Geriatric Oncology

for daily practice by

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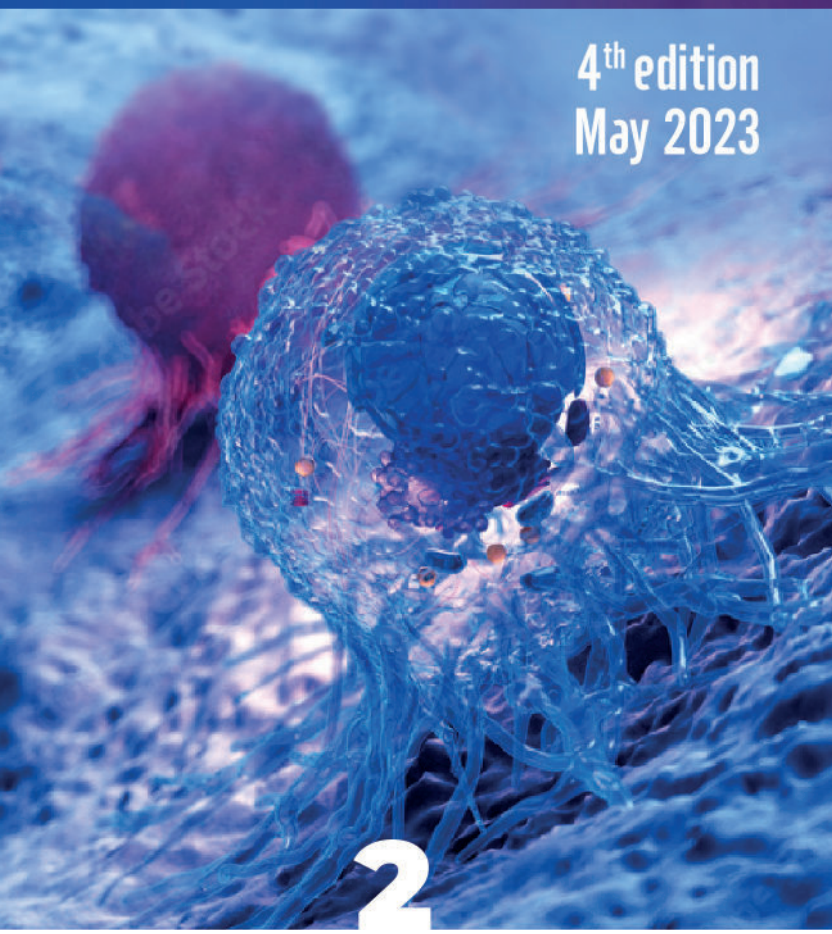

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Treatments and medical care

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INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

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SOCIÉTÉ FRANCOPHONE D'ONCO-GÉRIATRIE

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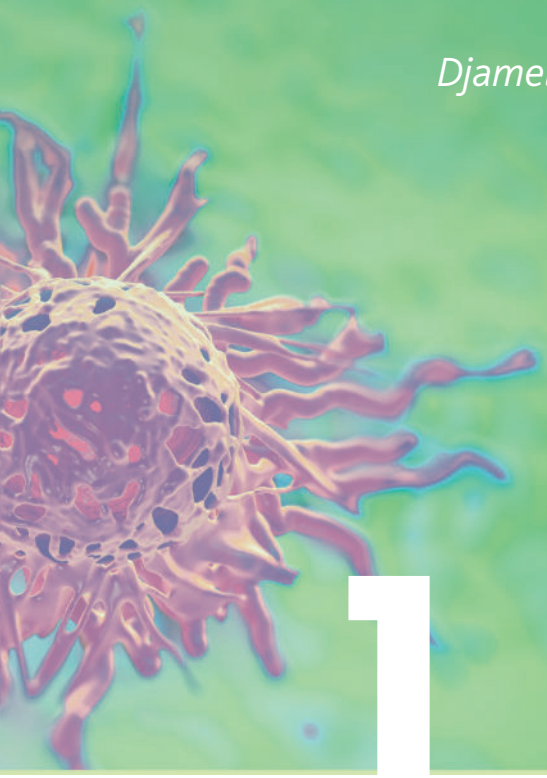
INTRODUCTION

Djamel Ghebriou



1

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.

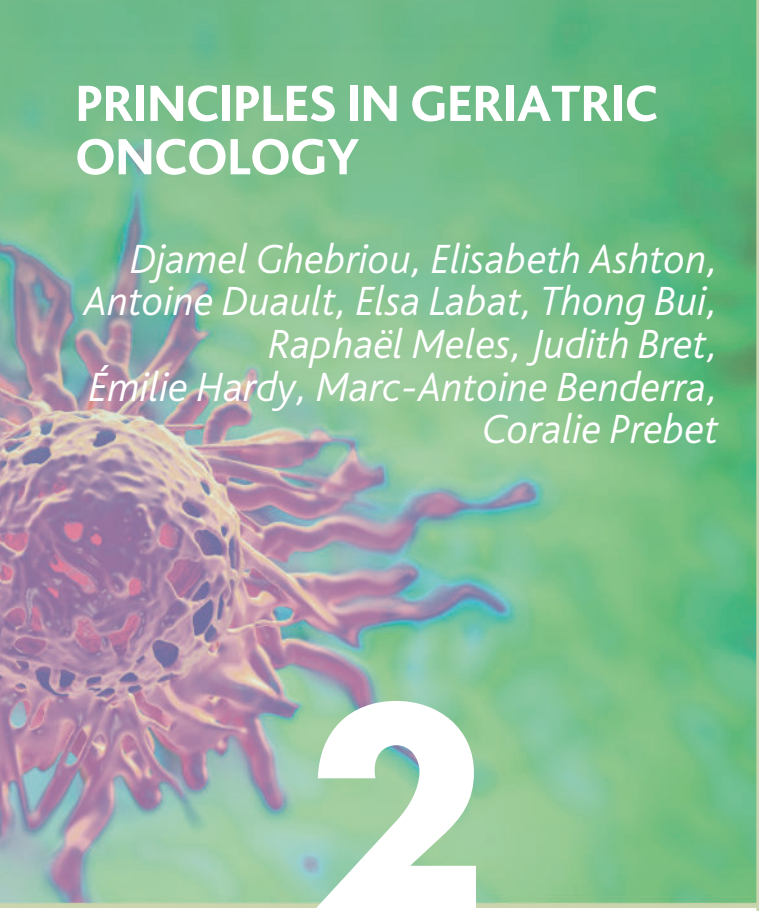
Patient functional age is a primary determination when considering appropriate therapy for an older patient with cancer. The Geriatric Assessment is used to determine the "right level" of cancer treatment ensuring the

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.

PRINCIPLES IN GERIATRIC ONCOLOGY

Djamel Ghebriou, Elisabeth Ashton, Antoine Duault, Elsa Labat, Thong Bui, Raphaël Meles, Judith Bret, Émilie Hardy, Marc-Antoine Benderra, Coralie Prebet



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The aim of geriatric oncology management is to analyse geriatric and oncological complexities in order to choose the most appropriate treatment. This chapter outlines several rules for optimising cancer management in older patients while considering these geriatric and oncological complexities. It is a question of offering the most appropriate treatment.

Life expectancy according to age

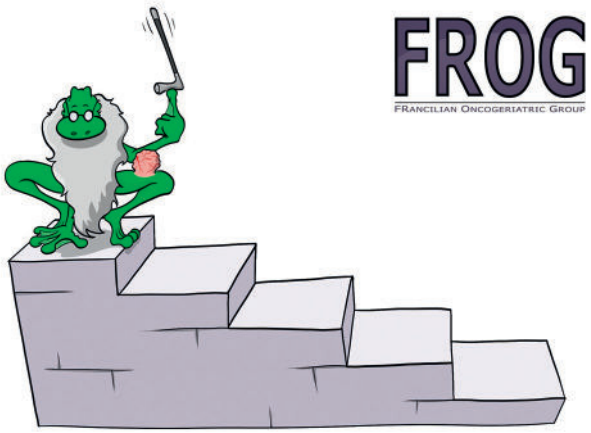
The most well-known life expectancy figures for women and men relate to life expectancy at birth. As an example, in France it is 85.6 years for women and 79.7 years for men (INSEE 2019). However, an 80-year-old man is not at the end of his life and has on average 8 more years of life expectancy (Table 1). Older patients are not necessarily at the end of their life but potentially have several years of life left. Data on life expectancy according to age is available for each country on the following website: https://www.worldlifeexpectancy.com/

Table 1: *Life expectancy according to age in France (INSEE 2019)*

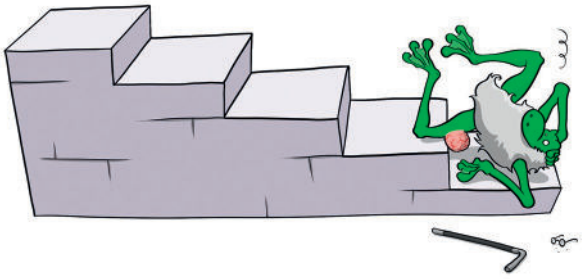
	WOMEN	MEN
At birth	**85.6 years**	**79.7 years**
At 65 years	21 years	17 years
At 70 years	17 years	13 years
At 80 years	**10 years**	**8 years**
At 85 years	7 years	5 years
At 90 years	4 years	3 years
At 95 years	3 years	3 years

Any medical event can be complicated by a loss of functional independence in older patients

Imagine an older patient on a flight of steps. This patient is unique in terms of their life history, resources (functional, cognitive and spiritual) and the quality of their environment.

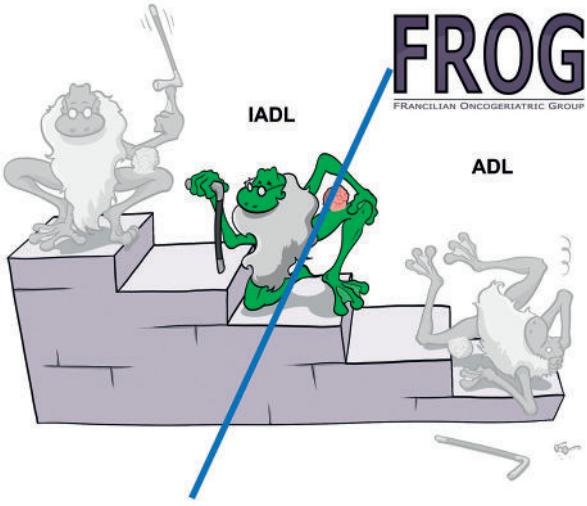


When a medical event occurs (infection, fall, complicated surgery, poorly tolerated chemotherapy, etc.), the older patient may tumble down the steps. There are numerous risks involved such as decompensation of chronic diseases, hospitalisation and loss of independence.



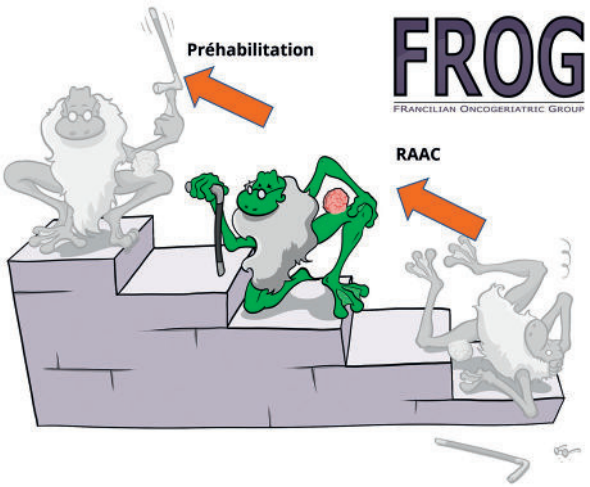
Along with treating the acute medical problem and any decompensated diseases, multifaceted interventions (physiotherapy, speech therapy, nutritional and psychology support, social care, etc.) are implemented to help them to "climb back up the steps".

A young patient will recover completely in a few days whereas an older patient will struggle to get back on the first step and their functional independence will suffer as a result. Therefore, the impact of events is often more detrimental in older or much older patients.



Our vulnerable patient, who started off independent, will see their activities of daily living abilities decrease. Each time the patient drops down a step, they lose abilities, firstly IADLs (instrumental activities of daily living), then ADLs (activities of daily living), from going to the shops to bed-to-chair transfers on the lowest steps. The patient's life plans may need to change, with some requiring hospitalisation for aftercare and rehabilitation, and others needing home care adjustments. Work on "climbing back up the steps" is therefore crucial and needs to be started as soon as possible to prevent the development of iatrogenic dependence.

This concept underpins the principles of prehabilitation (through physical activity and nutritional management) prior to surgery and enhanced recovery after surgery (ERAS).



Iatrogenic dependence

Iatrogenic dependence is the loss of functional independence experienced by an older individual following a period of hospitalisation. Early rehabilitation is essential for older patients after a serious medical event. It determines the recovery of functional independence and the length of the hospital stay. A period of time without added complications is required for optimal functional recovery. In fact, all intercurrent medical events contributing to geriatric cascade (falls,

organ decompensation, infection, deep vein thrombosis, etc.) carry the risk of preventing the patient from climbing back up the steps and recovering functional independence. The main progress must be made rapidly as the level of independence will plateau after a few weeks of rehabilitation. Although we all know of exceptions to this rule, it is a strong argument for early rehabilitation.

