution and anticoagulant activity are independent of diet whereas drug interference is limited. Hence, rivaroxaban and apixaban are selective inhibitors of factor Xa, whereas dabigatran inhibits thrombin. These three antithrombotic agents obtained marketing authorisation (MA) for prevention of thromboembolic events in adult patients who have been operated on for a total hip or knee replacement. Thromboprophylaxis is prescribed for a period of 20 to 35 days depending on circumstances. Moreover, rivaroxaban, apixaban and

dabigatran have an additional indication, in preventing ischaemic strokes in patients with non-valvular atrial fibrillation. Finally, rivaroxaban, apixaban and dabigatran are recommended in treatment of the acute phase and secondary prevention of VTE.

- *Direct inhibitors of factor Xa*

Rivaroxaban

Rivaroxaban is a direct selective inhibitor of free and prothrombinase- and fibrin-bound FXa. Rivaroxaban has a wide therapeutic window, predictable pharmacokinetic and pharmacodynamic properties, and can be administered orally once a day without dose adjustment. Rivaroxaban is available in the form of 10 mg, 15 mg and 20 mg tablets.

After oral administration, the bioavailability of rivaroxaban is 80 to 100% whether or not it is taken with food. The maximum concentration of rivaroxaban in plasma is dose-dependent and is reached 2 hours after oral administration. After it is absorbed in the intestines, rivaroxaban binds itself to the plasma proteins, especially albumin (a reversible process).

Rivaroxaban and its metabolites have two elimination routes: urinary (66% of the total) and the biliary/faecal route. 36% of the administered dose is eliminated unchanged by the kidneys, by glomerular filtration and active secretion.

Clearance and elimination of rivaroxaban occur as follows: 30% of the active drug is eliminated unchanged by the kidneys and 30% is converted into inactive metabolites then eliminated by the kidneys; 30% of the active drug is converted into inactive metabolites then eliminated by the faecal route. Excretion of rivaroxaban takes longer in patients aged over 75. The pharmacokinetic and pharmacodynamic properties of rivaroxaban are not influenced by renal clearance (provided that this is more than 30 mL/minute).

Apixaban

Apixaban is a direct selective inhibitor of active FXa administered orally. Apixaban is available in the form of 2.5 mg and 5 mg tablets. Its bioavailability is 60%. Its maximum plasma concentration is reached 2 to 4 hours

after oral administration. The plasma protein binding rate varies from 87% to 93%. Apixaban does not interact with food and its half-life is 10 to 14 hours. Approximately 25% of the dose administered in humans is excreted in the form of metabolites, the majority being recovered in faeces. Renal excretion of apixaban accounts for approximately 27% of the total clearance. Biliary excretion and direct intestinal excretion have also been observed, in the context of clinical studies and non-clinical studies respectively.

Rivaroxaban and apixaban are substrates of P-glycoprotein, responsible for active transport, and breast cancer resistance protein, responsible for transport of several drugs. Both are metabolised by isoenzymes 3A4/A5, 1A2, 2C8, 2C9, 2C19 and 2J2 of cytochrome P450. These isoenzymes are responsible for elimination of 20% of these drugs. Coadministration of rivaroxaban with CYP3A4 inhibitors or P-glycoprotein leads to an increase in the plasma concentration of rivaroxaban. The recommendations for modifying the dose of rivaroxaban and apixaban as a function of creatinine clearance are presented in Table 2.

- *Selective thrombin inhibitors*

*Dabigatran*Dabigatran etexilate is the prodrug of dabigatran. It is a selective thrombin inhibitor with low bioavailability after oral administration (approximately 7%). Food does not modify the drug's anticoagulant activity. Dabigatran etexilate is available in the form of 75 mg, 110 mg and 150 mg capsules. Approximately 35% of dabigatran is bound to plasma proteins. The maximum plasma concentration is reached 2 to 4 hours after taking it. Elimination via the kidneys represents 80% of the drug's clearance. Its half-life is 6 to 10 hrs for the 1st dose and 12 to 17 hrs after taking several doses. The pharmacokinetic properties of dabigatran allow the drug to be administered twice a day.

A lower dose is recommended if the patient is taking amiodarone. The drug is contraindicated if the patient is taking quinidine. The most common adverse effect of dabigatran is indigestion and symptoms such as gastritis.

Table 2: *Dose adjustment of LMWHs used in oncology according to renal function.*

	Dalteparin		Enoxaparin		Tinzaparin	
	Curative dose	Preventive dose	Curative dose	Preventive dose	Curative dose	Preventive dose
GFR (mL/ min/ 1.73 m^2)	(150-200 anti-Xa IU/kg s.c.o.d.)	(5,000 anti-Xa IU s.c.o.d.)	(100 anti-Xa IU/kg x 2 s.c. or 150 anti-Xa IU/kg o.d.s.c.)	(4,000 anti-Xa IU o.d.s.c.)	(175 anti-Xa IU s.c.o.d.)	(4,500 anti-Xa IU/kg s.c.o.d.)
30 to 59	no dose adjustment	no dose adjustment	no dose adjustment	no dose adjustment	no dose adjustment	no dose adjustment
15 to 29	monitoring of anti-Xa activity 4 hrs after s.c. injection	monitoring of anti-Xa activity	monitoring of anti-Xa activity	monitoring of anti-Xa activity	monitoring of anti-Xa activity	no dose adjustment
< 15	contraindicated	contraindicated	contraindicated	contraindicated	monitoring of anti-Xa activity	monitoring of anti-Xa activity

Table 3: *Dose adjustment of DOACs used in patients with NVAF and depending on renal function.*

GFR (mL/min/1.73 m^2)	Apixaban (5 mg x 2/d p.o.)	Rivaroxaban (20 mg x 1/d p.o.)	Dabigatran (150 mg x 2/d p.o. or 110 x 2/d p.o. 150 mg per os twice/day)
> 50	no dose adjustment	no dose adjustment	no dose adjustment
15-50	2.5 mg x 2/d p.o.	dose reduced to 15 mg/d p.o.	75 mg x 2/d p.o.
< 15	contraindicated	contraindicated	contraindicated

DOACs do not appear to pose any particular danger in patients with stage I-II renal insufficiency without the need to adjust the dose. Monitoring renal function is recommended at least once a year or sooner if factors likely to impair it are present (i.e. infections, hypovolaemia, dehydration, decompensation or acute heart failure, etc.). A lower dose (110 or 75 mg BID for dabigatran; 15 mg QD for rivaroxaban and 2.5 mg BID for apixaban) is recommended in patients with moderate renal insufficiency (CrCl 30-50 mL/min). In this case, monitoring renal function is recommended every six months or whenever renal function appears to have worsened. Older patients with low body weight are particularly exposed to a risk of haemorrhage associated with treatment with DOACs, especially dabigatran. DOACs are contraindicated in cases of creatinine clearance below 15 mL/min (Table 3).

New data on the place of DOACs in patients with renal insufficiency

In a recent meta-analysis, which consisted of five randomised controlled trials comparing DOACs with VKAs (ARISTOTLE, ENGAGE AF-TIMI 48, RELY, ROCKET AF, J-ROCKET AF), the sub-group of patients with CRI was analysed. This analysis looked at 12,155 patients with stage 3 CRI (CrCl 30 to 50 mL/min) and 390 patients with stage 4 CRI (CrCl 15 to 30 mL/min). It was observed that treatment with DOACs slightly reduced the number of strokes and systemic embolisms compared to warfarin, both in patients with stage 3 CRI (relative risk (RR) 0.82, confidence interval (CI) 95%: 0.66-1.02) and with stage 4 CRI (RR 0.68, CI 95%: 0.23 to 2.00). DOACs have reduced the number of major haemorrhages compared to warfarin in patients with stage 4 CRI (RR 0.30, CI 95%: 0.11-0.80). In addition, DOACs appeared to reduce the number of intracranial haemorrhages compared to warfarin in the total population of patients with CRI (RR 0.43, CI 95%: 0.27 to 0.69). However, they did lead to a slightly higher number of gastro-intestinal bleeding (RR 1.40, CI 95%: 0.97 to 2.01)[35]. In patients treated with apixaban, the risk of major haemorrhage showed a trend towards lower rates of major haemorrhage compared to those whose CrCl > 30 mL/min ($p = 0.8$) and clinically relevant major or non-major haemorrhage (interaction $p = 0,05$)[36]. Analysis of a mega-database covering 221 million people in France, Germany, the United

Kingdom and United States showed that in 527,226 new patients treated with apixaban, dabigatran, edoxaban or rivaroxaban the efficacy of all 4 DOACs was similar. Conversely, administration of apixaban was associated with a significantly lower risk of gastro-intestinal bleeding compared to treatment with dabigatran (RR, 0.81; CI 95%: 0.70 to 0.94), or edoxaban (RR, 0.77; CI 95%: 0.66-0.91), or rivaroxaban (RR, 0.72; CI: 0.66-0.79). The results were similar for older patients (aged > 80) and patients with chronic renal insufficiency[37].

A "network meta-analysis" conducted on all phase III trials studied the efficacy and tolerance of administration of VKAs, DOACs (apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban), LMWHs or aspirin in primary prevention of VTE, treatment of the acute phase and prolonged treatment of VTE in patients with chronic renal insufficiency, showed that treatment with VKAs appeared to be the most effective choice and was better tolerated during the acute phase of the VTE. Aspirin showed the best risk-benefit ratio in prolonged treatment of VTE, followed by apixaban, and betrixaban in prophylaxis for VTE, followed by enoxaparin[38].

In an industry-funded retrospective study, the researchers used a national database (covering 2014-2018) and an analysis adjusted by propensity score to compare the results of 11,500 patients with CRI and newly - diagnosed VTE who have received either apixaban or warfarin. Only 2% of patients received apixaban in 2014, but 47% received apixaban in 2018. Over the 6 months after treatment initiation, apixaban - compared to warfarin - was associated with a significantly lower incidence of major bleeding (10% as opposed to 14%), especially intracranial bleeding (1.8% as opposed to 2.5%) and gastro-intestinal bleeding (8.6% as opposed to 10.4%). Recurrent TEV and mortality from all causes were similar in both groups[39].

The place of direct oral anticoagulants in patients with renal insufficiency on dialysis

Currently there are no randomised clinical trials on the efficacy and tolerance of anticoagulant treatment and more specifically DOACs in prevention of thromboembolic episodes in patients being treated with haemodialysis. In the absence of solid clinical data, registers and observational studies were analysed in a recent review

of the literature[40]. This analysis concluded that the overall efficacy and tolerance of treatment with VKAs in preventing strokes in patients with NVAF being treated with haemodialysis are not confirmed.

Treatment with DOACs could be an effective alternative that is well tolerated in this group of patients. The major phase III studies which established DOACs as a first-line treatment in prevention of thromboembolic episodes excluded patients with renal insufficiency on dialysis. Nonetheless, the US *Food and Drug Administration* (FDA) approved the use of apixaban in patients whose eGFR is below 15 mL/min/1.73 m^2. In a retrospective analysis conducted on 25,523 patients with severe renal insufficiency and NVAF on dialysis, of whom 2,351 patients were on apixaban and 23,172 patients on warfarin, Siontis *et al.* found no significant difference in terms of risk of stroke between the two groups. In addition, this study showed a reduction in the risk of major bleeding as well as decreased mortality in patients who had received treatment with apixaban. Of course, the retrospective nature of this study is a major limitation which means its results cannot be applied widely. However, a retrospective analysis of the records of patients with NVAF being treated with rivaroxaban or dabigatran receiving haemodialysis for renal insufficiency also revealed encouraging results for the efficacy of DOACs, not ignoring the risk of haemorrhage[41].

Conclusion

In oncology like in geriatric oncology, anticoagulant treatment is a real challenge as the delicate balance between the risk of thrombosis and the risk of haemorrhage is influenced by the cancer's growth and side effects linked to the cancer treatments. In this context, the presence of a CRI is a risk factor for major haemorrhage.

Renal function has a direct effect on clearance of antithrombotic agents and DOACs in particular, and can indirectly influence the pharmacodynamic properties of VKAs. Conversely, it does not induce significant pharmacokinetic and pharmacodynamic deterioration of the polysaccharide chains present in UFH nor on chains with a higher molecular weight present in LMWHs.