Consultation approach for an older patient

The geriatric oncology consultation provides an opportunity to assess a patient's strengths and weaknesses at a specific point. Ideally, this should be carried out when the patient is in a stable state of health. Assessing a patient during an acute medical event, at the bottom of the steps, which reduces their cognitive and physical performance in a biased way, will often prevent a treatment decision from being made. It is therefore better to reassess the patient at a subsequent point.

The consultation begins in the waiting room where the practitioner should ideally go and fetch the patient him/herself. Observing any difficulties the patient may have getting out of the chair unaided and watching them walk to determine any mobility issues enables the practitioner to assess frailty at the beginning of the geriatric assessment.

It is advisable to start by addressing only the patient in order to form a clinical impression. It is strongly recommended that patients have an accompanying person who can confirm or rectify incorrect information they provide, particularly if they have cognitive impairment. Comprehensive geriatric assessment is covered in detail in Volume 1 and will not be detailed here.

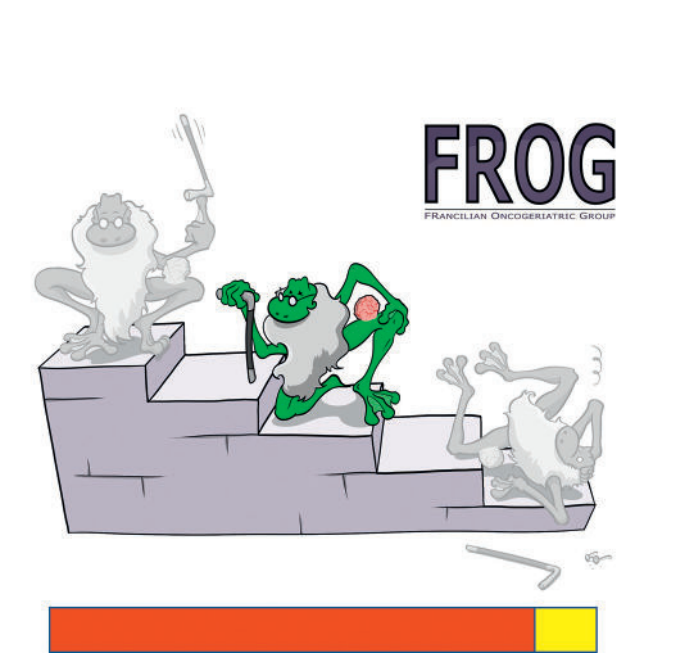
Functional reserve

Functional reserve can be roughly described as the ability to respond to stress. The patient in this picture seems to have a fighting spirit.

However, the treatment offered by the doctor will prove to be excessively toxic, resulting in unplanned hospitalisation and the patient moving down the steps.

It was, however, predictable as the patient's health bar was particularly low.

This health bar could be likened to a functional reserve bar. The identification of geriatric syndromes during the geriatric assessment gradually depletes this functional reserve bar. Social isolation, multiple comorbidities, polymedication, mobility issues with fall risk, sensory disturbances, malnutrition, cognitive and/or thymic impairment, dependency on ADLs and/or IADLs and continence disorders are all factors which weaken the older patient and position them on the functional reserve flight of steps.



A one-round fight

When there is a severe complication with cancer treatment (whether it is surgery, radiotherapy or systemic therapy, etc.) resulting in the older patient moving down the steps and being hospitalised, we need to strive for a minimum loss of functional reserve and hope for a good recovery without compromising the patient's life plans or ability to remain in their own home. Unlike for young patients, whose functional impairment is easier and quicker to reverse, meaning that toxic cancer treatment can be repeated, there will often be no second round for older patients, potentially precipitating the patient into palliative care.

Limit the number of sequential treatment cycles

As excessive toxicity can put an end to a cancer treatment plan, as explained above, in sequential treatment, it is important to avoid compromising the most important treatment. If, for example, localised cancer surgery is potentially curative, an older patient must not be made inoperable due to the excessive toxicity of neoadjuvant chemotherapy.

Prognostic significance of geriatric assessment

Decision-making algorithms are limited in terms of treatment recommendations for older patients with cancer

but do not include the Balducci classification of fit, vulnerable and frail patients. However, the geriatric oncology assessment has a prognostic significance as with the same stage of cancer, fit patients will live longer than vulnerable patients, who have a better prognosis than frail patients.

The frailest patients who benefit the most from cancer treatment are those who can receive anti-hormone therapy, like for breast or prostate cancer. Frail patients who need to receive chemotherapy often have a poor prognosis and do not always have the functional reserve to recover physically even if they are responding to the cancer treatment.

Discussing a tumour versus discussing a patient with a tumour

According to the literature, geriatric assessment results in changes to the treatment decision made in the multidisciplinary consultation meeting in 20% to 30% of cases. According to an ELCAPA cohort study (Caillet JCO 2011), it is usually necessary to reduce the treatment intensity in nearly 21% of patients. The factors associated with this change of decision are malnutrition and activities of daily living. As a reminder, ADLs assess the patient's ability to perform transfers independently, move around the house independently, wash and dress independently, eat independently and use the toilet independently. It is clear that this basic, essential information is all that is required to change the treatment decision one in five times. In conclusion, the heterogeneous ageing of our patients means that the wrong decision is made in 20% of cases if we focus on the tumour rather than on the patient who has the tumour.

Limitations of cancer treatment recommendations

The vast majority of current recommendations are based on studies of subjects who are generally young and in good health. Older patient subgroups, the lower age threshold of which is highly contentious (often 65 years), do not generally enable conclusions to be drawn as to how to treat patients in their eighties. There are numerous treatment recommendations involving geriatric oncology assessment to help with decision making.

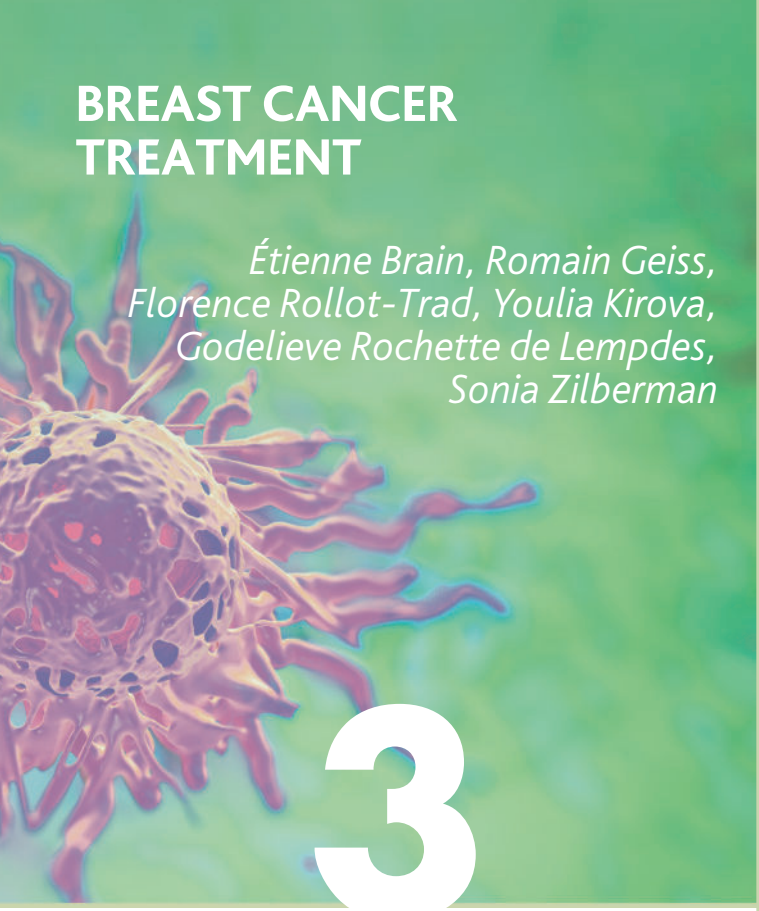
The recommendations try to offer a scenario that predominantly applies to a young, homogeneous population for each stage of the disease, but these cannot be strictly applied to an older, heterogeneous population without running the risk of proposing unsuitable care. Although we need to make every effort to apply best practice recommendations, these cannot be considered as an ultimate truth when treating older patients. Therefore, in geriatric oncology "there is no absolute truth, just stories". When it comes to an oncologist writing a new chapter of an older patient's life, they cannot write the same story for all patients and it can only be cohesive if the previous chapters of their life story are taken into account.

"How can I write the rest of the story when I don't know the start? "

These main principles, which are partly based on hands-on experience, should help with choosing the right treatment for older patients with cancer.

BREAST CANCER TREATMENT

Étienne Brain, Romain Geiss, Florence Rollot-Trad, Youlia Kirova, Godelieve Rochette de Lempdes, Sonia Zilberman



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This chapter includes specific recommendations for older patients by the Société Internationale d'Onco-Gériatrie (International Society of Geriatric Oncology or SIOG) and Nice/Saint-Paul-de-Vence.

Screening

There is no data to suggest that organised mass screening for breast cancer is required after the age of 74. However, continuing individual screening after this age may be appropriate depending on the patient's overall state of health.

Surgery

Surgery remains the first-line treatment for the majority of older patients with early-stage breast cancer.

Conservative surgical treatment must be carried out where possible, followed by (usually hypofractionated) radiotherapy.

Mastectomy is indicated for large tumours (which cannot be accessed with neoadjuvant therapy) or multicentric tumours, or when postoperative radiotherapy will not be possible.

The sentinel lymph node technique must be offered as often as possible.

If the sentinel lymph node biopsy is positive, axillary dissection must be discussed and avoided if possible. Instead, axillary radiotherapy must be used, particularly in cases of minimal lymph node involvement and hormone-dependent cancer requiring adjuvant hormone therapy.

For ductal carcinoma in situ (DCIS), treatment depends on the grade of the tumour and the patient's life expectancy:

- High-grade DCIS must be operated on and irradiated if the patient's condition permits and hypofractionated radiation regimens must be prioritised.

- For low- or intermediate-grade DCIS, delaying surgery or postoperative radiotherapy can be discussed according to life expectancy and comorbidities.

Finally, oncoplastic and reconstructive surgery may be performed on the older patient, taking into account their expectations and comorbidities.

Radiotherapy

It is used "properly" much less frequently in older women, with only 40% benefiting from it after the age of 75. Hypofractionated regimens are approved and can simplify logistics if the patient has to make a long journey or has difficulty travelling. Several trials have been conducted to find out if radiotherapy can be omitted in some situations, specifically in older women. They all showed that radiotherapy reduces the risk of locoregional recurrence but does not impact overall survival, despite a significant decrease of over 10 years in some cases. An Oxford meta-analysis showed the potential beneficial effect of locoregional radiotherapy on overall survival (demonstrable effect after 5 years of survival) in adults of no specific age, so it not being used in older women for small tumours with a good prognosis without lymph node invasion after conservative surgery is still much debated. But attitudes vary from country to country, sometimes with the choice of radiotherapy alone or hormone therapy alone.

Rather than not using radiotherapy for forms with a very good prognosis after conservative surgery, the SIOG Radiotherapy Group suggests adapting the technique used and prioritising hypofractionated regimens.

Interesting technique adaptations include protecting organs at risk (OAR) such as radiation in the lateral decubitus or ventral decubitus position (Figure 1), irradiated volume modulation (sometimes partial breast irradiation in selected patients) and fractionation tailored to the patient's condition. With modern equipment, hypofractionated radiotherapy can be used with one fraction a week and partial breast irradiation can be offered. Breast cancer radiation can be carried out in a highly tailored way in older individuals.

Systemic therapy at the neoadjuvant/adjuvant stage

- *Hormone therapy*

If the patient refuses a mastectomy, neoadjuvant aromatase inhibitor hormone therapy in tumours with oestrogen receptors (ER+) has a response rate of around 40%, with 40-45% for secondary conservative surgery. The maximum response rate is reached between 4 and 8 months. Depending on the tolerance problems, tamoxifen may be used with a slightly lower response rate.

But be aware that exclusive "neoadjuvant" hormone therapy (without considering surgery) is only indicated for ER+ tumours in patients with a life expectancy considered to be limited and/or who are considered as not being able to tolerate tailored surgical intervention and/or who refuse this. In these cases, aromatase inhibitors will be used instead of tamoxifen with 2- to 3-year tumour control.

The efficacy of adjuvant hormone therapy does not vary according to age, with aromatase inhibitors (anastrozole, letrozole or exemestane) having slight superiority over tamoxifen (anti-oestrogen) in terms of overall survival. The therapeutic choice must be primarily guided by tolerance and comorbidities to ensure the best compliance.