LMWHs with a low anti-Xa/anti-IIa ratio are the antithrombotic agents least influenced by renal function and

have the advantage of offering stable and predictable anticoagulation.

Although the majority of direct-acting oral anticoagulants (DOACs) cannot be used in patients whose creatinine clearance is below 30 ml/minute, apixaban at a dose of 2.5 mg twice a day is permitted even in patients with end-stage renal disease (ESRD) due to its primarily hepatic clearance. Nonetheless, the clinical data is currently insufficient for widespread use of apixaban in this context.

The dose of apixaban, rivaroxaban or dabigatran when prescribed for NVAF needs to be adjusted if the GFR is below 50 mL/min/1.73 m^2, whereas these antithrombotic agents are contraindicated if the GFR is below 15 mL/min/1.73 m^2. During treatment with DOACs, particular vigilance must be afforded to drugs likely to reduce their renal elimination such as chemotherapy, diuretics, non-steroidal anti-inflammatory drugs, converting enzyme inhibitors, frequently associated with DOACs in clinical practice.

For cancer patients with CRI, the use of antithrombotic treatment must be cautious and justified, and the choice of drug and dosage need to be adjusted on an individual scale, taking the patient's overall bleeding pattern into account.

DOACs appear to be just as effective as warfarin in preventing stroke and systemic embolism, without increasing or decreasing the risk of major haemorrhage in patients suffering from NVAF and CRI[42].

In the specific context of patients with CRI on haemodialysis, anticoagulant treatment is a challenge. In this group of patients, DOACs have not been tested in randomised trials and are not recommended as an antithrombotic strategy. The specific pharmacokinetic properties of DOACs can make them potentially-applicable therapeutic alternatives in patients who do not present with additional risk factors for haemorrhage. Ongoing randomised trials in patients on haemodialysis with NVAF could provide new evidence in this patient population.

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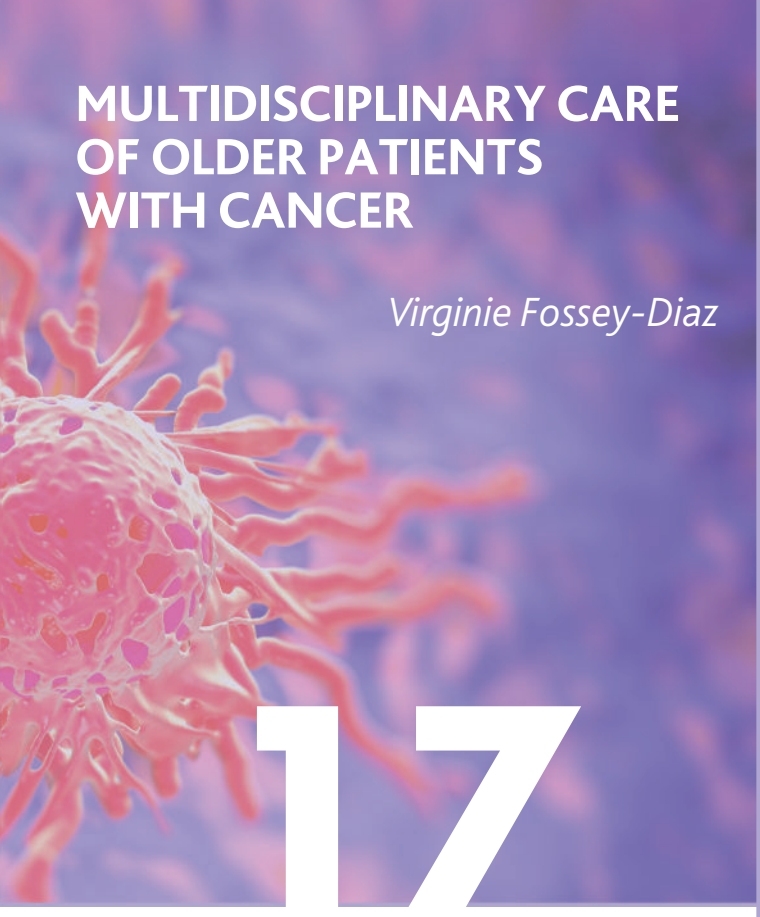
MULTIDISCIPLINARY CARE OF OLDER PATIENTS WITH CANCER

Virginie Fossey-Diaz



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Definition and context

Any patient, regardless of age, is starting on a difficult journey when they receive a cancer diagnosis and learn about the proposed care.

Such an announcement has a significant impact and requires prompt and coordinated multidisciplinary care, affecting the lives of both the older patient and their friends and family.

Aims

Multidisciplinary care can improve patients' quality of life, treatment compliance, determine the needs of the patient and carers (family, friends, professional carers). This care starts immediately after formal diagnosis and lasts until death.

Method

- clear diagnostic message, patient pathway mapped out as far as possible, role of the diagnosing and coordination RNs
- proposed treatment explained with support from the care team

- oncogeriatric assessment to uncover patient frailty factors and put in place, with the referring physician, the necessary aids for optimised care and propose the most suitable treatment for the patient
- breakdown of needs and organisation of care following patient assessment
- clear communication with all partners
- rapid contacting of the palliative care and supportive care teams, and pain relief team if necessary
- support throughout the care programme.

Partners

• *The patient*

They must:
- be aware of their diagnosis
- be able to take decisions about their care for as long as possible (role of the trusted person in geriatrics; care should be taken with patients under legal protection, the opinion of the legal representative may be needed)
- understand the proposed treatment
- accept their treatment
- name a trusted person
- write a living will.

• *Family and carers*

Good practice demands that they:
- have been made aware of the diagnosis
- are aware of the treatments and proposed care plan
- must know their limits
- must have people around them to whom they can appeal (attending physician, oncologist, home care nursing services, other family member, etc.)
- must not make decisions on the patient's behalf.

• *Professional carers (doctors, paramedics): from formal diagnosis to death*

- strong role of nurse coordinators
- all patient records must be studied and discussed in multidisciplinary team meetings (MDTMs) to reach a collective decision, depending on the guidelines and the patient's general health
- screen for social vulnerability with prompt interventions by hospital social services, links with the local authority (CLIC, MAIA, etc.)

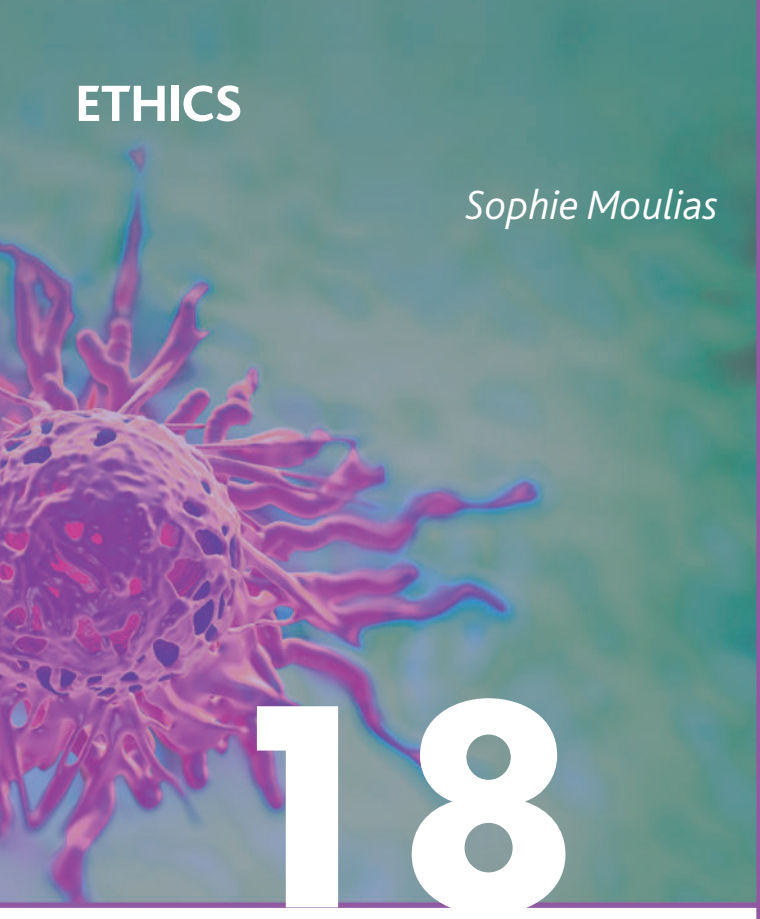
- support from palliative care teams and supportive care teams
- it is important to introduce appropriate assistance following oncogeriatric assessment: use of home care nursing services, Hospital at Home, health networks, palliative care networks, etc. in order to meet their needs, adapt the home (occupational therapist), so they can continue to live independently (physical therapy, psychomotor therapist, etc.), avoid malnutrition (nutrition networks, dietician, etc.), psychological support
- major role of follow-up in consultation by the geriatric oncologist or nurse coordinator/APN
- possibility of consulting organ specialists in the event of complications/failure due to comorbidities.

Conclusion

Care relies on communication and transmission of information. It is the result of working as a group, not as a collection of individuals, with a common goal to put together a care package.

ETHICS

Sophie Moulias



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Screening for cancer and the therapeutic approach to older patients with cancer require considerable ethical discussion. Some of this concerns access to care: cancer care, which is sometimes refused due to the patient's age; geriatric care, which is sometimes missing in the local sector, as is palliative care. Estimating the risk-benefit ratio is also one of the cornerstones of choice of treatment, which cannot happen outside a MDTM, the same as for any patient. At the same time, there are questions concerning patient rights.

The patient must be kept informed of their health status and the treatment they will receive. They have the right to refuse this information (right not to know), but it is the duty of the professionals to inform them, irrespective of their age, cognitive status and their legal status. Before care can be administered, the patient must give their consent, even if they are a ward of court. In the event of a breakdown in alertness or onset of somatic or psychological weakness, the patient must be able to be represented by legal methods to strengthen their independence, these being the trusted person and the living will.

However, nowadays, in services caring for older patients with cancer, too few patients take up their rights, which

is bad for patients but also for the professionals, who cannot access the patient's wishes at crucial times.

The patient's wishes

It is not always easy to know what the patient wants. They often having difficulty knowing and expressing this. Even when a patient with cancer has all their faculties, and is therefore able to make their own decisions, it is sometimes difficult for them to look into their own future, so strong is the bond of hope with those who care for them. The patient will then willingly put the doctor's suggestions ahead of their own wishes ("you know best, Doctor").

Some patients have no problem in expressing their values. For others, it is a lot more complex to access them, especially when the patient presents with cognitive disorders. Memory problems often mean that the patient consents to a treatment, surgical procedure or series of chemotherapy sessions, for example; but when the day of treatment arrives, they no longer remember and refuse. In most cases, this refusal is withdrawn if the patient is given the information again, ideally by an intermediary known to them.

The trusted person

One of the supports that can help the patient and practitioner during treatment is the trusted person. In France, the legal concept of a trusted person dates from the law of 4 March 2002, relating to patient rights and quality of the care system. It allows patients being treated in institutional care (hospitals, clinics, home care, nursing homes) to designate a person of their choice, named as a trusted person. This person will be able to accompany the patient when they see the doctor or care team and to receive medical information with them. There is a breach of medical confidentiality vis-a-vis the trusted person, although only a partial breach, as the doctor is not obliged to tell the patient's whole life story! Moreover, if the patient is no longer capable of speech, due to being in a coma or having a neurological disease for example, the first person the doctor should consult to ask the patient's opinion is the trusted person. Institutions are obliged to suggest that patients designate someone. The legal concept of trusted person allows the patient to assert their rights, even after they have lost the

power of speech. It also makes the patient less vulnerable in the face of the medical decision. It means the practitioner has someone to talk to despite not being able to communicate with the patient. The trusted person can of course only fulfil their role properly if informed that they have been nominated and about their role.

The role of trusted person is particularly useful for chronic diseases, especially in oncology. It is clearly an asset for the patient, as well as for the doctor. Patients can also appoint a trusted person in the community and inform the hospital of this appointment. The patient can change trusted person as often as they wish.

Since the law of 2 February 2016, creating new rights for patients and people at the end of life, the appointment of the trusted person must be jointly signed by the appointed trusted person, if possible.