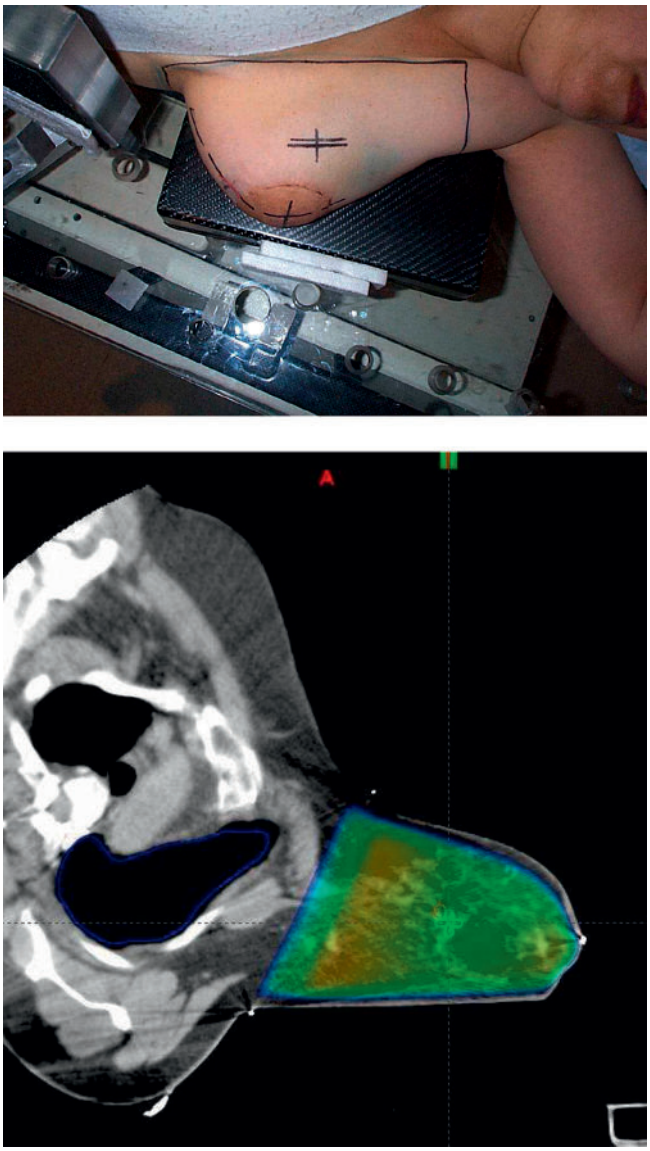

Figure 1: *A. Patient's position and immobiliser. B. Dosimetry of single breast irradiation in isocentric lateral decubitus position with even distribution of the radiation dose and completely avoiding the patient's heart and lungs.*

As adjuvant treatment, the standard length of hormone therapy is 5 years and an extension can be discussed for women in a good overall state of health, resulting in

longer life expectancy, particularly if there is a high risk of relapse due to significant lymph node invasion.

Adjuvant hormone therapy is not always necessary, particularly for small pT1a pN0 tumours (stage IA) and in cases of multimorbidity.

• Chemotherapy (Table 1)

Published data (clinical trials or cohorts) concerning older patient populations (> 65-70 years) large enough to be representative all show a major interaction between the efficacy of adjuvant chemotherapy and the status of hormone receptors. The impact of chemotherapy on survival is eliminated for ER+ status, whatever the other standard anatomo-clinical prognostic factors are (pT, pN, grade, proliferation, etc.). Therefore:

- ER- tumours: the value of adjuvant chemotherapy is clearly demonstrated for these hormone-resistant tumours, even at an advanced age, but depends on the life expectancy that needs to be estimated (> 45 years to exceed the peak recurrence incidence of these phenotypes);
- ER+ tumours: hormone therapy alone remains the standard adjuvant systemic treatment. For tumours with certain unfavourable prognostic factors, chemotherapy may be discussed as an option, no doubt with marginal benefit (see ASTER 70s trial below), but this decision must be justified and submitted to the MDTM, and formulated after seeking a specific geriatric opinion.

The risk of serious side effects (grade 3-5) from adjuvant chemotherapy can be determined by a specific score including geriatric variables, and where the most important factor is the planned duration of chemotherapy, with a threshold of 3 months: the CARG-BC score. Adjuvant chemotherapy must be accompanied by primary prophylaxis of febrile neutropenia when there is a 10% risk, given the more serious consequences of such a complication in older patients.

• Regimens

The most widely documented/approved regimen remains short (< 3 months): 4 cycles of adriamycin + cyclophosphamide (AC) anthracyclines or 4 cycles of taxotere + cyclophosphamide (TC), with the TC regimen

possibly being superior to the AC regimen, avoiding the cardiotoxic toxicity of anthracyclines.

Similar to the 4 TC regimen and its duration, but without a high level of proof, a regimen of 12 weekly sessions of paclitaxel is considered as an option due to the low toxicity of grade 3-4. We must, however, emphasise the higher risk of grade 2-3 neuropathy in older patients on taxanes. It is double (up to 30%) of that observed in younger patients.

Sequential regimens (anthracyclines then taxanes, for example 3 EC then 3 docetaxel) have not been documented in the older population. Almost doubling the duration of 4 AC or 4 TC regimens which do not exceed the critical threshold of 3 months for adjuvant chemotherapy (see CARG-BG score), they cannot be considered as standard and are associated with higher risks of severe toxicity and hospitalisation.

- *Anti-HER2 targeted therapy (Table 1)*

If chemotherapy is chosen (1st decision-making stage) and if the tumour is HER2 3+ (+++) and/or FISH+, the anti-HER2 monoclonal antibody trastuzumab is added with cardiac monitoring (opt for cardiac ultrasound in the case of cardiovascular comorbidities) due to the low risk of cardiac side effects. The standard duration of trastuzumab treatment remains a year, despite a recent meta-analysis showing that shorter regimens do not have inferior relapse-free survival, particularly for N0 tumours. These shorter durations can therefore be discussed, particularly in the presence of cardiovascular risk.

Despite having a European MA, dual blockade (trastuzumab + pertuzumab) in early treatment stages is not covered by the health insurance system in several European countries, including France. Discussions pertaining to its use in younger adults remain scarce so are highly theoretical when it comes to older patients.

The most commonly used and approved chemotherapy regimens associated with trastuzumab are 4 TC and 12 weeks of paclitaxel (called the "Tolaney" regimen). It is best to avoid anthracycline-based chemotherapy due to the increased risk of cardiac toxicity.

It is worth noting that a Japanese study suggests that treatment with trastuzumab only, without chemotherapy,

could be an alternative to standard chemotherapy + trastuzumab in patients aged 70-80. But its non-inferiority design was very ambitious and it is not sufficient to draw a conclusion on the validity of this de-escalation. Despite this, SIOG recognises the benefit of such a strategy for frail older patients unable to tolerate a systematic combination with chemotherapy, but regulations are in place linking the prescription of adjuvant trastuzumab to a chemotherapy prescription to ensure coverage by the French health insurance system.

In the case of neoadjuvant therapy with chemotherapy + anti-HER2 treatment and in the presence of an incomplete histological response, salvage treatment with T-DM1 may, in theory, be offered. It is an antibody drug conjugate or ADC ("vectorised" trastuzumab + DM1 chemotherapy). Due to having a better therapeutic index than standard chemotherapy, it can replace trastuzumab, but with caution and only in patients classified as fit as no sound data is available for the older population. It is what we call the "post-neoadjuvant strategy".

- *Signatures*

Prognostic and predictive genome signatures, developed to better identify adjuvant chemotherapy indications for mainly luminal breast cancers (the most frequent cancers in older patients), have unfortunately been rarely studied in older patients. TAILORx and RxPONDER non-inferiority trials using Oncotype Dx® recruited up to 15,000 subjects, including at best 10% over the age of 70. The trials showed no benefit of adjuvant chemotherapy in patients with RO+ HER2 0, N0 or N1 breast cancer (1 to 3 positive lymph nodes) and an OncotypeDX® recurrence score of ≤ 25. But no data is known relating to a higher score in older patients.

ASTER 70s/GERICO-11 remains the largest prospective trial examining such a tumour aggressiveness signature, the genomic grade index (GGI), in an adjuvant context over the age of 70 years. It recruited 2,000 patients over a period of 4 years, 1,100 of whom with a high GGI were randomised between chemotherapy (in accordance with approved data from the literature, i.e. 4 TC or 4 AC) and no chemotherapy, in addition to hormone therapy. Presented at ASCO 2022 with 6 years of median follow-up, its main "intention-to-treat" analysis does not show any significant benefit to overall survival by adding

chemotherapy to hormone therapy in cases of high GGI [90.6% *vs* 89.4% at 4 years, HR 0.79 (0.60-1.03), $p = 0.08$]. ASTER 70s therefore recommends extreme caution when choosing this treatment for older patients, as although there seems to be an identifiable benefit in the *per protocol* analysis, it remains marginal.

• *Bone resorption agents*

Bisphosphonates may be offered as adjuvant therapy for older patients with a high risk of relapse in addition to the recommended bone densitometry prior to commencing aromatase inhibitor hormone therapy. These reduce the risk of relapse or death in the postmenopausal population, even more significantly after the age of 70. However, the treatment methods are not well defined (product, dose, duration: for example 4 mg zoledronic acid every 6 months for 2 years).

• *Immunotherapy*

The use of checkpoint inhibitors such as pembrolizumab (anti-PD-1) is encouraging for aggressive forms (triple negative) of localised breast cancer. Unfortunately, data for the older population is limited (around 10% with a threshold of 65 years) and the tolerance profile raises a number of questions relating both to the immunotherapy and the accompanying polychemotherapy (sequential + carboplatin), which is far from being a tolerable regimen for older patients.

Table 1: *Adjuvant chemotherapy and trastuzumab.*

Chemotherapy	
Indications	Primarily ER- and HER2 3+ and/or FISH+ tumours (and if pT > 5 mm)
Regimens	
4 TC, 4 AC (or 6 CMF)	Approved
Weekly paclitaxel x 12	Option
Liposomal doxorubicin	Potential benefit as less cardiotoxicity, but no data

"Sequential" chemotherapy (anthracyclines then taxanes)	
No data for the older population	
Weekly capecitabine or docetaxel	No indication
Primary prophylaxis of neutropenia with G-CSF	Even if the risk of febrile neutropenia is > 20% (threshold used in young adults)
Trastuzumab	HER2 3+ and/or FISH +
Indications	No restriction if chemotherapy chosen
Regimens	
4TC + trastuzumab	The most widely approved
Weekly paclitaxel x 12 + trastuzumab (Tolaney regimen)	Option
Docetaxel carboplatin x 6 + trastuzumab	Highly unlikely for an older patient as carboplatin AUC 6!
Trastuzumab without chemotherapy	May be considered, particularly in unfit patients (+ hormone therapy if ER+ tumour)
Duration	1 year Possible shorter duration for small N- tumours or cardiac risk

Systemic therapy at the metastatic stage

- *Hormone therapy*

This is the standard treatment for metastatic ER+ breast cancer in older women. Its combination with CDK4/6 inhibitors is a new first-line treatment standard. This combination is usually well tolerated. But in older patients, it often has more grade ≥ 2 side effects resulting in treatment interruptions, requiring close haematological, digestive and pulmonary monitoring, particularly in frail or isolated patients, or those with cognitive impairment. Fulvestrant as first-line treatment is a good

alternative in frail hormone-naive patients, particularly with exclusive bone disease.

• *Chemotherapy*

This is indicated in cases of ER- phenotype, hormone resistance or visceral crisis. Monochemotherapy is preferred with specific doses which are adjusted according to the pharmacokinetic parameters (interactions with polydrugs, renal function) and functional decline. Polychemotherapy remains an uncommon option, in cases of rapidly changing criteria for example. G-CSF primary prophylaxis must be discussed in relation to the risk of myelotoxicity. Weekly paclitaxel (without G-CSF), capecitabine (without G-CSF), liposomal anthracyclines (with G-CSF), and vinorelbine (discuss G-CSF) are standard regimens. Eribulin and nab-paclitaxel (without requiring steroid premedication) are also effective treatments which, like taxanes, require particular vigilance relating to increased neurotoxicity.

Whether hormone therapy or chemotherapy is used, anti-HER2 targeted therapy is also required for HER2 3+ and/or FISH+ status. The choice of combination partner remains difficult. As first-line treatment, pertuzumab + trastuzumab dual blockade with docetaxel is only easy to use in fit patients. Weekly paclitaxel may be used instead of docetaxel due to its better clinical tolerance profile in older patients. Metronomic oral cyclophosphamide is another good alternative, particularly when the patient is considered vulnerable. As second-line treatment, despite beneficial HER2 targeting, T-DM1 ADC remains a form of chemotherapy with more grade 3-4 side effects in older patients. Trastuzumab and lapatinib can each be combined with hormone therapy. Trastuzumab deruxtecan (T-DXd) is the latest promising agent for HER2 3+ and/or FISH+ breast cancer, but also for breast cancer known as *HER2 low*, which means without clear HER2 overexpression (HER2 1+ or HER2 2+/FISH-). As usual, very few older patients participated in the registration trials and the tolerance profile is much less favourable with new side effects such as interstitial pneumonia. It is therefore currently impossible to make any serious recommendations relating to its use in the older population.

The antiangiogenic antibody bevacizumab is active in combination with weekly paclitaxel for metastatic breast

cancer. It should be reserved for triple negative forms. It is, however, essential to respect contraindications and be attentive to side effects which increase with age (such as high blood pressure, thrombotic accidents or proteinuria), often resulting in stopping treatment.

Immune therapy for metastatic triple-negative breast cancer seems effective as first-line treatment when combined with chemotherapy and if there is tumour expression of PD-L1 receptor (CPS ≥ 10), but available specific data for the older population remains too limited to enable serious recommendations to be made, particularly taking into account the tolerance profile.

Generally speaking, chemotherapy is often used at lower doses than in younger patients, like some targeted treatments, making a strong case for the (possibly pharmacokinetically guided) gradual dose escalation strategy (see Clinical Research chapter).

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OVARIAN CANCER TREATMENT

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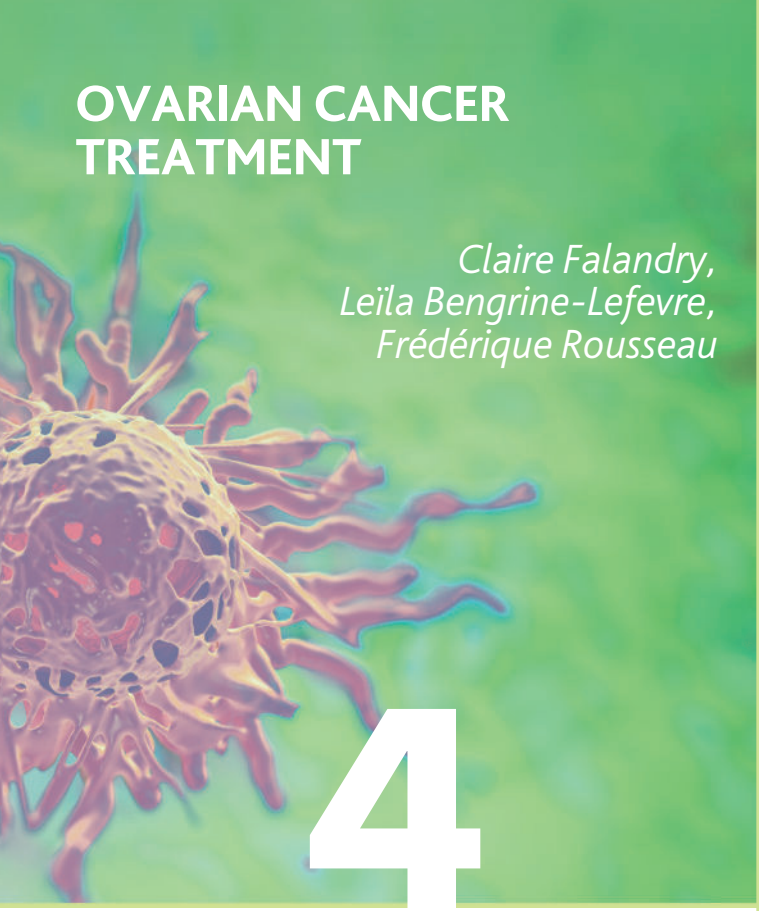

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Ovarian cancer is the leading cause of death due to gynaecological tumours, with a world standardised incidence rate (WSR) of 7.5 cases/100,000 people-years and a mortality rate of 3.9 cases/100,000 people-years (5139 incident cases and 3479 deaths in France in 2018). The median age at diagnosis is 68 years.

The average age of death is 74 years.[1] This increase is due to the longer survival times linked to the higher proportion of patients benefiting from an oncogeriatric approach.

This improved prognosis is not homogeneous and populations who are oldest at diagnosis have benefited least from the therapeutic innovations developed since the 2000s. Age remains a heterogeneous treatment criterion for ovarian cancer and surgical and medical subtreatments.

This chapter provides a summary of the literature relating to epithelial ovarian cancers in older adults based on recommendations by the INCa (French National Cancer Institute) made in 2018.[2,3]

Distribution of FIGO stages in women aged over 70[4]

STAGE I	14.9%
STAGE II	7.1%
STAGE III	53.4%
STAGE IV	19.8%
Unknown	4.6%

Treatment recommendations

The treatment principle usually involves (forms II and III) a sequential combination of surgery, adjuvant and/or neoadjuvant chemotherapy and maintenance treatment with targeted therapy(ies).

- *Histological diagnosis and surgery*

Whatever the stage of the disease, the aim is to achieve complete surgical cytoreduction (CC0). Although the benefit of complete surgery remains regardless of age, the rate of CC0 surgical procedures reduces significantly in the oldest patients and peri-operative morbidity and mortality increase. This means that primary surgery is not indicated in certain categories of patients, who are steered towards primary (neoadjuvant) chemotherapy instead:
- patients aged over 75 with a FIGO stage IV tumour;
- patients aged over 75 with a FIGO stage III tumour and one or more comorbidities.

Whatever the age of the patient, the surgical plan includes total hysterectomy with bilateral oophorectomy, omentectomy and appendectomy,[3] along with other surgical procedures based on observations (multiple peritonectomy procedures, digestive resections, etc.). It is recommended that treatment be carried out by specifically trained teams and, in many cases, based on staging including a coelioscopic exploration of the disease. This enables a standardised evaluation of the invasion of 9 peritoneal spaces (included in the record, PCI [Peritoneal carcinomatosis index] or Fagotti score, etc.) and multiple appropriately sized biopsies to be carried out for anatomical pathology testing, somatic BRCA mutation detection and homologous recombination deficiency (HRD) score calculation.

For early-stage cancer:
- surgery can be performed via coelioscopy if local conditions permit and there is no risk of rupturing the tumour mass, otherwise, it is performed via median laparotomy. A sample of peritoneal fluid is sent to anatomical pathology at the same time;
- it involves at least a total hysterectomy with bilateral oophorectomy, omentectomy and appendectomy[3].

For advanced-stage cancer:
- surgery will be performed via median laparotomy;
- in addition to the basic surgical plan, it includes a resection of all macroscopic intraperitoneal lesions.[5].

Lymphadenectomies (pelvic or para-aortic), which cause significant morbidity, are not beneficial in treating advanced-stage cancers (FIGO III-IV[6]). Lymph node samples can be taken if there are suspected radiological lesions on the scan. They are also used in anatomical pathology testing of early forms (stages I-II). Their omission in certain cases can be discussed at an MDTM.[2,3,7]

The surgical treatment decision is therefore guided by an assessment of the complexity of the surgical plan, the patient's motivations for surgery and the geriatric assessment. Complex surgery will be more readily approved for patients whose ageing presents no significant issues, and vice versa. Surgery must be performed by teams with ovarian cancer surgery experience and pre- and post-operative rehabilitation training.

When primary surgery does not seem possible due to the spread of the disease (unresectability criteria), the complexity of the surgery and/or the patient's geriatric condition, neoadjuvant chemotherapy can be offered. In non-geriatric populations, this has been shown to be an alternative to primary surgery, reducing procedure times and peri-operative morbidity and mortality.

In some situations where the geriatric condition of the patient at diagnosis appears incompatible with carrying out a coelioscopy (under short-term general anaesthesia), the cancer diagnosis is based either on performing a scan-guided biopsy[3] or an analysis of ascitic fluid +/- cytoblock. In the latter case, ovarian cancer is diagnosed if there is an associated pelvic mass, histology compatible with a gynaecological tumour and a CA-125/CEA ratio > 25 (to exclude differential diagnoses such as mucinous tumours in particular).

• *Chemotherapy*[3]

Primary chemotherapy must be considered after the age of 70 if there are comorbidities and/or extensive peritoneal carcinomatosis requiring initial complex surgery.[2]

Neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery (CRS) improves overall survival (OS) compared with chemotherapy alone in patients aged 75 or over with ovarian cancer, including in those aged over 80 with advanced disease and comorbidities.[8]

Standard chemotherapy includes six cycles of carboplatin AUC 5 paclitaxel 175 mg/m^2 every 3 weeks or a weekly regimen of carboplatin AUC 2 and paclitaxel 60 mg/m^2 D1D8D15 D1 = D21.[9]

The EWOC-1 trial conducted by the GINECO group in a selected population of older, vulnerable patients showed the deleterious effect of carboplatin monotherapy on overall survival.[10]

Hyperthermic intraperitoneal chemotherapy (HIPEC) showed a favourable impact on overall survival in patients with FIGO stage III ovarian cancer having undergone interval surgery, in a younger population, with tolerance (particularly nephrological) improved by the use of sodium thiosulphate.[11] It seems feasible in some selected older patients[12] at the cost of increased perioperative morbidity and mortality and longer hospital stays.

• *Therapeutic indications*

Stage IA and IB - grade 1

First-line treatment: surgery alone.

Stage IA and IB, grade 2 and 3, CI

First-line treatment: surgery and adjuvant chemotherapy, 6 cycles of carboplatin and paclitaxel.

Stage III - IIIb

First-line treatment: surgery and adjuvant chemotherapy, 6 cycles of carboplatin and paclitaxel.

Stage IIIC (& stage IV pleural)

First-line treatment: there are 2 equivalent options:[4,5] either primary cytoreduction followed by adjuvant chemotherapy

with carboplatin and paclitaxel or open coelioscopy to assess lesion spread (Sugarbaker score), then primary chemotherapy with 3 cycles of chemotherapy, followed by morphological reassessment and surgical cytoreduction if resectable disease, if not, continuation for up to 6 cycles and reassessment.

Both therapeutic strategies have equivalent overall survival but lower post-operative mortality in the neoadjuvant chemotherapy arm.

Stage III unresectable, stage IV

Palliative surgery can sometimes be offered, providing a quality of life benefit.

• *Therapeutic alternatives*

If the patient is allergic to paclitaxel, it can be replaced by docetaxel or pegylated liposomal doxorubicin.

• *Maintenance treatments*

Older patients must not be excluded from maintenance strategies which extend control of the tumour and cancer symptoms and increase the interval between lines of chemotherapy, which are often difficult to tolerate and a source of cumulative toxicity. Access to somatic tumour analysis as soon as the diagnosis is made must be encouraged and different molecules may be proposed in line with current guidance, based on registration studies which usually exclude the oldest patients.

- The addition of bevacizumab to adjuvant and maintenance chemotherapy needs to be assessed at an MDTM if there is macroscopic tumour residue after initial cytoreduction surgery for FIGO stages IIIB to IV or IIIC-IV which are permanently unresectable. 4 to 6 weeks must elapse before starting surgery. For HRD tumours, olaparib can be added for 2 years based on the evidence of data from the PAOLA-1 trial.[13]

- For HRP tumours, niraparib (PRIMA trial) or rucaparib (ATHENA trial) can be offered for their respective indications for up to 3 years, or bevacizumab (independently of the HRD/HRP status) can be offered for 15 months, but these cannot be combined.

The specific data available, from subgroup analyses of registration studies, does not show any difference in

efficacy according to age (< 60, 60-70, > 70 years). An increase in certain cardiovascular toxicities associated with bevacizumab, haematological toxicities, and fatigue associated with PARP inhibitors (PARPi) must prompt increased monitoring. No systematic dosage reduction is recommended in first-line treatment. PARP inhibitors have complex drug interaction profiles which vary according to the molecules. This means that medicines optimisation, working closely with specialist pharmacists, is required for older patients, who are often polymedicated.

Tumour response assessment

CA 125 and CT.

A PET-CT scan can reveal lesions that are not visible on a CT scan and can be used to select patients who are candidates for secondary debulking surgery.

Monitoring[3]

Clinical and CA 125 assessment at 3 months and 6 months, then every 6 months for 2 years, followed by once a year.

PET-CT if clinical manifestation or raised CA 125 levels.

Treatment of recurrence

The majority of patients will experience a recurrence.

Starting chemotherapy based on raised CA 125 levels only has not been shown to impact survival.

There is no standardised approach for older patients. Systemic treatment identical to that in younger patients (platinum salt-based dual therapy) is recommended for the treatment of ovarian, fallopian tube and primary peritoneal cancers in older, non-vulnerable patients.

The recurrence time after the end of the initial treatment is a decisive factor when choosing the treatment.

- ***Relapse eligible for treatment with platinum salts***

Treatment strategies have traditionally taken the disease-free interval into account. Now, a disease is considered to be "eligible for treatment with platinum salts" if it is not resistant or refractory to treatment, or if the patient is allergic to and therefore denied carboplatin treatment.

- Platinum-based chemotherapy:
  - carboplatin AUC5 paclitaxel 175 mg/m^2/3 weeks;
  - carboplatin AUC4 D1 gemcitabine 1,000 mg/m^2 D1D8, D1 = D21;
  - carboplatin AUC 5 + liposomal doxorubicin 30 mg/m^2 (D1 = D21).[8]

Bevacizumab can be added for the first platinum-sensitive relapse until progression, combined with carboplatin and gemcitabine, in patients not already treated with first-line bevacizumab.

- *PARP inhibitors may be offered as maintenance treatment for patients with complete or partial response receiving platinum salt-based chemotherapy, with olaparib (SOLO2 trial) in cases of BRCA1 or BRCA2 mutation and with niraparib (NOVA trial) or rucaparib (ARIEL 2 trial) regardless of the mutational status. As mentioned below, clinical, haematological and pharmaceutical monitoring must be intensified.*

- *Platinum-resistant relapse (disease-free interval < 6 months) or refractory relapse (progression during treatment)*

- Monochemotherapy:
  - liposomal doxorubicin 40 mg/m^2;
  - weekly paclitaxel;
  - topotecan 1.25 mg/m^2 D1 to D5 (D1 = D21) or 4 mg/m^2 weekly;
  - gemcitabine;
  - oral cyclophosphamide;
  - oral etoposide.

Bevacizumab can be added for the first platinum-resistant relapse until progression, combined with paclitaxel, topotecan or pegylated liposomal doxorubicin if not pre-exposed to VEGF-targeted treatment.

The administration of bevacizumab in addition to chemotherapy will be discussed if the patient has not already received it, after conducting a further GA and checking that there are no contraindications.

Surgery must only be indicated if the patient has responded to chemotherapy and if the disease seems to be fully resectable (in particular for operable patients

with localised recurrence and in complete remission for over 12 months after initial treatment).