Living wills

Another way for our patients to have their say if they should end up in a coma or experience neurological disorders, is to draw up a living will. It is now strongly recommended that patients should do so. Any adult can draw up a living will, in the event that they may be one day unable to express their wishes. These living wills allow the patient to express their wishes for their end-of-life care as concerns situations in which medical treatment or procedures will be continued, restricted, discontinued or refused.

These directives are drawn up in writing, dated and signed, and are valid until a new instruction is given. They can be revised and revoked at any time and by any means. They can be drawn up on the basis of a template whose content has been established by a decree of the Council of State, after an opinion by the French Health Authority. This template allows for the person's situation depending on whether or not they know they have a serious condition at the time of writing the directives. It is drawn up alone or with two witnesses, possibly the trusted person, if the patient is unable to write.

It is the doctor's responsibility to find out whether a living will exists, consult it and abide by it. Doctors must comply with the living will when taking any decisions concerning investigation, intervention or treatment, except in a life-threatening emergency, while a

comprehensive assessment of the situation is carried out. When living wills appear to be manifestly inappropriate or inconsistent with the medical situation, the doctor can decide not to comply with it. This decision is taken after a peer review procedure defined by legislation. It is recorded in the medical records. It is brought to the attention of the trusted person appointed by the patient or, failing this, by the family or next of kin.

The attending physician must inform their patients of the possibility and conditions of drawing up a living will.

If someone is a ward of court, as defined in Chapter II of Title XI of Book I of the French Civil Code, they can draw up a living will with consent from the judge or family council if one has been formed. Their guardian can neither assist them nor represent them on this occasion. They can also designate their trusted person, who will be confirmed by the guardianship judge as part of their mission.

These directives can be kept at the patient's home, or at the offices of their doctor, notary or lawyer. They should ideally be rapidly accessible if the patient requires hospitalisation. A national register is being envisaged but is not yet active.

If the patient is conscious, they remain the primary person the practitioner will speak to, ahead of their trusted person, their living will and next of kin.

The option for a patient to designate their trusted person and draw up their living will is one of the rare opportunities for them to assert their rights. The fact remains that few caregivers and even fewer patients are informed of this.

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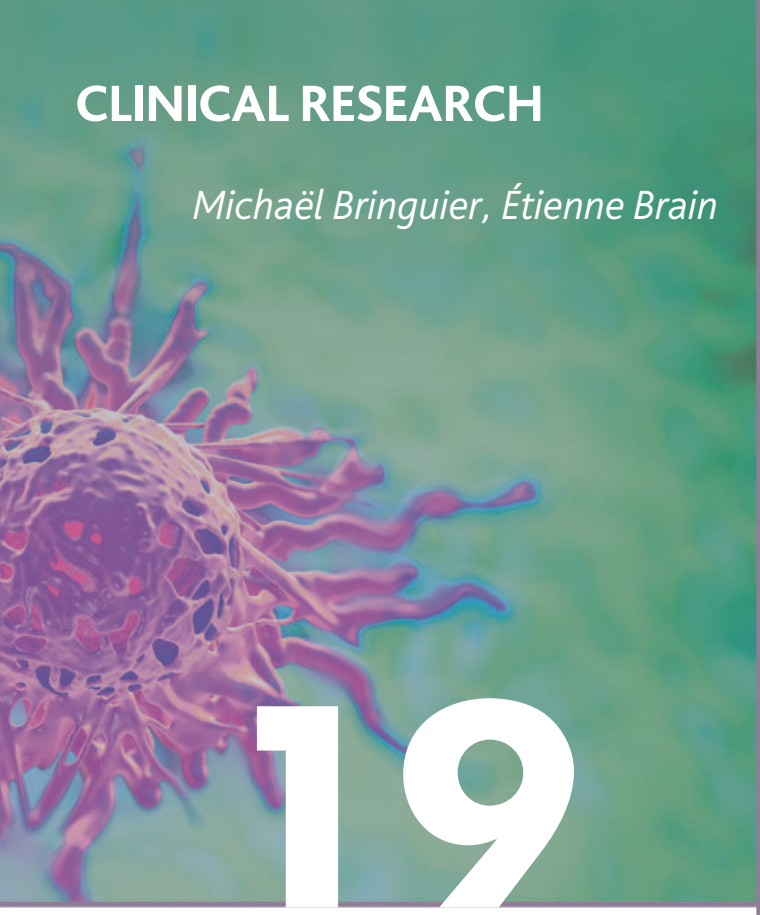
CLINICAL RESEARCH

Michaël Bringuier, Étienne Brain



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This chapter summarises the specific recommendations for older patients in the DIALOG geriatric oncology clinical research intergroup [which combines the GERICO/Unicancer and Oncogeriatric coordination Units (UCOGs) under the aegis of SoFOG] approved by the national body (INCa) since 2014, the International Society of Geriatric Oncology (SIOG) and the European Organisation for Research and Treatment of Cancer (EORTC).

Standard clinical research (clinical trials) conducted in oncology in adult patients often includes an older population, but this is limited or selected, whereas clinical research specific to the older population is rare. In fact programmes assessing the various innovative anti-cancer diagnostic and therapeutic strategies are still mainly conducted in younger patient populations before their conclusions are applied to older patients by extrapolation, usually without much-needed adaptations. According to a brief summary on ClinicalTrials.gov, out of almost 9000 therapeutic trials currently open worldwide in cancer treatment, barely 3% are specifically aimed at an older patient population.

Several types of research programme covering the older population have been identified in the literature:
- specific trials conducted on older patients, often rare, sometimes difficult to bring to completion
- trials conducted in adults without an age limit, but where the older population included is usually very selective and rarely representative of the standard older population
- epidemiological research conducted from databases, cohorts and registers.

This acknowledgement of a relative lack of data is accentuated by a much lower number of older patients included in clinical trials than in the younger adult population, without any measure of their representation in the general population. This underlines the importance of and need for clinical research specific to this increasingly older population, in order to be able to meet the universal demographic challenge. Successive Cancer Plans have therefore made it one of their aims, even though the 2021-2030 ten-year strategy to tackle cancers focuses more on a certain equity of access to care without stressing age.

As life challenges may differ according to age (older population more often focused on "quantity of quality life" and maintaining satisfactory functional independence than on "quantity of life"), they justify a special clinical research methodology "beyond a certain age" with several orientations, questions and themes.

1. Systematic identification of **geriatric parameters** in the various research programmes involving the older population, then integration of these parameters in multifactorial models: predictive of toxicity for example such as CARG and CRASH scores for chemotherapy, or prognostic models with several scales approximating life expectancy in the context of adjuvants (life expectancy of 4 years) or metastases (life expectancy of 1 year).

2. Repositioning of innovative oncology strategies according to **life expectancy**: numerous scales are available and may correspond to questions in the context of adjuvants (life expectancy of 4 years) or metastases (life expectancy of 1 year). This can demonstrate the value of this information to at-risk clinical care.

3. **Judgement criteria**: choice of a geriatric criterion as the main criterion for judging a clinical trial, such as

functional status (ADL, IADL for example) rather than the standard oncological criteria such as response rate, recurrence-free survival or progression-free survival; or use of co-criteria or composite judgement criteria (progression-free survival + feasibility of ADL, tumour response + minimal feasibility of treatment, quality of life/preference + recurrence-free survival, discontinuation rate of the treatment studied reflecting efficacy and tolerance, etc.). The work done by the GERICO group illustrates this strategy very well.

4. Studies of **geriatric interventions**, assessing the usefulness of targeted interventions (physical therapy, nutritional support, etc.) in terms of the cancer prognosis, feasibility of treatment, morbidity/mortality, etc. Several recent major phase III studies thus demonstrated the superiority of a strategy guided by the geriatric assessment *vs* the standard approach on severe side effects, quality of life, functionality and chances of successfully completing treatment. Demonstration of the generally positive impact of the geriatric assessment on the cancer prognosis still remains to be seen, as in the current PREPARE phase III trial, but an encouraging indirect response has already been given by the lack of unfavourable impact on the prognosis of an often lesser intensity of treatment in cases of geriatric guidance, with better tolerance and quality of life.

5. Breaking the older population down into different groups (reflecting the molecular breakdown of tumour pathologies) to adjust the tested strategies, with **stratified trials on the geriatric assessment**: integration of fit patients in programmes for adult patients without an age limit, trial design centred around vulnerable (reversible risk situation) or frail (non-reversible risk situation) populations such as the ELAN/ONCOVAL programmes developed by GORTEC and the GERICO group in head and neck oncology.

6. **De-escalation** or cautious escalation strategies: by making the best use of targeted therapies or by starting at lower doses than those approved in young or fit patients, with the assistance of pharmacokinetic data and the functional reserves approach respectively.

7. Development of tools to **screen** for geriatric problems in order to rationalise management of the standardised and/or in-depth geriatric assessment and access to it:

the Oncodage programme and the G8 tool are the best illustration of this research component.

8. **Ethical** angle: areas of acceptability and preference; situations with advanced cognitive disorders (Alzheimer's disease).

9. Research on registers/cohorts or real world data (RWD): conducted on people in several thousand dossiers; this can sometimes reflect reality more closely than clinical trials, emphasising over- and under-treatment. The Surveillance, Epidemiology, and End Results (SEER) programme in the United States is thus an important source of epidemiological data on this population, like Unicancer's Epidemio-Strategy-Medico-Economic (ESME) database. Cohort initiatives more focused on the older population do exist, with potential detection of geriatric issues, such as the Ile-de-France cohort ELCAPA. It is however clear that this research on real-life data is no substitute for prospective clinical trials, with randomisation if applicable, because the selection of treatments in real-life data is strongly influenced by the patients' characteristics, with significant impact on the results. Multivariate regression analyses or propensity scores do not totally eliminate this risk of bias.

10. Translational research exploring the links between carcinogenesis and ageing, between cancer treatments and ageing, with 5 main themes: variations in tumour biology according to age, senescence and epigenetics (including telomeres and methylome), cognition, inflammaging and metabolism (polar and lipid metabolites).

11. Pharmaco-economic aspect: this is essential in the context of costly innovation to prove its worth: organised de-escalation of some unnecessary treatments and correction of some severe prognoses.

Finally, given that expansion of clinical research is one of the UCOGs' 4 key missions, international collaboration is essential when strategic questions asked require significant numbers of staff and/or supporting action by European regulatory bodies, such as the European Medicines Agency (EMA). Cooperative groups such the Older Adults Council of the EORTC and SIOG are therefore essential to supporting and leading this action.

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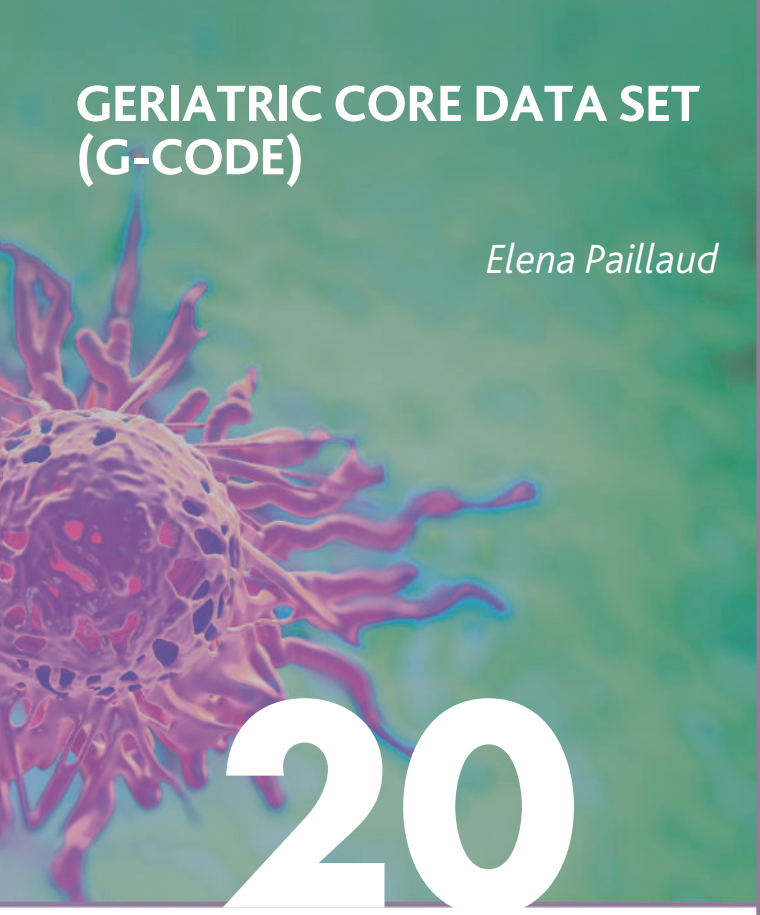
GERIATRIC CORE DATA SET (G-CODE)

Elena Paillaud



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Introduction

The G-CODE is a geriatric minimum data set for use in clinical research that is able to describe the older population with cancer and make the collection of geriatric data in therapeutic trials more uniform. This minimum data set was constructed by French expert geriatricians and oncologists from the DIALOG intergroup according to a consensus method such as DELPHI which is modified, then validated at national level and then international level by two successive groups including oncologists, geriatricians, clinical research technicians and nurses according to a modified RAND acquisition method. The G-CODE consists of 2 questions assessing the social environment, basic activities of daily living (6-ADL) and instrumental activities of daily living (4-IADL) for independence, the Timed Get Up and Go test, unintended weight loss in the last 6 months and Body Mass Index for nutrition, recalling 3 words and the clock test for cognition, the Mini Geriatric Depression Scale (Mini-GDS) for depression, the updated Charlson index score for comorbidity.

Constructing the G-CODE

This G-CODE is a mini-geriatric assessment designed to be short and easy to conduct by oncologists, clinical research assistants or nurses when including patients aged over 70 with cancer in therapeutic trials[1].

This assessment relies on validated and reproducible measuring tools and explores all 7 geriatric areas in the in-depth geriatric assessment, consisting of social environment, functional status, mobility, nutritional status, cognitive status, mood state and comorbidities.

The method used to obtain the G-CODE definition is a DELPHI type consensus method. This consensus method formalises the level of agreement between experts using iterative, individual and anonymous scoring with information feedback.

A steering group from the DIALOG group, consisting of 4 oncologists, 3 geriatricians and 1 epidemiologist, defined the scientific rationale and the procedure, appointed the experts and organised the consensus.

A scoring group of 14 French expert geriatricians, trained in geriatric oncology, defined the initial list of items from the literature and recommendations made by learned societies: SIOG, EORTC and NCCN and scored the tools using a modified DELPHI method.

The consensus process was achieved in 6 steps:

- literature search
- creating the initial list of measuring tools to be used for each of the 7 areas during a plenary session
- individual anonymous scoring by 14 expert geriatricians of the relevance of the selected tools, with 3 rounds
- returning the results obtained between each round to the expert geriatricians
- final presentation to the steering group of the results of the 3 scoring rounds and determination of the final list of 10 geriatric measuring tools in the G-CODE
- the last step in this process of creating this mini-geriatric assessment for clinical research was validation of the G-CODE through adoption first by a national jury of 42 professionals from 20 different towns and then an international jury of 31 professionals from 13 different countries according to a RAND

methodology (Appraisal of Guidelines for Research and Evaluation II Instrument).

The national and international juries were made up of oncologists, radiotherapists, surgeons, nurses, geriatricians and research technicians.

Composition of the G-CODE

This G-CODE is made up of the following tools by area explored[2] (Table 1):

- **Social**: 2 questions
- **Independence**: basic and instrumental activities of daily living (ADL-6; 4-IAD)[3,4]
- **Mobility**: Timed Get Up and Go test (TGUG)[5]
- **Nutrition**: unintended weight loss in 6 months and BMI
- **Cognition**: recalling 3 words and clock test[6,7]
- **Mood state**: Mini-Geriatric Depression Scale (Mini-GDS)[8]
- **Comorbidity**: *updated Charlson index score*[9]

Table 1: *G-CODE Geriatric-Core Dataset Questionnaire*

Social status: 2 questions "Do you live alone?" Y/N * For patients who live in a nursing home/retirement home, the answer is no. "Do you have a person or caregiver able to provide care and support? Y/N * Answering yes to the question means that the patient has a primary caregiver or circle of family, friends or neighbours able to help them.
Independence: ADL, 4-IADL Independence at home: ADL Score: ...../6 Score 1: independent; 1/2: partial assistance; 0: total assistance Personal hygiene: Dressing: Toilet hygiene: Walking: Continence: Meals: Independence at home: IADL Score: ...../4 Score 1: capable; 0: incapable Ability to use the telephone: Means of transport: Responsibility for their own treatment: Ability to handle money:
Mobility: Timed Get Up and Go test During the assessment, the subject should be seated, with their back resting on the back of the chair. The examiner should give the following instructions: "When I say GO, I want you to stand up from the chair, walk three metres at your normal speed, turn around and come and sit down with your back touching the back of the chair". They should start timing on "Go" and stop timing when the subject's back touches the back of the chair. The examiner should then write down the time the subject took to complete the activity. Invite the person to: • Get up from an armchair with armrests: • Cross the room - distance of 3 metres: • Turn around 180 degrees: • Sit down again: Completed: 1; Not completed: 0; Unable to complete Score: ___/4 Time taken: _____ seconds.

Nutrition: unintended weight loss in the last 6 months and body mass index

Unintended weight loss in the last 6 months
Body mass index (weight in kg/(height in m)^2

Cognition: Recalling 3 words and clock test

a. Recalling 3 words: the examiner asks them to memorise the following three words:
- Key
- Lemon
- Ball

b. Clock test
The examiner draws a clock and asks the patient to place the numbers indicating the time on the dial (1 to 12), then indicate 11.10 am with the hands. Correct clock: Yes/No; Score = 2 or 0
c. Recalling 3 words: Score = 0-3 (1 point per correct word)

Mood state: Mini-GDS

The examiner asks the following 4 questions:
- Do you often feel sad and depressed?

Yes = 1 No = 0
- Do you feel that your life is empty?

Yes = 1 No = 0
- Do you feel happy most of the time?

Yes = 0 No = 1
- Do you feel that your situation is hopeless?

Yes = 1 No = 0
Score ___ / 4

Comorbidity: Modified Charlson comorbidity index (max = 24)

Tick the boxes of any diseases present and count up the points (cancer should be scored as follows):
Metastatic solid tumour: 6 pts
- AIDS: 4 pts
- Moderate to severe liver disease: 4 pts
- Any tumour including leukaemia and lymphoma: 2 pts
- Mild liver disease: 2 pts
- Hemiplegia: 2 pts
- Congestive heart failure: 2 pts
- Dementia: 2 pts
- Chronic lung disease: 1 pt
- Rheumatic disease: 1 pt
- Renal failure: 1 pt
- Diabetes with chronic complications: 1 pt

Maximum score: ..../24

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PALLIATIVE CARE

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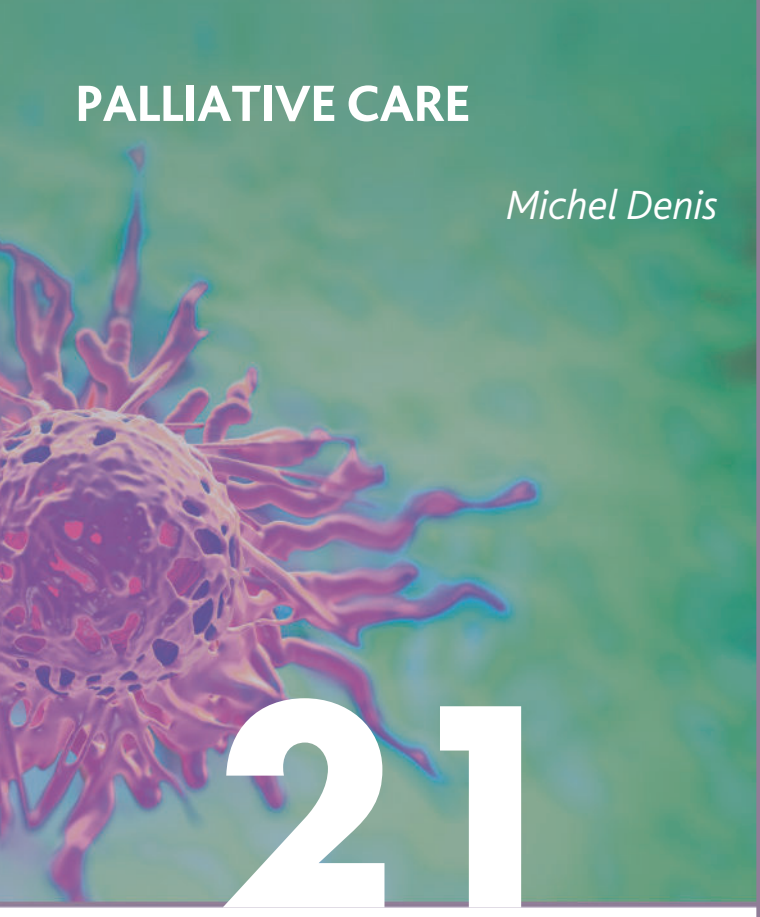

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Introduction

The French Society for Support and Palliative Care (SFAP) defines palliative care as active and continuing care provided by a multidisciplinary team in an institution or at home. It aims to relieve pain, alleviate mental suffering, safeguard the patient's dignity and support their friends and family.

Palliative care is defined by the World Health Organisation (WHO) as an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-limiting illness, usually progressive. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual.

The vast majority of patients treated in geriatrics are in complex situations combining a multiplicity of pathologies, gradual progression of symptoms with ups and downs between worsening and periods of stability, and cognitive disorders. Their care by geriatric teams should incorporate multidimensional clinical, psychological and social expertise at a very early stage.

When an older person is diagnosed with cancer, they remain in their geriatric specificity and are not in the same situation as a young person with cancer.

Due to the profile of geriatric patients, there is a lot of common ground between the geriatric and palliative approach.

In the specific context of geriatric oncology, one of the challenges will be to target and identify the right time for palliative care to be included in the patient's care.

Moreover, in France, the law on people's rights at the end of life has evolved over the last twenty years, and prioritises patient autonomy, prohibits unreasonable therapeutic obstinacy, and allows deep sedation to be maintained until death in certain conditions. It is essential to be familiar with this law and know how to apply it in geriatrics, where people are often no longer able to express their wishes with regard to their care.

Any patient with cancer in the palliative stage is likely to be exposed to a variety of symptoms, of which pain is a prominent feature. However other sources of physical and mental suffering will need to be managed. In older people with numerous comorbidities, assessment and treatment of these symptoms is a challenge. This chapter suggests points of reference for dealing with this complexity.

Addressing and initiating the palliative dimension in the patient pathway

It is not a question of choosing a geriatric approach, geared towards curative goals, over a palliative approach, which firmly shuts the door on life-prolonging treatment. This would expose the patient to the double risk of overzealous therapy or premature discontinuation of treatment.

We need to find and define points of reference that allow us to manage care in a way that creates an overlap between the geriatric and palliative cultures.

On what should an argument in favour of palliative care be based when asking oneself which treatments should take priority, at the point when cancer treatments reveal their limits in terms of efficacy and the patient is deteriorating?

In many cases the patient will have been subject to a comprehensive special assessment, including a standardised geriatric assessment, assessment of frailty and identification of the presence of one or more geriatric syndromes.

These scales do of course have a recognised indicative value in terms of independence, quality of life and mortality. They highlight whether or not the disease is irreversible and the possibility of compensating for a disability. These elements all help to identify the priority care and the aims of treatment. As a result, they can help to identify the point at which palliative care can intervene.

However, they do have limits. Setting up the standardised assessment is a complex process. Also, these three tools fail to take account, in a targeted way, of how the disease evolves in real life, nor the patient's position on their care.

Palliative care has also developed scales which help identify the time when palliative treatment should be started in geriatrics.

In 1995, Dr Sebag Lanoë[1] proposed a list of ten questions which include the severity of the disease process and the perceptions of the patient, their friends and family, and their care team.

In 2016, an SFAP group drew up the Pallia 10 tool, whose aim is to help geriatric teams identify the time when palliative treatment should be considered. It is a simple tool whose aim is to introduce palliative care teams into the patient pathway at an early stage.