- *If patient is not eligible for chemotherapy*

Low-toxicity hormone treatments will need to be considered if hormone receptors are positive, but are not recommended.[3]

Finally, all older patients must be provided with supportive care in addition to chemotherapy.

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ENDOMETRIAL CANCER TREATMENT

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In the absence of existing, specific recommendations for elderly patients, the authors have prepared general treatment proposals based on the medical literature [1].

Base level treatment is surgical and is based on a total hysterectomy with a bilateral adnexectomycombined with lymph node staging through a sentinel node biopsy (if necessary). Systematic pelvic and lumbo-aortic lymph curettage are no longer indicated (only in the event that ganglionic masses are shown on the imaging). Histological analysis of surgical specimens allows for classification of the lesion according to FIGO staging and for the establishment of 4 types depending on their recurrence risk (low risk, intermediate risk, high-intermediate risk or high risk)[1]. Previously, "type 1" endometrial adenocarcinomas were contrasted with other, rarer histologic types with a poorer prognosis (type 2): papillary serious[A2], adenocarcinoma, hyalinising clear cell carcinoma and carcinosarcomas (previously referred to as malignant mixed Mullerian tumours). These days, it is customary to apply a molecular classification[2] to identify four histo-molecular types: the "ultra-mutated" type - often endometrial and related to a POLE mutation with a very good prognosis despite its often high classification; the "microsatellite instability" type (MSI) related to

a defect in mismatch repair (due to MLH1 promoter methylation, MLH1, MSH2, MSH6 or PMS2 mutations) with a good prognosis; the "low number of chromosome copy number alterations (CNA)" more or less correspondant[A3] to endometroids; and the "serious-like[A4]" type associated with several CNA's and TP53 mutations, with a poor prognosis.

Treatment should be discussed in a multidisciplinary meeting: it will be adjusted according to the patient's age and co-morbidities following screening for frailty and a geriatric assessment - if necessary.

Low-risk tumours: stage 1A, grade 1/2, histological type 1 (POLE, MSI, wild-type TP53)

• *First-line treatment:*

- simple hysterectomy with non-conservative bilateral adnexectomy;
- lymph node staging through sentinel lymph node biopsy (SNB) may be proposed but it is not mandatory (it can be postponed for elderly patients, so if a vaginal route is pursued to limit the operative risks, a SNB will not be performed);
- no adjuvant treatment.

Intermediate risk tumours: stage IA grade III, IB grade I/III, histological type 1 or stage 1A without myometrium Invasion, histological type 2 (TP53 mutation without MSI or POLE mutation)

• *First-line treatment:*

- simple hysterectomy with bilateral adnexectomy;
- omentectomy in the case of a serious[A5] carcinoma or an undifferentiated tumour;
- lymph node staging through sentinel lymph node biopsy is proposed (this also can be considered depending on the operative risks).

• *Adjuvant treatment:*

- single vaginal brachytherapy (postoperative brachytherapy of the vaginal fundus) above 60 years-old;
- consider chemotherapy in the case of an aggressive histological type (typeII/TP53 mutation) depending on the geriatric oncology assessment.

High-intermediate risk tumours: stage I with embolism or stage II, histological type[A6] I

• First-line treatment:

- hysterectomy with bilateral adnexectomy. The hysterectomy will be simple or extended, with or without vaginectomy, depending on the tumour's characteristics, and will aim to obtain healthy margins;
- lymph node staging through sentinel lymph node biopsy is recommended.

• Adjuvant treatment:

- single vaginal brachytherapy (postoperative brachytherapy of the vaginal fundus);
- concurrent radiotherapy +/- chemotherapy to be considered in the case of embolisms or stage II. In the case of concurrent chemotherapy, a PORTEC-3 protocol will be considered (cisplatine 50 mg/m^2/3 weeks, or carboplatin if contra-indication).

Particular case depending on molecular classification:

In the case of a POLE mutation, no adjuvant treatment is recommended for stages I and II. In the case of a P53 mutation and myometrial invasion, the lesion is classified as High risk and adjuvant radiotherapy treatment is recommended regardless of the stage (PORTEC-3 Trial)[3].

High risk tumours: stages III and IVA

• First-line treatment:

A complete surgical resection, including the removal of suspected adenopathies without systematic curettage, must be considered - if tolerance allows for it - in the case of serious carcinoma, carcinoma or an undifferentiated tumour;

• Adjuvant treatment:

- sequentially concurrent chemoradiotherapy and chemotherapy is recommended.

Radiotherapy without chemotherapy or chemotherapy without radiotherapy are still the alternatives for stages III and IV for vulnerable patients, depending on the presentation of the tumour.

Stade IVB-M+

First chemotherapy will be recommended, and eventually completed by local treatment if there is a good response. Complete, curative cytoreductive surgery (identical to that which is performed for ovarian cancer) may be considered, only in the case of resectable peritoneal carcinosis and no distance metasis[A7], for a patient in good general health. External radiotherapy on the primary tumour may also be considered depending on the location of the lesions.

- in chemotherapy, a combination treatment will be recommended of carboplatine AUC[A8] 5/6 - paclitaxel 175 mg/m^2 every 3 weeks[4], usually for 6 cycles (or just four cycles for adjuvant treatment before or after the radio(chemo)therapy). Using an analogy with the ovary, for vulnerable, geriatric patients, an attempt at maintaining a dual therapy may be made, by reducing the doses in the first cyles[A9] or by applying a weekly protocol;
- hormone therapy may be considered in the case of a slowly evolving, grade I-II endometrial tumour which presents with hormone receptors. The molecules used are progestogens (medroxyprogesterone acetate, megestrol acetate), tamoxifen and aromatase inhibitors.
- the combination of a targeted tyrosine kinase inhibitor, levatinib, with an anti- PD-1, pembrolizumab, is currently available for early access. This combination has demonstrated benefit not only in progression-free survival but also in overall survival [PMID: 35045221]. However, this combination is toxic with asthenia, hypertension, mucosal diseases, hand-foot syndrome and has a risk of weight loss, limiting its administering in the elderly population who often present with a metabolic syndrome;
- immune checkpoint inhibitors (in particular anti-PD1) have demonstrated strong activity with excellent tolerance in MSI tumours. There are currently no such medications available on the market as monotherapy for these patients, but access should be actively sought - most often through a clinical trial.

In the case of inoperable patients

As a result of the co-morbidities often associated with endometrial cancer, certain patients may not be

operated on due to a contra-indication to general anaesthesia. In this situation, utero-vaginal brachytherapy only (stage I tumours) or a combination of external radiotherapy followed by brachytherapy at an expert facility may be suggested. The results of these alternative strategies are satisfactory in terms of specific survival, but overall survival is affected by the assosicated[A10] co-morbidities. In the case of a contra-indication to radiotherapy/brachytherapy, a systemic hormone therapy treatment may be proposed.

Monitoring

Monitoring is carried out with regular clinical examinations, every 4 to 6 months during the first 3 years, then annually, for stage I and II tumours, and every 4 to 6 months for the first 5 years, then annually, for more advanced tumours.

There is no indication to re-conduct imaging tests, biological examinations, or systematic vaginal smears.

Testing for Lynch syndrome should be performed if there is an association with other tumours in personal or family history.

Elderly patient

If there is no specific recommendation for elderly women, the options should be chosen at each stage of care.

- **surgery**: the laparoscopic route should be chosen over the laparatomic route[A11], where technically feasible. The vaginal route may be considered in the case of contra-indication to other preferred routes. Opt for a sentinel lymph node biopsy which is now the recommended lymph node staging technique for endometrial cancer.
- **radiotherapy**: opt for intensity-modulated radiotherapy (volumetric arc therapy), which is less harmful for digestion and significantly improves tolerance.
- **brachytherapy**: opt for high dose-rate brachytherapy versus pulsed brachytherapy, particularly for post-operative irradiations of the vaginal fundus, allowing for outpatient care with a limited number of sessions - and a limited thrombo-embolic risk usually associated with hospitalisation.

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CERVICAL CANCER TREATMENT

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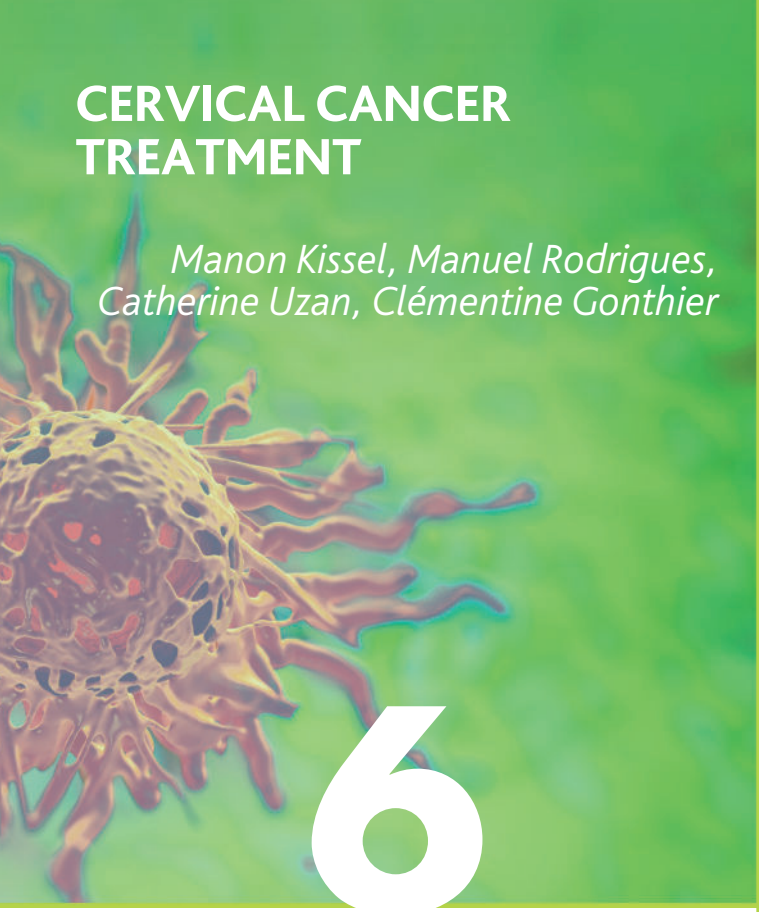

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A geriatric assessment must be offered to older patients, prior to the MDTM if possible, to help guide the treatment decision. The proposals below should be interpreted according to the new FIGO 2021 staging system.

Stage IA microinvasive lesions

An initial cone biopsy must be performed if there is colposcopic, cytological or histological suspicion of microinvasion.

Stage IA1

• ***First-line treatment:***

- simple monitoring if the cone biopsy margins are *in sano* and there is no lymphatic embolus on the cone biopsy specimen;
- simple total hysterectomy if the cone biopsy is *in sano*;
- if there are lymphatic emboli, the treatment is the same as for stage IA2 cancer with the presence of emboli;
- older patient: no specific treatment. Additional simple total hysterectomy can avoid the constraints of monitoring.

Stage IA2

• First-line treatment:

- pelvic lymphadenectomy, usually carried out via coelioscopy;
- simple total extrafascial hysterectomy if the cone biopsy is not *in sano* (but without an embolus);
- if there are lymphatic emboli on the cone biopsy specimen, an extended colpohysterectomy is indicated (Wertheim procedure combining hysterectomy with vaginal cuff and paracervical resection);
- if the patient presents with lymph node invasion, additional concomitant chemoradiotherapy is indicated (see below).

• *if patient is not eligible: no lymphadenectomy,* use the sentinel lymph node procedure which is currently being evaluated due to its reduced morbidity, after being discussed at the MDTM.

Stage IB1-IB2

• First-line treatment

No standard treatment. These lesions are immediately accessible for surgery. The strategy must aim to avoid the combination of radiation and surgery, which is a source of morbidity. A pre-treatment PET scan is useful for immediately reclassifying stage IIIC or IV patients if necessary.

The different treatment options are:
- primary pelvic lymphadenectomy:
  - if N+, para-aortic lymphadenectomy then chemoradiotherapy (similar treatment to advanced stages, see below);
  - if N-, extended colpohysterectomy then chemoradiotherapy and/or brachytherapy according to histological risk factors (size, emboli, margins, parametrial involvement) or uterovaginal brachytherapy followed by a colpohysterectomy;
- surgical treatment: extended colpohysterectomy and pelvic lymphadenectomy followed by chemoradiotherapy (if R1, parametrial involvement or N1) or postoperative vaginal brachytherapy (if accumulation of risk factors including tumour size, infiltration of the chorion and the presence of emboli);

- radiosurgical combination, usually: pre-operative brachytherapy (preferred if stage IB2) followed by a colpohysterectomy and lymphadenectomy 6 to 8 weeks later;
- treatment with radiotherapy only (external radiotherapy without concomitant chemotherapy followed by uterovaginal brachytherapy). This option is not very common in France despite a well-organised randomised trial with 20 years of results demonstrating its equivalence with surgery.

In patients treated with surgery possibly preceded by brachytherapy, and with lymph node invasion, parametrial involvement or positive margins, additional concomitant pelvic (and possibly para-aortic) chemoradiotherapy is indicated in patients able to receive it. In the case of prior uterovaginal brachytherapy, target volumes concern the lateral pelvic areas (protection of the central pelvic area already irradiated during brachytherapy).

• If patient is not eligible for surgery

If there are general contraindications to surgery (age, renal failure), external pelvic radiotherapy followed by uterovaginal brachytherapy is a curative-intent option (radiotherapy only).

Stages IB3-IVA

• Standard treatment

The standard treatment is concomitant chemoradiotherapy. Primary resection colpohysterectomy is not indicated.

Pelvic +/- para-aortic irradiation is delivered over 5 weeks. Hypofractionated regimens which would reduce the length of radiation treatment do not have a sufficient level of proof to be routinely offered for curative purposes, even to older patients. Radiation volumes are based on imaging tests (MRI, FDG-PET) and/or on the results of the primary laparoscopic para-aortic lymphadenectomy. The total treatment duration (radiotherapy and brachytherapy) must not exceed 55 days due to the risk of compromising local control. Para-aortic lymph node areas must only be irradiated if involvement is proven. However, if the risk of para-aortic invasion is

deemed to be very high (> 3 cases of pelvic adenopathy, primary iliac involvement) and staging para-aortic lymphadenectomy is not possible, prophylactic irradiation is discussed on a case-by-case basis. The extension of radiation fields at this level increases morbidity even if modern radiotherapy techniques, particularly daily image-guided intensity-modulated techniques, reduce the toxicity of the radiation. FDG-PET is used to assess pre-treatment para-aortic lymphatic spread. Primary para-aortic lymphadenectomy remains indicated in the case of negative FDG-PET due to the false-negative risk. However, given the improvement in FDG-PET, it has been shown that the risk of para-aortic lymph node invasion when the pelvic FDG-PET is negative is very low, around 4%. Therefore, it may be reasonable to delay it when the PET is negative in the pelvic area.

The most common chemotherapy is platinum based (cisplatin, 40 mg/m^2) administered weekly during radiotherapy, so 5 to 6 courses. It causes thrombocytopenia but has a minimal or no neutropenic effect and does not cause alopecia. The main toxic risks in geriatric patients are linked to vomiting (dehydration, malnutrition), renal failure, neuropathy (risk of falling) and ototoxicity. Alternatively, weekly AUC2 carboplatin could be offered despite the lack of formal proof of equivalence.

In the absence of proven benefit and due to its morbidity, closing surgery is only rarely discussed in this situation in young patients and even less so in older patients.

- *If patient is not eligible after geriatric oncology assessment*

If the patient's general health contraindicates chemoradiotherapy treatment, they can be treated with radiotherapy alone. In particular, cisplatin's toxicity risks in older patients will be monitored, especially malnutrition, dehydration, asthenia, neuropathy, risk of falling and risks of drug interactions. Although there is no formal proof of the efficacy of these measures, we can offer frail patients adaptations by reducing the dose of cisplatin or replacing it with carboplatin.

• *Specific considerations in geriatric oncology*

Most teams set an age limit for staging para-aortic lymphadenectomy. PET is the standard examination for assessing para-aortic involvement. Salvage hysterectomies or pelvic extenteration are often refused for older patients due to the peri- and post-operative risks.

Stage IVB (distant metastases)

These situations are rare and are discussed on a case-by-case basis according to the spread of the disease and the patient's general condition. Treatment is based on chemotherapy and/or palliative radiotherapy. Surgery is uncommon. Local radiotherapy treatment may be discussed to ensure pelvic control and prevent local changes which are often debilitating and painful, or for haemostatic purposes.

• *In older patients*

The first line of treatment recommended for relapse or metastasis is the combination of carboplatin/ paclitaxel/ pembrolizumab/bevacizumab based on the results of the KEYNOTE-826 trial [PMID: 34534429]. Bevacizumab must be used with caution in older patients due to the slightly increased risk of complications (fistulas and vascular toxicities in particular) relating to this tumour. In frail patients, eliminating paclitaxel could be discussed, at least for the initial cycles. Chemotherapies such as gemcitabine, vinorelbine or topotecan are not very effective as second-line treatment. However, anti-PD1 immune therapies such as cemiplimab, balstilimab, pembrolizumab or nivolumab appear to be beneficial, particularly as they have excellent tolerance.

Locoregional or metastatic recurrence

Recurrences usually appear within 2 years but 10% appear after 5 years.

Palliative chemotherapy is the preferred option for most patients. Treatment will be chosen by weighing up the risks and benefits based on the patient's general condition and associated comorbidities. Salvage pelvic surgery (often requiring pelvic extenteration which is often refused by older patients) or radiotherapy are options in certain cases of locoregional recurrence. The very low

response rate for relapse in the irradiated area should be noted, particularly in the first year of follow-up, and should be included in the risk-benefit analysis for these patients.

Monitoring

• During treatment:

- particular attention to maintenance of independence, nutritional status (hypoalbuminemia), support of family and friends, decompensation of comorbidities (renal failure, etc.) and polypharmacy;
- use of aftercare services may be helpful;
- the role of the attending physician is key, working with other professionals such as gynaecologists, surgeons, medical oncologists, radiation oncologists, radiologists, pathologists, obstetrician-gynaecologists, urologists, geriatricians, psychologists and social workers.

• Post-treatment:

- detect local (whether symptomatic or not) or distant recurrences;
- detect adverse effects of the treatment;
- detect secondary cancer (vulva and vagina mainly);
- organise the necessary supportive care;
- improve quality of life.

Patients are followed up every 4 months for 2 years, then every 6 months for 3 years, then annually.

This regimen can be adapted to the specific patient and clinical situation.

• Clinical examination

Monitoring is based on asking questions and clinical and gynaecological examinations, particularly looking for complications or symptoms indicating a recurrence. Systematic paraclinical examination is not recommended if the clinical examination is normal.

No systematic Pap smear in patients having received radiotherapy (interpretation difficulties). The HPV test has not yet been evaluated for this indication.

• *Biology*

For squamous cell carcinomas, a follow-up SCC test may be useful if there is initial elevation. Similarly, for adenocarcinomas, a CEA test may be useful if there is initial elevation.

• *Imaging*

Follow-up does not include systematic additional imaging.

Following conservative treatment (trachelectomy or exclusive chemoradiotherapy), an MRI may be offered in the first 5 years, and beyond that if there are warning signs.

FDG-PET may be offered for monitoring purposes, particularly if there are warning signs, after discussion at the MDTM.

Painful symptomatology must prompt a renal ultrasound to look for urethral dilation, particularly after radiosurgical treatment and including some time after the initial treatment.

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VULVAL CANCER TREATMENT

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In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature.

Stage I

The first-line treatment is surgery.

• *Vulva*

Stage IA (lesion ≤ 2 cm in diameter without adenopathy and an invasion depth of ≤ 1 mm): skinning vulvectomy without lymph node procedure.

Stage B (lesion > 2 cm in diameter without adenopathy and an invasion depth of > 1 mm):

- partial radical vulvectomy, depending on the anatomical possibilities, 2 cm macroscopic margins (8 mm histological margins):
  - if lateral lesion: wide resection or hemivulvectomy;
  - if medial lesion (< 1 cm from the midline): wide resection or anterior or posterior hemivulvectomy.
- total vulvectomy in the case of associated multifocal precancerous lesions;
- dermatological treatment of associated lesions (lichen sclerosus, lichen planus, Paget's disease).

• *Inguinal lymph nodes*

- Initial sentinel lymph node detection if the lesion measures less than 4 cm (radioisotopic +/- colorimetric method).
- For medial tumours, a lymph node assessment using the sentinel lymph node technique must be performed on both sides.
- If the sentinel lymph node is not found (detection failure) on one side, ipsilateral inguinofemoral lymphadenectomy is indicated.
- Contralateral lymph node treatment will be considered in the case of extemporaneous positivity or a definitive positive result.

If patient is not eligible:

- surgical resection under local anaesthetic of the cancerous vulvar lesion for local control of the disease;
- inguinal lymph node surgical exploration is postponed and may be replaced by inguinofemoral and vulval radiotherapy;
- dermatological treatment of associated lesions (lichen sclerosus, lichen planus, Paget's disease).

Stage II (vulva lesion < 4 cm, N0)

• *Vulva*

- Partial radical vulvectomy, depending on the anatomical possibilities, 2 cm macroscopic margins (8 mm histological margins):
  - if lateral lesion: wide resection or hemivulvectomy;
  - if medial lesion (< 1 cm from the midline): wide resection or anterior or posterior hemivulvectomy.
- Total vulvectomy in the case of associated multifocal precancerous lesions.
- Dermatological treatment of associated lesions (lichen sclerosus, lichen planus, Paget's disease).

• *Inguinal lymph nodes*

- Initial sentinel lymph node detection if the lesion measures less than 4 cm (radioisotopic +/- colorimetric method).

- For medial tumours, a lymph node assessment using the sentinel lymph node technique must be performed on both sides.
- If the sentinel lymph node is not found (detection failure) on one side, ipsilateral inguinofemoral lymphadenectomy is indicated.
- Contralateral lymph node treatment will be considered in the case of extemporaneous positivity or a definitive positive result.
- Inguinal pelvic EBRT.
- If unilateral pN+: contralateral inguinal cavity exploration or contralateral radiation may not be possible to perform if tumour is well lateralised ≤ 2 cm with a depth of ≤ 0.5 mm and if contralateral clinical N-.
- If ≥ 2 pN+ or if 1pN+ with capsular rupture or ≥ 2 mm: Inguinal pelvic EBRT* ± concomitant CRT**.

*Inguinal pelvic EBRT (radiotherapy)**

- IMRT EBRT (intensity-modulated, use if EBRT extended to the pelvis including inguinal areas).
- Target volume: vulva, inguinal ± pelvic lymph node areas.
- After surgery:
  - N-: 45 to 50 Gy in 25 sessions over 5 weeks (1.8 to 2 Gy per fraction);
  - N+: 55 to 60 Gy;
  - Boost to the surgical site, with a total of 56-60 Gy;
  - Within 6-8 weeks following surgery.
- If exclusive radiotherapy/tumour in place or R1:
  - N-: 45 to 50 Gy in 25 sessions over 5 weeks (1.8 to 2 Gy per fraction);
  - N+: 60 to 70 Gy;
  - Boost with a total of 60 to 70 Gy on the target tumour volume.

*** CRT (concomitant chemoradiotherapy)*

- Weekly cisplatin 40 mg/m^2 in an outpatient clinic.
- Or weekly 5-FU + cisplatin.

If patient is not eligible:
- surgical resection under local anaesthetic of the cancerous vulvar lesion for local control of the disease;
- inguinal lymph node surgical exploration is postponed and replaced by inguinofemoral and vulval radiotherapy;
- exclusive palliative vulval radiotherapy.

Advanced stage: stage II (vulva lesion > 4 cm) and operable stage III

- *If inguinal N+ (positive fine-needle aspiration)*

Inguinal and pelvic CRT (concomitant chemoradiotherapy): weekly cisplatin 40 mg/m^2 in outpatient clinic or weekly 5-FU + cisplatin.

- *If N0*

- Option: Pre-operative concomitant CRT +/- primary SLN.
- Enlarged radical vulvectomy + bilateral inguinal lymphadenectomy:
  - if N0: vulva radiotherapy if margins < 8 mm and if margin revision is not possible;
  - if N+: vulva and inguinofemoral radiotherapy ± pelvic radiotherapy if ≥ 2 pN+ or 1 pN + with capsular rupture or ≥ 2 mm: inguinal pelvic EBRT* ± concomitant CRT**.

- *If patient is not eligible:*

- surgical resection under local anaesthetic of the cancerous vulvar lesion for local control of the disease;
- inguinal lymph node surgical exploration is postponed and replaced by inguinofemoral and vulval radiotherapy;
- exclusive palliative vulval radiotherapy;
- palliative chemotherapy.

Inoperable stage II and III or stage IV

- *IVA: tumour with invasion of the upper 2/3 of the vagina and the upper 2/3 of the urethra or the bladder mucosa or the rectal mucosa or attached to the pelvis*

First-line treatment

- Either pre-operative concomitant combination of radiotherapy and chemotherapy at a dose of 45 to 50 Gy over 5 weeks (5 times 1.8 Gy/week) combined with 5-FU and/or platinum salts (depending on comorbidities), followed by surgery.
- Or primary exenteration surgery with flap reconstruction procedure.
- If positive margins or margins < 8 mm (5 mm for the urethra) or emboli or deep infiltration > 5 mm: vulva EBRT 45 to 50 Gy over 5 weeks and additional interstitial brachytherapy (or EBRT) at a dose of 15 Gy on positive or inadequate margins.
- If positive lymphadenectomy or no dissection:
  - use pelvic and inguinal EBRT, 45 to 50 Gy;
  - discuss concomitant chemotherapy according to the risk factors and comorbidities.

If patient is not eligible:
- supportive care;
- palliative chemotherapy, usually platinum salt based, or paclitaxel;
- symptomatic palliative EBRT;
- clean vulva surgery.

- *IVB: distant metastases (including pelvic adenopathies)*

First-line treatment

- Palliative chemotherapy. The most common regimen involves a combination of carboplatin and paclitaxel, like for cervical cancers. There is no targeted therapy that can be used in common practice for metastatic vulvar cancers. An interesting indicator of efficacy was reported in favour of using trastuzumab in adenocarcinomas developed in Paget's disease of the vulva, as well as immunotherapy (cemiplimab) for cutaneous squamous cell carcinomas.
- Symptomatic palliative EBRT.
- Early management in a palliative care unit.