In 2017, Dr S Taurand[2] proposed a more accurate reflection model which aims to reduce decision-making uncertainty. The name of this model is FRAG, each letter of which in the French term corresponds to an assessment area:

- F: Frailty assessed on the basis of whether there are one or more geriatric syndromes.
- R: Refusal of treatment, an item enshrined in the Claeys-Leonetti law of 2016 protecting patient autonomy in decisions concerning their end-of-life care. This item takes account of what the patient says or what they show us in their daily life.
- A: Autonomy, as determined from autonomy scales.

- G: Progressive severity, illustrated by repeated episodes of decompensation.

There are plenty of tools to help insert palliative care in the pathway of a geriatric patient with cancer, and these can risk complicating understanding of a situation, especially if more than one is used. It is therefore important to prioritise the resources available to us.

As concerns the geriatric assessment, it therefore appears that the frailty criteria and geriatric syndromes take precedence. In the field of palliative care, the Pallia 10 scale is the reference tool.

The FRAG model is an interesting reflective proposal in terms of reasoning and more precise analysis.

Legal framework

Patients at the palliative stage of cancer expose medical and healthcare teams, wherever they work, to questions of an ethical nature. Limiting curative or life-sustaining treatments such as food/hydration, and management of refractory symptoms sometimes requiring recourse to treatments with a risk of double effect, are the two main situations affected by these questions.

There is also the need to support patients and treat them in a manner as close as possible to their wishes.

In France, the legislative framework constitutes a helpful point of reference that guides decisions and stipulates the conditions in which these should be taken.

The law of 4 March 2002 on patients' rights and quality of the healthcare system allows anyone in hospital to name a **trusted person** (nominated in writing and jointly signed). This person assists the patient during the various medical procedures, and advises the medical and healthcare teams of their willingness to take decisions on behalf of the patient once the latter is no longer able to express their wishes. It is not compulsory to nominate a trusted person. It lasts for as long as the person is in hospital or longer. The trusted person can be revoked by the patient at any time.

The law of 2 February 2016[3] creating new **rights for patients and people at the end of life** (Claeys-Leonetti law) strengthened access to the patient's wishes and how much weight they are given in decisions about care.

It clarifies the concept of unreasonable therapeutic obstinacy and prohibits this, authorises the risk of double therapeutic effect in certain conditions, and gives the patient the right to deep and continuous sedation until death in three situations.

Access to the patient's wishes is documented by the writing of a **living will**. This allows the patient to express their wishes for their end-of-life care and concerns the situations in which medical treatment or procedures will be continued, restricted, discontinued or refused.

It can be revised and revoked at any time. Doctors must comply with its instructions except in a life-threatening emergency, while a comprehensive assessment is carried out.

HAS offers a template which can help with drafting a living will. It must be easy to access, so patients are advised to inform their doctor and next of kin of its existence and where it is kept. It can be included in the shared medical records. Any adult can draw up a living will[4].

If someone is a ward of court, they can draw up a living will and nominate a trusted person with consent from the judge or family council if one has been formed.

There is a hierarchy of access to the patient's wishes. When the patient is capable of expressing their wishes, what they say takes precedence over the living will and any information reported by the trusted person or next of kin. When the patient is no longer capable of expressing their wishes, the living will takes precedence over the trusted person's testimony, which itself over takes precedence over the family's or next of kin's testimony.

Also in the context of respecting patients' wishes at the end of life, the law stipulates that anyone has the right to refuse treatment. In these situations, the doctor is obliged to respect the patient's wishes. If there is a risk of death, the patient must reiterate their decision within a reasonable time that is not defined in law.

Unreasonable therapeutic obstinacy (or overzealous therapy) is defined in law as follows: no acts of care, investigation or therapy should be carried out or continued if they appear to be unnecessary and disproportionate, or when their only effect is providing artificial

life support. They can be suspended or not undertaken in accordance with the patient's wishes. If the patient is unable to express their wishes, discontinuation or non-implementation of treatment will follow a peer review procedure defined by the decree of 3 August 2016[5].

The law stipulates that artificial nutrition and hydration constitute treatment, and can be questioned as being unreasonable therapeutic obstinacy.

Double effect: when patients in an advanced or terminal phase of an illness have refractory pain, the doctor prescribes full analgesic and sedative treatment, even though this may have the effect of shortening life. The law stipulates that they must inform the patient, trusted person and family or next of kin of this fact.

The right for a patient at the end of life to benefit from deep and continuous sedation, maintained until death: the law allows patients with a serious and incurable condition who wish to avoid suffering and do not wish to be subject to unreasonable therapeutic obstinacy, to ask for deep sedation maintained until death in one of two situations:

12. Their life expectancy is at risk in the short term and they are suffering refractory pain from the treatment

13. The patient decides to stop treatment, a decision which is likely to shorten their life in the short term, and may lead to unbearable pain.

Moreover, when the patient is unable to express their wishes, the doctor can stop life-sustaining treatment on the basis of refusing unreasonable therapeutic obstinacy. In these conditions they prescribe deep and continuous sedation until death.

Regardless of the situation, this deep sedation maintained until death is implemented after a peer review procedure involving a palliative care team, to check that the conditions for its use provided for by the law have been fulfilled.

The law stipulates that deep sedation maintained until death can be implemented at the patient's home.

The law does not claim to have an answer to all delicate end-of-life situations. Nonetheless, it strengthens patients' rights, and is a point of reference for health

professionals that can be very useful in the reflective decision-making process.

Symptoms and treatment

The majority of studies conducted in cancer patients receiving palliative care show that the most commonly found uncomfortable symptoms are pain, respiratory problems, digestive disorders and neuropsychological disorders.

They often coexist in the same patient, and need to be assessed and treated because they have a significant effect on quality of life.

In older people, specific problems arise due to the frailty of patients and frequent presence of cognitive and neurosensory impairment. Assessing pain relies to a large extent on asking questions, and is therefore likely to be less than comprehensive, especially when screening for neuropathic pain. Treatment should take account of patient frailty, and consideration of the risk-benefit ratio should guide the prescriber's actions.

Irrespective of the symptoms, some guiding principles govern how they should be managed. The simplest and most lasting route of administration should be chosen. It is essential to eliminate reversible causes such as faecal impaction or retention of urine that are the source of pain and neuropsychological disorders. Finally, the adage "*Start low - go slow*" is key when prescribing drug treatments[6].

Pain

- *Quantitative and qualitative assessment*

Pain should always be on the doctor's radar in the context of geriatric oncology. This assessment period consists of two phases, a quantitative assessment which can detect pain, and a qualitative assessment which can among other things uncover neuropathic pain, which occurs more often in geriatrics and oncology.

Self-assessment should be used, if possible, using simple scales such as the Numerical Pain Rating Scale (NPRS), the Visual Analogue Scale (VAS) which requires a capacity for abstraction, and the Verbal Rating Scale (VRS).

If neuropsychological disorders are present, rater-administered assessment scales should be used (DOLOPLUS, ECPA, ALGOPLUS), and let us point out here how easy the ALGOPLUS scale is.

The limiting factor with all these scales is that they are unable to screen for neuropathic pain. DN4 is the only scale approved for detecting neuropathic pain.

It is very sensitive (80%) and very specific (90%). It requires patient participation because of the 10 items discussed, 7 are obtained through a question-and-answer session. In geriatrics, its use is limited due to the frequency of cognitive disorders in patients.

So how can we identify neuropathic pain in patients who are unable to communicate?

A 2-step process could be proposed:

Initially, it is worth asking yourself 4 questions:

1. Are there times when DN4 can be used?
2. Some items of DN4 can be identified in these patients. These are itching, pinprick hypesthesia and allodynia caused by touch, friction, heat or cold.
3. Does rater-administered assessment allow a painful area to be pinpointed?
4. Is there a history of lesions or illness affecting the neurological system?

This initial stage is used to answer a set of 4 further questions corresponding to a graded diagnostic system for neuropathic pain, proposed by R-D Treede's team[7].

Pain possibly has a neuroanatomical distribution: yes/no.

14. Clinical history of lesions or illness affecting the peripheral or central nervous system: yes/no.
15. Demonstration of a plausible neuroanatomical distribution by at least one test in the clinical examination (looking for sensory disorders): yes/no.
16. Demonstration of lesion or illness by at least one test: yes/no.

The diagnosis of neuropathic pain can then be established with more or less certainty depending on the answer to the questions:

- An affirmative answer to the first and second question indicates hypothetical neuropathic pain.

- An affirmative answer to the first, second, third or fourth question indicates probable neuropathic pain.
- An affirmative answer to all the questions indicates definite neuropathic pain.

• Assessing the developmental profile

In conjunction with the quantitative and qualitative assessment of pain, it is important to detect its developmental profile. Is there any background pain? If yes, daily treatment should be envisaged. Are there any incidents of spontaneous or provoked fleeting pain? The first should be treated by painkillers on demand, the second will need the setting up of pre-care.

As regards incidents of spontaneous fleeting pain, it is important to identify PPAs (Paroxysmal Pain Accidents), during which the maximum pain happens within 3 minutes and lasts for around one and a half hours. These episodes require specific treatment.

• Treating nociceptive pain

It is advisable to adhere to the WHO analgesic ladder.

Step 1 is represented by paracetamol which can be used as a first-line treatment up to a dose of 4 g/day with a gap of at least four hours in between.

Step 2 includes weak opioids represented by combinations of paracetamol and codeine, paracetamol and opium powder, and tramadol on its own or in combination with paracetamol. It is not advisable for older people to use painkillers containing tramadol as these are very often poorly tolerated. Some teams advise older people undergoing treatment for cancer to bypass step 2, and go straight to step 3 when the pain is not controlled by paracetamol.

Step 3 includes strong opioids, namely morphine, oxycodone, fentanyl. They constitute the treatment of choice for cancer pain that is resistant to step 1. They can be administered orally, subcutaneously, intravenously or transcutaneously in the form of a patch.

In order to optimise their tolerance, it is imperative to apply the "*start low - go slow*" rule.

As concerns management of baseline pain, the prescription of morphine sulfate syrup (ORAMORPH) at a

dose of 2 or 3 mg orally every 8 hours is recommended in frail older patients. The possibility of interdoses of 2 mg in the event of intercurrent pain should be given with a maximum of four interdoses taken per day and a gap between two doses of one hour. This could be replaced by a sustained-release oral form administered twice daily twelve hours apart, for which the dosage should be established according to the total dose of morphine syrup given over the 24 hours.

The same logic can be used with oxycodone.

If oral administration is impossible, the subcutaneous route can be used with morphine chlorhydrate and reducing the doses from 2 mg to 1.5 mg.

This method allows the dose to be adjusted quickly depending on the level of pain and tolerance.

For its part, fentanyl is reserved for balanced pain, replacing oral or subcutaneous morphine. Remember that the fentanyl patch of 12 µg/hour corresponds to an oral dose of 20 mg of morphine per 24 hours.

A downloadable application called OPIOconvert, published by 3 learned societies (SFAP, ASSOS, SFETD) can be used to switch from one type of morphine to another in compliance with equianalgesic guidelines.

Once the background treatment has been established, incidents of fleeting pain, whether spontaneous or caused by the treatment, should be treated by interdoses given orally or subcutaneously at a dosage of 1/10th to 1/6th of the daily dose. A maximum of 6 interdoses per day with a lockout interval of one hour between two interdoses is the rule.

When organising treatment and assessing how to relieve painful incidents, it is important to know the time to onset of action of these interdoses. It is 30 to 60 minutes for the oral and subcutaneous routes.

PPAs (Paroxysmal Pain Accidents) are managed with interdoses of transmucosal fentanyl (abstral, instanyl, etc.) which require the assistance of an experienced team to set them up.

Any treatment with morphine must be accompanied by prescription of a laxative as soon as treatment begins.

On starting and throughout treatment with morphine, it is important to stay vigilant for the appearance of signs of an overdose. These are characterised by drowsiness, the first sign of an overdose, combined with a respiratory rate of 10 breaths per minute or less. When an overdose occurs, treatment with naloxone may be necessary.

Pain can also be treated with MEOPA, an equimolar mixture of nitrous oxide and oxygen. This is useful for short-lasting pain events (less than an hour), because it has an analgesic effect in a few minutes. It requires the patient's cooperation. The contra-indications are intracranial hypertension, occlusive syndrome and lack of concentration.