Monitoring

- Perineal examination and pelvic examinations, lymph node palpation every 3 to 4 months for 1 year, then every 6 months for 2 years.
- Monitoring on an alternating basis: surgeon, dermatologist ± radiotherapist ± oncologist.
- No systematic imaging (apart from exclusive chemoradiotherapy treatment without surgery →FDG-PET/CT at 10-12 weeks ± pelvic MRI).

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NCCN guidelines, vulvar cancer.

COLON CANCER TREATMENT

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This chapter includes recommendations from the Thésaurus National de Cancérologie Digestive 2019 *(French digestive oncology guidelines group www.tncd.org*) and SoFOG concerning metastatic colorectal cancer.[1]

Specific recommendations for older patients were updated by the authors based on recent medical literature.

Staging

- **Stage I:** the tumour is limited to the submucosa or muscularis without lymph node invasion or distant metastasis.
- **Stage II:** the tumour has grown through the muscularis into the subserosa and may spread into the visceral peritoneum or a nearby organ, but without lymph node or distant invasion.
- **Stage III:** existence of at least one regional lymph node invasion whatever the degree of parietal invasion without distant metastasis.
- **Stage IV:** distant metastasis.

The oncologist will consult with the geriatrician when they consider that the patient's level of dependency and

comorbidities could interfere with the oncological treatment. A G8 score of less than 14 must result in geriatric assessment.[2] The aims of geriatric assessment include assessing the patient's frailty, identifying active comorbidities and offering treatment for them in order to adapt the cancer treatment as effectively as possible. This assessment is used at MDTMs to confirm the cancer and geriatric care.

Stage I

- *First-line treatment: surgery*

Surgical resection: This involves removing the segment of the colon containing the tumour with a margin of 5 cm below the tumour and around 15 cm above, in order to perform a lymphadenectomy while maintaining a well vascularised colon. Coelioscopic resection of colon cancer in older patients is authorised. At least 12 lymph nodes need to be analysed.

Endoscopic resection: (SFED 2011 recommendations). Endoscopic resection of intraepithelial or intramucosal cancer is sufficient.

For lesions with submucosal carcinomas, endoscopic resection is considered as sufficient only when there is superficial submucosal invasion (< 1 000 µm if sessile lesion or 1/3 higher than the peduncle if pedunculated lesion) AND if the polypectomy specimen meets all the safety criteria:

- no budding (small, poorly differentiated clusters of tumour cells, separating the stroma at the tumour invasive front);
- well or moderately differentiated adenocarcinoma;
- absence of vascular or lymphatic emboli;
- safety margin > 1 mm.

For cases of low-risk superficial cancer after R0 curative cancer, an additional imaging examination is not necessary but a follow-up endoscopy is required after 1 year, 3 years and 5 years. Additional surgical treatment indications, after endoscopic resection of an adenoma which has degenerated into submucosal carcinoma, must be discussed at an MDTM if the above criteria are not met, and analysed in terms of risk and benefits for patients with a life expectancy reduced by comorbidities.

For high-risk superficial cancer in an operable patient, additional surgery with lymphadenectomy is recommended after the standard initial staging assessment.

If the resection is incomplete or does not meet all the safety criteria and surgical resection has not been offered, an early follow-up endoscopy of the resection site should be performed after 3 months (HAS 2004 recommendation). For high-risk superficial cancers, it makes sense to combine endoscopic monitoring with morphological monitoring since the risk is mainly related to the lymph nodes. In all cases, the monitoring strategy must be approved at an MDTM.

The decision to leave a non-obstructing tumour in place must be made at a multidisciplinary team meeting (MDTM) after consulting a geriatric expert.

Stage II

- *First-line treatment: surgery +/- adjuvant chemotherapy*

Surgical resection: (see Supratotal).

Adjuvant chemotherapy: stage II is characterised by a low risk of recurrence.

The only positive study in favour of adjuvant chemotherapy showed a benefit with 5 fluorouracil (5-FU) monotherapy and only in patients younger than 70 years.[2] The presence of tumour microsatellite instability indicating a frequent carcinogenesis pathway in older patients (Mismatch repair deficiency) is associated with adjuvant chemotherapy[3] inefficacy and an excellent spontaneous prognosis, particularly in older patients.[4]

Adjuvant chemotherapy with 5-FU monotherapy may be discussed if there is a "high" risk of recurrence: tumours without microsatellite instability **and** with one or more of the following factors: T4, analysis of fewer than 12 lymph nodes, presence of venous, perinervous and/or lymphatic emboli, poorly differentiated tumour, perforation and for some, revealing occlusion.

The decision must be taken at an MDTM after geriatric assessment of life expectancy and comorbidities. The chemotherapy decision must involve the patient fully after informing them of the benefits (5-year survival is increased by 2% to 3%) and risks (complications after

installing implantable site, sepsis and haematological, mucosal and cardiac toxicity).

- *If patient is not eligible*

If short-term survival is foreseeable, the decision to leave a non-obstructing tumour in place must be made at an MDTM after consulting a geriatric expert.

If the tumour is obstructing: discuss the insertion of an endoscopic prosthesis in a patient considered to be inoperable.

Stage III

- *First-line treatment: surgery and chemotherapy*

Surgical resection: (see Supratotal).

Adjuvant chemotherapy: an analysis of individual data from patients included in 7 phase III trials comparing bolus 5-FU-based chemotherapy with surgery alone revealed that patients aged over 70 years benefited from adjuvant chemotherapy both in terms of recurrence-free survival and overall survival. However, in this trial, the older patients were highly selected (15% over 70 years and 0.7% over 80 years).[5] The current standard treatment is chemotherapy with 12 courses of FOLFOX or 8 courses of XELOX. However, a meta-analysis of several trials evaluating oxaliplatin + fluoropyrimidine compared with a monotherapy of fluoropyrimidine as adjuvant treatment found no benefit of intensifying the treatment with oxaliplatin after the age of 70 years.[6] The results of the IDEA trial suggested that treatment with XELOX for 3 months was the equivalent of 6 months for low-risk stage 3 cases (T1-3, N1).[7] There is no specific approval for older patients.

Six months of monochemotherapy with fluoropyrimidine is recommended as adjuvant treatment after resection of stage III colon cancer. The use of bi-chemotherapy with FOLFOX or XELOX can be discussed on a case-by-case basis according to the risk of recurrence (T4, N > 1) and the patient's comorbidities. If bi-chemotherapy is chosen, 3 months of XELOX may be sufficient for T1-3N1 tumours according to the results of the IDEA trial. [7]

- *If patient is not eligible*

Treatment is the same as for stage II.

A therapeutic trial specific to patients aged over 70 is in progress: PRODIGE 34 - FFCD 1402 - ADAGE: phase III randomised trial evaluating adjuvant chemotherapy after resection of stage III colon adenocarcinoma in patients aged 70 and over - intergroup trial: FFCD, GERCOR, GERICO, UNICANCER-GI.

Stage IV

- *First-line treatment: metastasis surgery, chemotherapy, targeted therapies: on a case-by-case basis!*

Surgery: metastasis surgery (liver metastasis in particular) must always be discussed at an MDTM regardless of the age of the patient.

Chemotherapy: there are numerous effective chemotherapy or targeted therapy drugs for treating metastatic colon cancer. The therapeutic strategy must be chosen according to:
- the cancer objectives;
- the geriatric oncology assessment of the patient.

The decision not to use chemotherapy must be discussed after consulting a geriatric oncologist, particularly in the case of severe comorbidities, advanced dementia and/or uncontrolled psychiatric disorders as well as a high level of dependency.

Two randomised trials did not reveal increased overall survival with bi-chemotherapy compared with monochemotherapy as first-line treatment.[8,9] The FFCD 2001-02 trial showed that a loss of independence and impaired cognitive function are associated with an increase in chemotherapy toxicity, particularly with bi-chemotherapy.[10]

Where targeted therapies are concerned, several randomised trials specific to older patients have evaluated antiangiogenic and anti-EGFR drugs.

For bevacizumab, a phase III randomised trial showed improved progression-free survival in patients treated with an antiangiogenic drug compared with patients treated with chemotherapy alone without an improvement in

overall survival.[11] Another phase II randomised trial showed good tolerance of bevacizumab in older patients.[12] However, some trials showed an increased risk of cardiovascular toxicity with antiangiogenics in older patients. It is best to consult a cardiologist before using an antiangiogenic drug in patients with heart disease.

In patients for whom an objective response is not the main objective, monochemotherapy with 5-fluorouracil combined with bevacizumab is recommended as first-line treatment.

There is less data for anti-EGFR drugs. The combination of 5-FU + panitumumab is a possible alternative for patients with *RAS* mutation according to the results of the PANDA trial.[13]

In patients with symptomatic metastatic disease or for whom metastasis ablation is required, bi-chemotherapy (5-fluorouracil combined with irinotecan or oxaliplatin), combined with bevacizumab or an anti-EGFR antibody (cetuximab or panitumumab) in the absence of tumour *RAS* mutation, is recommended as first-line treatment.

For tumours with microsatellite instability, immunotherapy treatment (pembrolizumab) must be offered as first-line monotherapy treatment.[14]

For tumours with *BRAF* mutation, treatment combining encorafenib + cetuximab has been shown to be effective.[15] There is no specific data for older patients.

- *Endoscopic prosthesis*

For occlusive tumours, only if the patient is inoperable, or for unresectable metastases.

- *COLAGE trial*

Phase III trial in progress, evaluating different therapeutic strategies according to geriatric parameters.

Monitoring

The monitoring objectives for localised tumours are:

- Check for **metastatic recurrence** for 5 years following resection of the primary tumour. This involves regular thoracic-abdominal-pelvic scan-based or ultrasound assessments (every 3 months for the first 3 years then

every 6 months for the following 2 years). This monitoring is only useful if the patient is able to tolerate surgery or chemotherapy in the event of recurrence. If not, simple clinical monitoring may be offered every 3-6 months for 5 years.

- Check for **colonic preneoplastic lesions** via colonoscopy. A colonoscopy must be performed within 6 months following surgery if the initial colonic investigation was incomplete. If the complete investigation of the remaining colon was normal, a colonoscopy must be performed after 2 to 3 years, then 5 years if it is normal. This endoscopic monitoring is only useful if life expectancy is several years. If there is an anaesthetic risk, an air colonoscopy can be offered but a therapeutic colonoscopy must be carried out if a lesion is found.

For metastatic tumours, the efficacy of the chemotherapy treatment needs to be checked every 2 to 3 months. If there is a good response, metastasis surgery must be discussed.

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RECTAL CANCER TREATMENT

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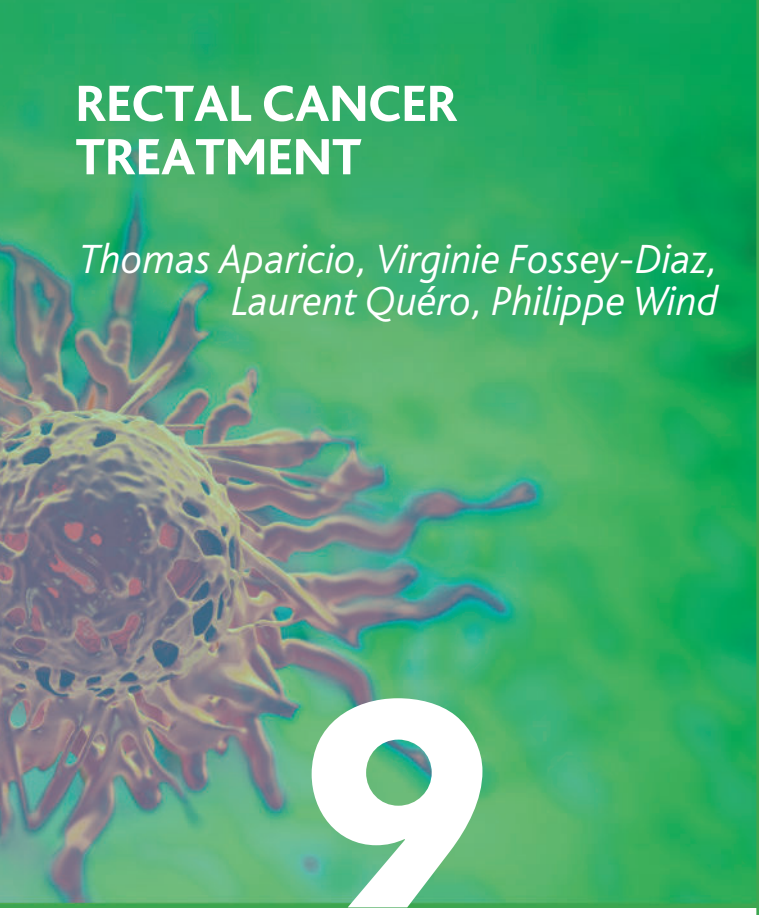

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This chapter includes recommendations from the Thésaurus National de Cancérologie Digestive 2021 (French digestive oncology guidelines group) (*www.tncd.org*).

Specific recommendations for older patients have been updated by the authors based on recent medical literature. It should, however, be noted that there is no prospective study on rectal cancer specific to older patients and very few analyses of subgroups of patients aged over 70 or 75 years in prospective trials evaluating the different therapeutic strategies for rectal cancer. There is, therefore, a low level of evidence concerning older patients.