- *Treating neuropathic pain*

It can prove difficult to relieve neuropathic pain. It comes from specific drug treatments that act on the central nervous system, some of which may result in neuropsychological and cardiac adverse events. They should be used with caution in the over-75s.

The following proposed treatments were inspired by the French guidelines in 2020[8].

In cases of peripheral neuropathic pain with a small area of pain, and maintained residual sensitivity to mechanical or thermal stimulation, lidocaine plasters (1 to 3 plasters/day) and/or transcutaneous electrical nerve stimulation (TENS) are recommended as a first-line treatment. In France, TENS is unfortunately only reimbursed if prescribed by a chronic pain clinic.

In cases of peripheral or central neuropathic pain, when there is a large area of pain, it may be necessary to resort to the use of drugs to treat it. As a first-line treatment, the recommendation is to use duloxetine at a dosage of 60 to 120 mg/day, or gabapentin at a dosage of 900 to 3,600 mg/day, or a tricyclic antidepressant, starting with 5 mg/day, and not exceeding 75 mg/day in patients aged over 70.

If this fails or is not tolerated, pregabalin can be used at a dosage of 150 to 600 mg/day. Another alternative consists of combining an antidepressant with a gabapentinoid at the following dosage: 60 mg of duloxetine

or 25 to 75 mg of tricyclics + 1200 to 1800 mg of gabapentin or 150 to 300 mg of pregabalin.

The dosage indicated should of course be adapted to the metabolism and frailty of the older patient.

It is advisable to maintain these treatments at a well-tolerated dose for six weeks at every stage before taking the decision to move on to the next stage.

- *Co-analgesics*

In the context of geriatric oncology, corticosteroids appear to be the most useful co-analgesics due to their peritumoral anti-inflammatory action.

A low dose of methadone syrup (2 mg twice or three times per day) constitutes an effective therapeutic option in cases of neuropathic pain or hyperalgesic phenomena[9].

- *Refractory pain*

Any tumours that develop close to the plexus or nerve trunks (pelvic tumours, pancoast tumour) are likely to cause pain resistant to well-conducted analgesic treatment. This should then be viewed as refractory pain caused by a specific drug treatment (ketamine, injectable fentanyl, mephenon, etc.) or invasive treatment (intrathecal pain relief, nerve block, etc.) requiring the expertise of a palliative care or pain management team[10].

Respiratory symptoms

The two most common respiratory symptoms in the palliative phase of cancer are shortness of breath and congestion.

Before envisaging symptomatic treatment purely to make the patient more comfortable, it is important to talk about the possible curable causes, and discuss in terms of the risk-benefit ratio whether additional investigations should be carried out and specific treatments prescribed.

- *Shortness of breath*

According to the studies, this affects 32 to 79% of patients with advanced cancer. It is defined as a subjective

feeling of respiratory discomfort, which the patient might describe in terms of qualitative sensations such as tightness in the chest, struggling to breathe and at its worst a feeling of choking or suffocation. Only the person experiencing it can appreciate it.

There is no specific self-assessment scale for shortness of breath. However the simple NPRS, VAS and VRS scales used to assess pain can be useful to assess shortness of breath.

There is a scale, the Respiratory Distress Observation Scale, which can be used to assess the intensity of shortness of breath in a patient who is unable to communicate[11].

A score higher than 3 out of 16 can detect moderate to severe shortness of breath.

Symptomatic treatment of shortness of breath initially involves applying basic common sense. A well-ventilated bedroom, calm atmosphere, minimal expenditure of energy (toilet visits, visitors, moving around, etc.), position in bed, wearing loose clothing, are all details that should be taken into consideration.

It is important in cases of congestion to ask whether physiotherapy might be of benefit, especially massages and parietal stimulation.

Oxygen therapy often has little effect on oxygen saturation but can bring relief because it reassures the patient and their next of kin.

Drug treatments essentially include opioids and anxiolytics. In morphine-naive patients, doses of 2 to 2.5 mg *per os* of morphine sulfate or 1.5 mg SC of morphine chlorhydrate every four hours are recommended.

For patients on morphine, it is advisable to increase the background treatment by a maximum of 25%; another solution is to treat the shortness of breath alone with interdoses of morphine at a dosage of a tenth of the daily dose.

As far as anxiolytics are concerned, benzodiazepines with a short half-life are preferable, such as oxazepam 10 mg prescribed in half-tablets. When the oral route is not possible, midazolam can then be prescribed by the

IV or SC routes at doses of between 0.5 and 1 mg every 30 minutes.

Relaxation hypnosis or musical therapy techniques all have their place because they allow the patient to be diverted.

- *Terminal respiratory congestion (TRC)*

This section discusses the congestion present in the terminal phase when life expectancy is very short (a few hours to a few days).

In 2012, a study showed an average 35% prevalence of death rattle in patients receiving palliative care. This symptom has a negative impact on carers and the patient's friends and family. A study conducted in 2004, focusing on the perceptions of next of kin, shows that 46% of them were distressed by this symptom.

There is no approved scale for assessing terminal respiratory congestion. However the literature mentions a scale that is very simple to use, the Victoria Respiratory Congestion Scale, which can be used to classify this rattle according to its sound level.

Several pathophysiological mechanisms have been identified. In 2008, Vinay[12] proposed classification death rattles according to their causative mechanism:

- Type I is represented by rattles resulting from cholinergic stimulation due to an increase in parasympathetic tone (local vasodilatation) which leads to production of mucus. This category responds well to antisecretory medication.
- Type 2 is represented by rattles resulting from a local mechanism (local progression of the cancer, lymphangitis carcinomatosis, infection, etc.). This category responds less well to antisecretory medication. Corticosteroids can be a good option, as well as antibiotic therapy in some cases.
- Type 3 includes rattles resulting from an intrapulmonary expansion mechanism with water retention. These respond well to diuretics.

Treating the symptoms of death rattle inevitably brings into question how much liquid intake should be administered. This should be cut down or even stopped.

Aspiration should be done carefully so as to be the least traumatic possible.

As we have just noted, excess fluid in the lungs may be relieved by the prescription of a diuretic.

Antisecretory medication constitutes the reference treatment for death rattle. In France, two specialities are available to medical staff:

- Scopolamine in patches or ampoules (0.5 mg SC). It has an MA for agonal gasping. Patches are reserved for moderate rattle situations as the dosage cannot be adjusted quickly. They need to be changed every 72 hours. The injectable form is suitable for rattles which are progressing, and the maximum dose is 8 amp/day. Scopolamine passes through the blood-brain barrier and is responsible for neuropsychological disorders and mydriasis.
- Butylbromide (in 20 mg ampoules). It doesn't have an MA for TRC. The route of administration is subcutaneous or IV. The maximum dose per 24 hours is eight ampoules. Butylbromide doesn't pass through the blood-brain barrier.

Any prescription of antisecretory medication is routinely accompanied by mouth care and a prescription for artificial tears due to its drying effect.

Clear and comprehensible information should be given to the next of kin with the aim of reassuring them, especially since, as concerns patients' feelings, stopping hydration often feels like abandonment or unspoken euthanasia.

Digestive symptoms

We will be discussing the following topics: constipation, nausea and vomiting, hiccups, occlusive syndromes.

• *Constipation*

This is a constant worry in geriatric oncology and palliative care due to the terrain, and the treatments prescribed, which for a number of patients cause the intestinal tract to slow down[13].

According to studies, 33 to 95% of in-patients in PCUs receiving opioids complain of constipation.

Hygiene and dietary advice should be given to patients and their next of kin. Physical exercise should be encouraged, even if at a low level.

Osmotic laxatives are given as a first-line treatment. If they are not effective after 4 days, they can be combined with a stimulant laxative. Make sure there are no contra-indications such as presence of inflammatory bowel disease and an occlusive syndrome. They can lead to abdominal pain and diarrhoea. Lubricant laxatives can be an alternative to stimulant laxatives, however they should be avoided in cases of swallowing problems.

In patients on morphine with intractable constipation despite proper treatment with laxatives, it is possible that peripheral morphine antagonists such as naloxegol (12.5 and 25 mg tablets) could be helpful. They are contra-indicated in cases of cancer or ulcer of the intestinal wall because of a risk of perforation, and in combination with NSAIDs and bevacizumab. Their adverse events are the appearance of abdominal pains, diarrhoea and nausea. When they are prescribed, treatment with the usual osmotic laxatives is continued.

In the specific case of patients with spinal cord neurological disorders, twice-weekly rectal enemas (Normacol, enemas with warm water and paraffin oil) combined with abdominal massages are recommended.

- *Nausea and vomiting*

In this case it is worth looking for hypercalcemia and hyponatremia which can be corrected.

Symptomatic treatment is based on 2 families of drugs: prokinetics and dopamine antagonists. The frontrunner of prokinetics is metoclopramide, which stimulates peristalsis in the upper digestive tract. It is contra-indicated in cases of an obstructed digestive tract.

The reference dopamine antagonist is haloperidol. It has an MA for post-radiotherapy vomiting. It is prescribed orally or subcutaneously at an initial dosage of 2 mg two to three times per day.

Simple measures should be implemented alongside medical treatments. These consist of adequate ventilation

of the living space, giving mouth care to combat bad breath and reduction of any olfactory stimulation.

• *Hiccups*

This corresponds to an involuntary sudden rhythmic contraction of the diaphragm. There are multiple mechanisms which may originate from the digestive system, chest or brain. Never disregard the simple tactics (drinking a glass of water while holding breath, tongue pull-back), but the first-line treatment is metoclopramide. Haloperidol is prescribed as a second-line treatment. These two drugs are prescribed at the same doses as for nausea and vomiting.

• *Occlusive syndrome*

Digestive tumours occur frequently in geriatrics. The risk of occlusion due to intrinsic or extrinsic compression (peritoneal carcinomatosis) is present. This complication occurs in 10 to 28% of colorectal cancers and 20 to 50% of ovarian cancers.

The clinical presentation can help distinguish between an upper and a lower digestive obstruction. In cases of upper digestive obstruction and severe gastric distension, a nasogastric suction tube should be inserted. This should give some relief until the other treatments kick in.

Symptomatic therapeutic management of occlusive syndrome in palliative care is now well codified[14].

It combines anti-emetics with haloperidol as a first-line treatment at a dosage of 5 to 15 mg/day, analgesics including primarily morphine, corticosteroids at a dosage of 1 to 4 mg/kg per day for 5 to 10 days and antisecretory medication, starting with butylbromide at a dosage of 60 to 120 mg/day.

Phloroglucinol has not yet proved its efficacy.

PPIs should be prescribed in cases of upper digestive symptoms.

Octreotides are given as a second-line treatment during a first episode of occlusion. They can be prescribed as a first-line treatment if occlusion recurs, and there is no reason not to combine butylbromide and octreotide. Mouth care, making sure the patient is comfortably

installed in their bed, reassuring them and their next of kin are an integral part of treating their obstructions.

Neuropsychological disorders

Confusion is the neuropsychological disorder most commonly encountered in palliative care. Its prevalence in the last weeks or hours of life is estimated to be 60 to 80%. It has a poor prognosis[15,16].

Although the stable phase is quickly established, it can be preceded by warning signs such as disturbed sleep (insomnia, agitation, circadian rhythm disorders), altered behaviour with irritability and anger, minimal treatment compliance and hypersensitivity to visual or auditory stimulation.

The stable phase has a polymorphous presentation whose semiology has fluctuated over time. However, the diagnosis is confirmed by the triad of altered consciousness combined with cognitive disorders and perceptual disturbances, such as hallucinations and sometimes delirium.

There are periods of lucidity which lead to a state of anxious bewilderment in which the patient is aware that something abnormal is happening.

There are two forms, which can affect the same patient. A slow form, the most common in a palliative situation, and an agitated form in which perceptual disturbances are common.

In geriatrics, confusion is differentiated from dementia by its onset mode, which is more sudden. However, dementia and confusion both involve cognitive disorders, which can complicate diagnosis.

The causes are multifactorial, however faecal impaction and retention of urine that can be relieved quickly should be eliminated as soon as they are diagnosed. After this stage, an inventory of reversible causes should be taken. There are a number of them: uncontrolled pain, metabolic disorders (hypercalcemia, hyponatremia), sepsis, anaemia, iatrogenic condition. Then a discussion should take place, considering the risk-benefit ratio, about specific treatment of these causes.

Treatment of confusion is particularly multi-dimensional[17]. The aim is to preserve cognitive function, ensure the safety of patients, their next of kin and care teams, and to improve symptoms.

For the patient, careful reframing can be therapeutic. It is important to keep their bearings in time and space and create a secure environment by eliminating any confusing objects and dimming the lights at nightfall, a time when confusion often increases.

Next of kin without resources need explanations of the causes and how the symptoms can be managed.

In terms of drugs for older people, it is preferable to start with anxiolytics with a short half-life such as oxazepam or midazolam if the oral route is not possible. In cases of perceptual disturbances with agitation that threaten the safety of the patient and their friends and family, the use of anti-psychotics is justified. Start with haloperidol via the oral or subcutaneous route at a dosage of 5 to 15 mg/day. If this does not work, more sedating neuroleptics can be prescribed, such as cyamemazine or chlorpromazine. It is then advisable to resort to a specialist team.

Refusal of nutrition and hydration

Remember that medically-assisted nutrition and hydration are now recognised as treatment under French law and can therefore be questioned as being unreasonable therapeutic obstinacy.

Nutrition and hydration are highly symbolic of life for both patients and their next of kin. The more the disease leaves its mark on the body, as death approaches and after refusal of much curative treatment, we see a reinforcement, especially on the part of next of kin, of the vital symbolic value of nutrition and hydration[18]. This is expressed by sometimes very insistent encouragement by next of kin for the patient to eat and drink when there are significant issues with swallowing and concentration.

Conflict situations between the next of kin and the medical and healthcare team can quickly arise when stopping hydration or taking a decision not to put it in place. Attentive care with proposals for tasty food and frequent mouth care may not to be enough to dissolve the tensions.

There are two conflicting paradigms. A physiological one based on a medical model, and one that finds its reference points in symbols outside the realm of scientific discussion. Everyone shares this one – caregivers, next of kin and patients.

The challenge is to build common points of reference.

Drs P. Vinay and D. Oriot studied the physiology of dying and stopping nutrition and hydration[12-19]. Their articles provide and explain mechanisms that can be understood by everyone, such as endogenous secretion of water at the very end of life (P. Vinay).

It is essential to meet these next of kin, allow them to express their opinions, and share with them the symbolic value of nutrition and hydration. Secondly, medical explanations are given based on medical and healthcare expertise, the physiological mechanisms of end of life, the law, and always putting the patient at the centre of concerns. This is the way to try to build a shared paradigm.

Conclusion

The palliative care and geriatric teams share a holistic approach to patients and multidisciplinary thinking. For a long time, palliative care activity has been dominated by caring for patients with cancer when specific treatments are clearly no longer working. The teams have acquired expertise in this field which justifies their inclusion in teams supporting older people with cancer.

In an approach which puts the patient and their next of kin at the centre of concerns, organisational structures are essential if the goals of supporting patients while adhering to their wishes are to be achieved. In-patient units (AGUs, PCUs, FCRs, long-term care units), mobile palliative care and geriatric teams within and outside hospitals, day hospitals, coordination support facilities constitute an essential graduated care offer to meet the needs of patients and their next of kin, wherever the patient is living.

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CACHEXIA IN OLDER ADULTS WITH CANCER

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Introduction

Cancer cachexia is associated with poorer health outcomes, especially in older adults[1]. Age is a major risk factor for cancer and malnutrition. In 2017, approximately 70% of cancer cases worldwide occur over the age of 50 years where 27% were over 70 years[2]. Globally, the prevalence of malnutrition among cancer patients varies between 20%-70%, and 10–20% of cancer deaths can be attributed to malnutrition and its complication rather than the cancer itself[3]. Among older adults older than 70 years, the prevalence of malnutrition ranges from 22.8 to 46.2%[4]. As the aging process is associated with sarcopenia, comorbidity, and increased vulnerability to frailty, delineating age-related versus cancer-related effects of malnutrition could be challenging, as often there is an overlap.

Several factors such as disease, advanced age, physical inactivity, or immobilisation contribute to the development of an inflammatory state by promoting catabolism and muscle degradation. Whilst inflammation has been heavily implicated with cachexia, other factors could also contribute to nutritional impairments, including limited access to food from poor mobility or poverty,

malabsorption syndromes, cognitive impairment, or psychocultural preferences. Despite the increased prevalence and poorer outcomes, cancer cachexia has been poorly characterised in older adults due to lack of data from under representation in clinical trials. This chapter highlights the outcomes of cachexia in older adults with cancer and the role for nutritional assessment and interventions.

Nutritional impairments in older adults with cancer

Older adults are at increased risk for developing nutritional impairments due to cancer and toxicities from its treatment, and/or from cachexia and anorexia of ageing, which could manifest in various ways. Malnutrition occurs from either suboptimal intake of nutrients or increased nutritional requirements. Its prevalence in older adults with cancer ranged from 3 to 83% depending on the assessment tools used, cancer site and stage, and has been associated with increased hospital admissions, longer hospital stay, and lower quality of life[5]. Sarcopenia is diagnosed by loss of muscle strength and function. It is prevalent in up to 57% of older adults with cancer, and has been associated with increased risk for falls, fractures, physical disability, and mortality[6]. Cachexia on the other hand, is characterized by an irreversible loss of weight, depletion of muscle and/or fat due to an inflammatory response to a pathological process, including cancer[7,8]. Table 1 summarises the definition and classification of cancer cachexia based on the international consensus[8].

The risk of cachexia increases with various tumour types and patients in the very high-risk group have the worst 5-year survival rate[9] as shown in Table 2. Nutrition impact symptoms such as poor appetite, dysphagia, early satiety, diarrhoea or constipation, and nausea or vomiting are common among patients with cancer. Often these are present even before the diagnosis of cancer was made. Similarly, anticancer therapies may further perpetuate such symptoms, exacerbating the risk of cachexia. Whilst cachexia commonly involves malnutrition and sarcopenia, not all malnourished and/or sarcopenic patients have cachexia. The prevalence of cancer cachexia in older adults is around 52-62% and the risk of mortality is two-fold[1,7]. The presence of upper gastrointestinal tract cancer, metastatic disease, poor

performance status, poor mobility, previous surgery, cognitive disorders, depression, and low food intake all contribute to higher risk for cachexia[1]. Notably, cachexia and sarcopenia are both progressive and debilitating disorders of muscle deficiency that impair functional performance, leading to frailty. This is concerning as frailty in older adults with cancer is associated with increased chemotherapy-related toxicities and surgical complications, poor tolerance to treatment, early cessation or withdrawal of treatment, and higher mortality[10], highlighting the need for early diagnosis and intervention.

Table 1: *Definition of Nutritional Impairments based on international consensus*[6,8].

Malnutrition: a reversible condition resulting from an insufficient intake or utilisation of nutrients causing an alteration in body composition, reduction in lean body mass, and compromised physical and mental functions
Cachexia: a complex, irreversible metabolic syndrome associated with underlying illness and is characterised by loss of muscle with or without loss of fat mass.
1. pre-cachexia, prior to the actual cachectic manifestation, when there is ≤ 5% weight loss, anorexia and metabolic changes. **2. cachexia,** occurs in the presence of a systemic inflammation, associated with one of the following: • unintentional weight loss > 5% of usual weight in the last 6 months, or • BMI < 20 kg/m^2 and weight loss > 2%, or • sarcopenia and weight loss > 2%
3. refractory cachexia, occurs in undiagnosed cachexia, in advanced (preterminal) stage, or in the presence of a rapid and progressive metastatic disease that is refractory to cancer therapy; This is usually characterised by a ECOG performance status score 3-4, a life expectancy less than three months and an irreversible hypercatabolism.
Sarcopenia: a reversible muscle disorder best characterised by decreased strength and can be caused by a multitude of factors including normal aging and physical inactivity or can occur secondary to disease.

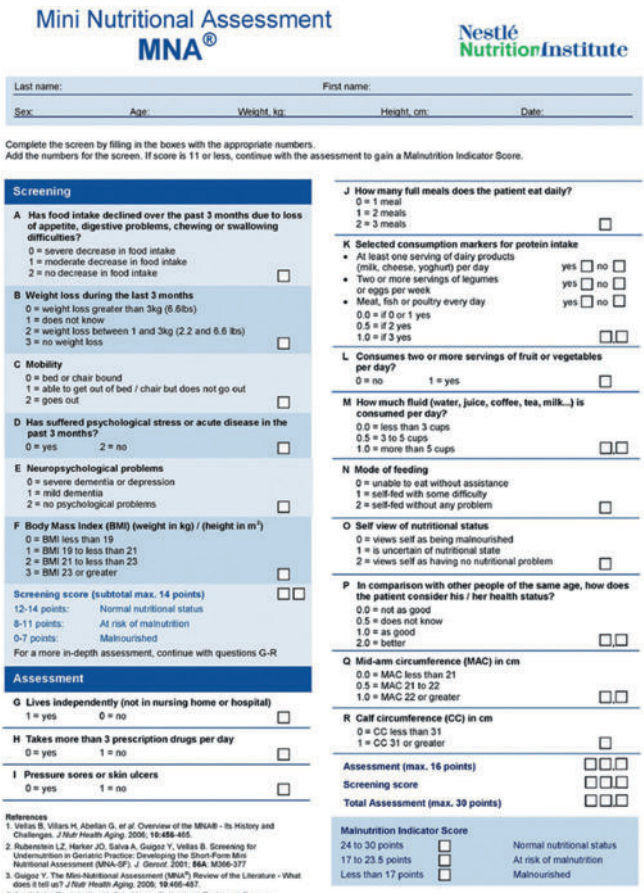
Table 2: *Risk of Cachexia based on cancer type and 5-year survival rate*[9].

Cachexia Risk Group	Cancer Type	5-year survival rate (%)
Very high risk (80-90%)	Liver Pancreas lung	0-30
High risk (50-70%)	Head and neck Gastric Colorectal	31-66
Middle risk (30-40%)	Endometrial Kidney and renal pelvis Non-Hodgkin lymphoma Urinary bladder	67-90
Lower risk (20-30%)	Thyroid Breast Melanoma Prostate	91-100

Nutritional Screening and Assessment

Recognising the physiologic age-related deficits as well as cancer- and treatment-related factors contributing to nutritional impairments are important in the assessment to identify patients at risk and to provide timely interventions. Several malnutrition screening tools exist, such as Mini Nutritional Assessment (MNA) (Fig 1) [11,12], Malnutrition Universal Screening Tool (MUST) (Figure 2)[13,14], and Patient Generated Subjective Global Assessment (PG-SGA) (Figure 3)[15,16]. These are widely available, easily replicated, and have been validated in patients with cancer. These tools predict malnutrition by measuring body mass index (BMI), non-volitional weight loss in 3 to 6 months, nutritional impact syndromes, mass and fat loss, and functional status. There are also objective tools available to measure muscle mass and density (e.g., CT or DEXA scans), muscle strength (e.g., dynamometry), and physical performance (e.g., short physical performance battery or 6-minute walk test). However, the use of radiological scans require access to equipments and the added costs may be prohibitive in some cases.

As sarcopenia can occur in normal ageing process and could overlap with cancer cachexia, assessment of weight, muscle mass or muscle density alone are usually insufficient to characterise the nutrtitional disorders in older adults with cancer. A serial measurement of functional performance, health status and patient-reported outcomes, may provide a more accurate and comprehensive assessment of overall nutritional state[17]. G8, as shown in Fig 4 is an 8-item screening tool[18,19], which covers both nutritional and age-associated variables, including decrease in food intake, weight loss, difficulty with mobility, neuropsychological problems, body mass index, polypharmacy, age, and self-rated health status to identify older patients needing a comprehensive geriatic assessment (CGA). CGA involves a multi-domain assessment of the overall health status that includes demographic and social factors, comorbidities, functional status, cognition, mood, nutrition, geriatric syndromes, and risk of treatment-related toxicity, which may help inform decision-making and improve outcomes[20].



Mini Nutritional Assessment
MNA®

Nestlé Nutrition Institute

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Complete the screen by filling in the boxes with the appropriate numbers.
Add the numbers for the screen. If score is 11 or less, continue with the assessment to gain a Malnutrition Indicator Score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake

B Weight loss during the last 3 months
0 = weight loss greater than 3kg (6.6lbs)
1 = does not know
2 = weight loss between 1 and 3kg (2.2 and 6.6 lbs)
3 = no weight loss

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems

F Body Mass Index (BMI) (weight in kg) / (height in m²)
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater

Screening score (subtotal max. 14 points)
12-14 points: Normal nutritional status
8-11 points: At risk of malnutrition
0-7 points: Malnourished
For a more in-depth assessment, continue with questions G-R

Assessment

G Lives independently (not in nursing home or hospital)
1 = yes 0 = no

H Takes more than 3 prescription drugs per day
0 = yes 1 = no

I Pressure sores or skin ulcers
0 = yes 1 = no

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals

K Selected consumption markers for protein intake
- At least one serving of dairy products (milk, cheese, yoghurt) per day — yes / no
- Two or more servings of legumes or eggs per week — yes / no
- Meat, fish or poultry every day — yes / no

0.0 = if 0 or 1 yes
0.5 = if 2 yes
1.0 = if 3 yes

L Consumes two or more servings of fruit or vegetables per day?
0 = no 1 = yes

M How much fluid (water, juice, coffee, tea, milk...) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups

N Mode of feeding
0 = unable to eat without assistance
1 = self-fed with some difficulty
2 = self-fed without any problem

O Self view of nutritional status
0 = views self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem

P In comparison with other people of the same age, how does the patient consider his / her health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 = MAC 21 to 22
1.0 = MAC 22 or greater

R Calf circumference (CC) in cm
0 = CC less than 31
1 = CC 31 or greater

Assessment (max. 16 points)
Screening score
Total Assessment (max. 30 points)

Malnutrition Indicator Score
24 to 30 points — Normal nutritional status
17 to 23.5 points — At risk of malnutrition
Less than 17 points — Malnourished

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Figure 1: *Mini Nutritional Assessment (MNA) was developed for the older population in all care settings and has been validated in full and short-form versions*[11].

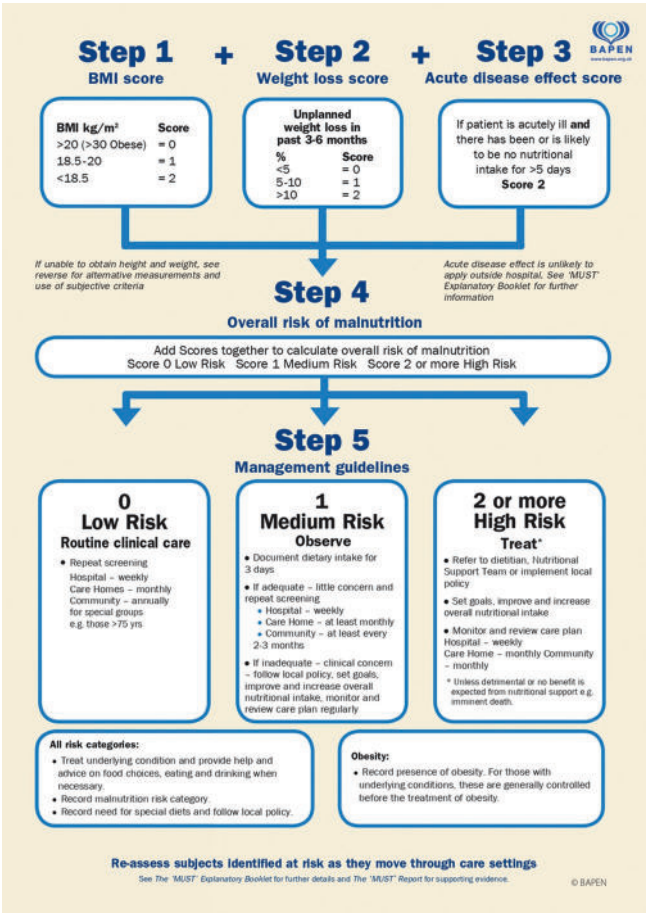
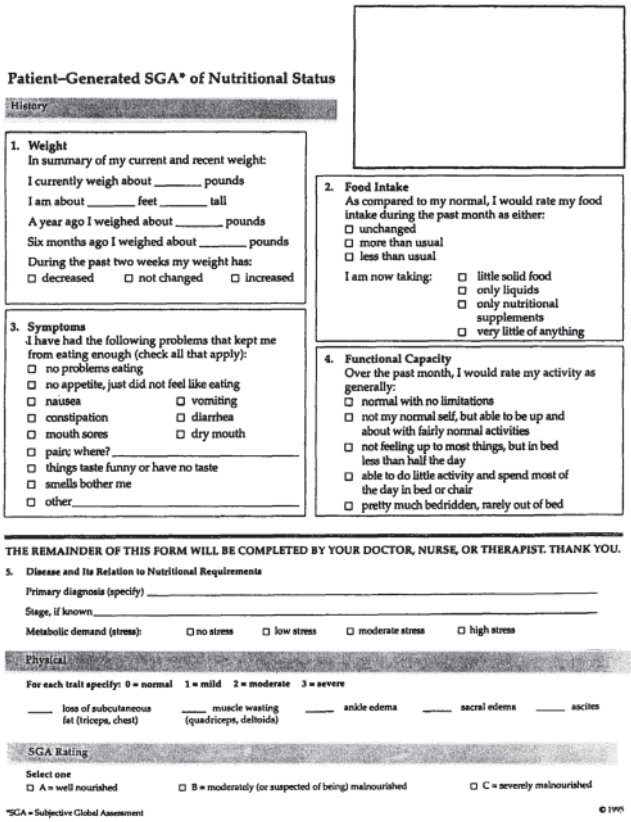


Figure 2: *Malnutrition Universal Screening Tool (MUST) is a 5-step screening tool used to identify patients who are malnourished or at risk of malnutrition*[11].



Patient–Generated SGA* of Nutritional Status

History

1. Weight
In summary of my current and recent weight:
I currently weigh about _____ pounds
I am about _____ feet _____ tall
A year ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds
During the past two weeks my weight has:
☐ decreased ☐ not changed ☐ increased

2. Food Intake
As compared to my normal, I would rate my food intake during the past month as either:
☐ unchanged
☐ more than usual
☐ less than usual
I am now taking:
☐ little solid food
☐ only liquids
☐ only nutritional supplements
☐ very little of anything

3. Symptoms
I have had the following problems that kept me from eating enough (check all that apply):
☐ no problems eating
☐ no appetite, just did not feel like eating
☐ nausea ☐ vomiting
☐ constipation ☐ diarrhea
☐ mouth sores ☐ dry mouth
☐ pain; where? _____
☐ things taste funny or have no taste
☐ smells bother me
☐ other _____

4. Functional Capacity
Over the past month, I would rate my activity as generally:
☐ normal with no limitations
☐ not my normal self, but able to be up and about with fairly normal activities
☐ not feeling up to most things, but in bed less than half the day
☐ able to do little activity and spend most of the day in bed or chair
☐ pretty much bedridden, rarely out of bed

THE REMAINDER OF THIS FORM WILL BE COMPLETED BY YOUR DOCTOR, NURSE, OR THERAPIST. THANK YOU.

5. Disease and Its Relation to Nutritional Requirements
Primary diagnosis (specify) _____
Stage, if known _____
Metabolic demand (stress): ☐ no stress ☐ low stress ☐ moderate stress ☐ high stress

Physical

For each trait specify: 0 = normal 1 = mild 2 = moderate 3 = severe

____ loss of subcutaneous fat (triceps, chest) ____ muscle wasting (quadriceps, deltoids) ____ ankle edema ____ sacral edema ____ ascites

SGA Rating

Select one
☐ A = well nourished ☐ B = moderately (or suspected of being) malnourished ☐ C = severely malnourished

*SGA = Subjective Global Assessment

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Figure 3: *Generated Subjective Global Assessment (PG-SGA) is comprised of patient and professional components that provide a quick diagnosis of malnutrition and triaging recommendations for nutritional interventions*[15].

	Items	Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake
		1 : moderate decrease in food intake
		2 : no decrease in food intake
B	Weight loss during the last 3 months	0 : weight loss > 3 kg
		1 : does not know
		2 : weight loss between 1 and 3 kgs
		3 : no weight loss
C	Mobility	0 : bed or chair bound
		1 : able to get out of bed/chair but does not go out
		2 : goes out
E	Neuropsychological problems	0 : severe dementia or depression
		1 : mild dementia or depression
		2 : no psychological problems
F	Body Mass Index (BMI (weight in kg) / (height in m²)	0 : BMI < 19
		1 : BMI = 19 to BMI < 21
		2 : BMI = 21 to BMI < 23
		3 : BMI = 23 and > 23
H	Takes more than 3 medications per day	0 : yes
		1 : no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0 : not as good
		0.5 : does not know
		1 : as good
		2 : better
	Age	0 : >85
		1 : 80-85
		2 : <80
	TOTAL SCORE	**0 – 17**

Figure 4: *G8 is comprised of 8 questions that is used to screen for frailty. It was developed based on MNA and has been validated to use among older patients with cancer before treatment*[19].

Nutritional Interventions for Older Adults with Cancer

The approach to nutritional intervention of older adults is dynamic and targeted to aetiologic and contributory factors. Intervention starts at recognising the risks, followed by screening and assessment to diagnose the nutritional deficits, correcting these, and monitoring and management of any unresolved or emerging deficiencies.

Hence nutritional assessment is a key component in the treatment process and is required for all older patients at risk. Strategies for nutritional intervention involve a personalised approach, targeting the cause or in some circumstances, alleviating the signs and symptoms. For example, choosing a less emetogenic or gut-toxic chemotherapy regimens that do not aggravate any pre-existing nutritional impact symptoms may be more tolerated by older patients. Pharmacologic (e.g., prokinetics, antiemetics, corticosteroids) and non-pharmacologic (e.g., avoiding fat and very sweet or salty foods, opting for dry, bland food) strategies may be used to reduce symptoms and improve nutritional intake[21]. For patients where malnutrition is a prominent feature, offering a dietary treatment plan, food education,

nutritional counselling, and coordination of nutritional supports are essential. This may involve referral to a dietitian for a comprehensive assessment to identify deficiencies in energy, protein, and micronutrient intake. If the diet was insufficient, prescription of individualised diet and oral nutritional supplements (ONS) are warranted. If persistent or remaining suboptimal despite ONS (e.g., < 50% of dietary requirements for a week), enteral feeding should be considered. Enteral feeding may also be considered if food absorption is preserved but the site of the cancer precludes adequate oral intake or food transport (e.g., head and neck or oesophageal cancers). Parenteral feeding may be useful if gut absorption is impaired. However, in some circumstances, supportive care alone and end of life care may be more appropriate, particularly in the setting of a rapidly progressive, terminal disease.

The European Society for Clinical Nutrition and Metabolism (ESPEN)[22] recommends that older adults need an energy intake of at least 30 kcal per kg body weight and day, and this is individually adjusted to nutritional status, physical activity level, disease status, and tolerance. The recommended protein intake for older patients at risk of malnutrition (e.g., frail, multimorbid) should be at least 1 g/kg, and up to 2 g/kg BW and day in case of severe illness or malnutrition[23]. Notably, protein requirements are inversely proportional to energy intake, thus both must be concurrently managed. Surgeries involving gastrectomy or intestinal resections can cause impaired absorption of calcium, vitamin B12, folate, or iron and lead to micronutrient deficiencies, and should be monitored and corrected with supplementation. Similarly, patients with pancreatic insufficiency either from surgery or cancer are at high risk of micronutrient deficiencies, such as fat-soluble vitamins (A,D,E,K) and minerals (calcium, magnesium, iron), and must also be managed proactively.

Provision of social supports for transport and meal shopping, meal planning and preparation, supervised mealtimes, or meal delivery may improve food access or intake, particularly for patients with functional or cognitive impairments. Regular physical activities and referral to exercise programs are essential to optimise muscle strength, endurance, and wellbeing of patients with sarcopenia and frailty.

Conclusion

The combined presence of age-related sarcopenia, increased prevalence of malnutrition, and cachexia from acute and chronic illness, including cancer make older adults more vulnerable to nutritional impairments and associated negative outcomes. Assessment of the patient's overall health status must be incorporated in the routine oncological care and the optimal nutritional intervention must be tailored to specific patient needs and preference.

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