Staging

TNM staging is the same as for colon tumours concerning tumours limited to the digestive wall, lymph node involvement and distant metastatic involvement. T3 stage subperitoneal rectal tumours infiltrate the whole rectum wall and can develop in the mesorectum. Tumours are distinguished by their position in the rectum, requiring different therapeutic strategies:

- ***lower rectum:*** 0 to 5 cm from the anal margin or 2 cm or less from the upper border of the anal sphincter;
- ***middle rectum:*** > 5 to 10 cm from the anal margin or > 2 to 7 cm from the upper border of the anal sphincter;
- ***upper rectum:*** > 10 to 15 cm from the anal margin or over 7 cm from the upper border of the anal sphincter;
- ***rectosigmoid junction:*** > 15 cm or more from the body of the 3rd sacral vertebrae.

The oncologist will consult with the geriatrician when the patient is identified as frail or after G8 screening (score of 14/17 or lower). The aim of geriatric assessment is to identify active comorbidities and offer treatment for them in order to adapt the cancer treatment as effectively as possible. This assessment is used at MDTMs to confirm the cancer and geriatric care.

The pre-treatment assessment is based on a complete colonoscopy looking for a second synchronous lesion, a local examination with digital rectal exam to establish the distance from the lower pole of the tumour to the anal margin and the state of the sphincters, a thoracic-abdominal-pelvic CT scan and a pelvic MRI scan. For a tumour limited to the rectum wall, an endorectal endoscopic ultrasound is more effective for defining parietal extension, particularly for tumours in the lower rectum.

Treatment principles

Treatment involves surgical sigmoid-rectal resection to remove the tumour and mesorectum along with lymphadenectomy. Rectal cancer surgery in older patients, even over 80 years, can be carried out with morbidity, mortality and survival results which are comparable to the younger population in selected patients.[1] In a population-based study, the benefit of surgery after mesorectum resection is not clearly demonstrated after the age of 75 years.[2]

Abdominoperineal amputation may be necessary for a tumour in the lower rectum infiltrating the external sphincter. However, improved local control with preoperative chemoradiotherapy and the development of intersphincteric dissection techniques have considerably pushed the boundaries of sphincter conservation. In selected older patients, tolerance and functional results seem comparable to those of younger patients.[3]

Although there is no reason to refuse to restore digestive continuity with colorectal or coloanal anastomosis in older patients due to often identical functional results to younger patients, the possibility of a damaged anal sphincter and/or impaired ambulation mean it should be discussed fully with the patient and anyone looking after them. First of all, a temporary ileostomy when performing a colorectal or coloanal anastomosis can generate episodes of dehydration with renal failure if not properly monitored. Next, defecation disorders such as fragmentation, urge incontinence and liquid stool incontinence can be highly debilitating, particularly at first, and are especially difficult to manage in older patients with limited physical resources and ambulation. In these conditions, even if sphincter conservation is technically possible, it is sometimes best to dismiss it and instead offer, from the outset, a low Hartmann's procedure or amputation with permanent terminal colostomy depending on the height of the tumour. In all cases, in older patients, precise information on the consequences of rectal surgery for the patient and their family and friends must be provided to them.

Post-operative treatment will depend on the lymph node invasion identified on the surgical specimen according to the same rules as for colon cancers (see colon information).

T1N0M0 tumours

- *First-line treatment: surgery*

Surgical resection: standard colorectal resection or transanal resection for tumours on the lateral or posterior surfaces of the lower or middle third of the rectum, at least 3 cm in diameter and histologically well or moderately differentiated, or endoscopic resection according to the same rules as for colon cancers.

Contact radiotherapy: if surgery is contraindicated, endorectal low-energy X-ray photon radiotherapy (RT) is an option in older patients with small T1 lesions when this technique is locally available. Low-energy contact RT provides excellent local control (95.5%) and 74% survival for favourable T1 and T2 tumours.[4]

- *If patient is not eligible*

The decision to leave a non-obstructing tumour in place must be made at a multidisciplinary team meeting (MDTM) after consulting a geriatric expert.

T2N0M0 tumours

- *First-line treatment: surgery ± pre-operative chemoradiotherapy*

Surgical resection: proctectomy.

Pre-operative chemoradiotherapy: chemoradiotherapy is generally indicated if there is a high risk of R1 resection, which is the main source of pelvic recurrences after surgery, or to allow good quality sphincter conservation without compromising oncological safety. In this T2 tumour situation, it is mainly indicated for a distal and anterior tumour in the lower rectum in order to reduce the tumour to enable conservative surgery and R0 resection. Chemoradiotherapy is not useful in this case if abdominoperineal amputation is planned and the anterior marginal border is over 1 mm.

- *If patient is not eligible*

If short-term survival is foreseeable, the decision to leave a non-obstructing tumour in place must be made at an MDTM after consulting a geriatric expert.

If the tumour is obstructing: discuss colostomy in a patient considered to be inoperable after consulting a geriatric expert.

T3 or T4 M0 or N1-3 M0 tumours

- *First-line treatment*

Upper rectum (tumour cannot be accessed in digital rectal exam): surgery with rectum and mesorectum resection up to 5 cm below the lower pole of the tumour, when sphincter conservation is not compromised. Neoadjuvant chemoradiotherapy is recommended for T4 tumours.

Middle and lower rectum: neoadjuvant chemotherapy followed by surgery with complete mesorectal resection.

However, the PRODIGE 23 trial recently showed that pre-operative treatment intensification improved the histological complete response rate as well as metastasis-free survival. The standard treatment for highly selected patients (PS 0-1, aged < 75 years or favourable geriatric assessment) involves 6 courses of FOLFIRINOX then chemoradiotherapy (capecitabine + 50 Gray for 5 weeks), followed by adjuvant chemotherapy with 6 courses of mFOLFOX6.[5] This treatment has not been evaluated in older patients.

The RAPIDO trial showed that pre-operative treatment involving short-course radiotherapy (5x5 Gray) followed by neoadjuvant chemotherapy with 6 courses of CAPOX or 9 courses of FOLFOX4 was also a valid alternative.[6] This treatment has not been specifically evaluated in older patients.

- *If patient is not eligible*

For patients not considered eligible for neoadjuvant chemoradiotherapy, pre-operative RT alone according to a short protocol (25 Gray in 5 fractions, delivered in 1 week) in a small volume is possible. However, with this regimen, and despite identical disease-free survival and toxicity (peri- and post-operative) to younger patients, the risk of complications after 30 days and 6 months increases with age.[7]

In some specific cases, exclusive chemoradiotherapy followed by monitoring or local resection, for non-fixed T2-T3 with complete response, resulted in prolonged remission.[8] This approach, which remains experimental, should be evaluated in patients who are not eligible for surgery.

The PRODIGE 42-NACRE trial showed that radiotherapy alone delivered in a short-course regimen (25 Gray in 5 fractions, delivered in one week) followed by surgery had a better risk-benefit ratio than standard chemoradiotherapy in patients aged over 75.[9] This regimen must therefore be considered as an alternative to the intensified regimen in frail patients.

Adjuvant therapy

- *ypT3-4 N0 M0 tumour*

No adjuvant chemotherapy.

- *yp all T N1-2M0 tumour*

Adjuvant chemotherapy discussed according to the same rules as for colon cancers (see colon information). However, the benefit of adjuvant chemotherapy is less well established for rectal cancer than for colon cancer in any age of patient. A careful risk-benefit analysis must therefore be carried out.

Stage IV

Like for all stage 4s, the decision to offer palliative treatment or include the patient in a curative strategy depends on the spread of the disease and condition. Palliative treatment generally involves chemotherapy (see colon cancer information) or comfort care for non-eligible patients.

If metastases are potentially resectable in a patient able to receive aggressive treatment, a curative strategy must be used, especially as the current efficacy of treatments allows less aggressive treatments on metastatic sites, such as limited resection or percutaneous radiofrequency. The strategy must always include the best treatment for the primary tumour.

The patient's case must be discussed at an MDTM including an expert in these complex cases.

Monitoring

The same rules will be observed as for colon cancer. Clinical examination will systematically include a digital rectal exam. Investigation using endorectal endoscopic ultrasound or MRI will be discussed in cases of suspected local recurrence. The risk of developing exclusive pulmonary metastases is higher for lower rectum cancers than for colon cancers.

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OESOPHAGEAL CANCER TREATMENT

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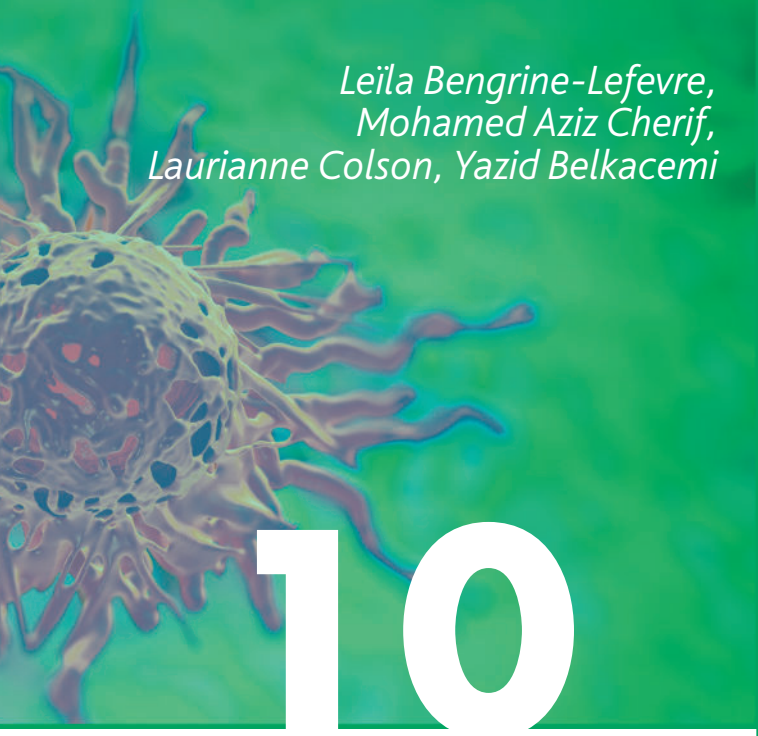

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In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the literature.

Stage I and II

- *First-line treatment*

Surgery: discussed on a case-by-case basis, taking into account geriatric parameters (comprehensive geriatric oncology assessment).[1,2] Beware of the negative impact of comorbidities on post-operative survival, with a post-operative mortality rate of 12% at 3 months.[3] Minimally invasive surgical techniques in selected patients, carried out in expert centres, could reduce post-operative morbidity and mortality.[4,5] They are not appropriate for treating cervical oesophageal tumours. Post-operative survival: 16% to 30% improvement at 5 years.[6]

Chemoradiotherapy: treatment considered to be equivalent to surgery in the case of localised tumours.[7-10]

For exclusive radiation, total dose limited to 50.4 Gy (5 x 1.8 to 2 Gy/week). Specific study in progress: OSAGE.[11]

• *Feasibility of peri-operative chemotherapy:* discussed for lower oesophageal adenocarcinomas, specifically in older patients, with a protocol combining 5-FU, leucovorin, oxaliplatin (FLO) +/- taxotere[15] but increased toxicity in the arm with taxotere. In France, the FLO protocol is usually replaced by the Folfox protocol.

• *If patient is not eligible:* concomitant chemoradiotherapy or palliative treatment. The recommended protocol is the Folfox regimen with neuropathy that may be limiting. The AUC 2 carboplatin taxol 50mg/m2 regimen tends to be favoured even if recommended in pre-operative regimens due to its more favourable toxicity profile. The OSAGE trial is still open and is testing chemotherapy dose escalation in conjunction with radiotherapy.

Stage III

• *First-line treatment*

Concomitant chemoradiotherapy: Folfox regimen preferred. Recently, taxol carboplatin regimen.

Pre-operative chemoradiotherapy: only discussed for patients in excellent general condition and restricted to expert centres. The chemotherapy regimen is taxol carboplatin with an excellent tolerance profile.[16] This treatment regimen opens the door to adjuvant immunotherapy in the case of residual disease after chemoradiotherapy (nivolumab). The maximum treatment duration is 12 months.[17]

Radiotherapy alone: less effective in the overall population.[12]

• *If patient is not eligible*

- palliative treatment;
- chemotherapy: if the patient is inoperable and not eligible for radiotherapy.

Oesophageal prosthesis +++: this improves quality of life by prioritising oral feeding.

Metastatic stage

• *First-line treatment*

Chemotherapy combined with supportive care.[18] Impact of geriatric care assessed by the PREPARE study. Impact

of early palliative care assessed by the EPIC protocol (not specific to older patients).

Immunotherapy is introduced with nivolumab combined with chemotherapy. There are no studies specific to older patients for advanced or metastatic HER2- oesophageal adenocarcinomas with a CPS score > 5 in early access programs. All as first-line treatment. The recommended dose is 240 mg every 2 weeks or 480 mg every 4 weeks for 16 weeks then 480 mg every four weeks. The recommended duration is 24 months in the case of stable disease.[19] Pembrolizumab was approved for Siewert type 1 oesophageal cancers or oesogastric junction adenocarcinomas with PD-L1 expression or a CPS score > 10, combined with platinum- and fluoropyrimidine-based chemotherapy. Early access obtained for 30 March 2022.

Most frequently encountered metastatic sites: lungs, bones and lymph nodes.

As first-line treatment, the REAL218 trial showed the benefit of treatment with a combination of docetaxel, capecitabine and oxaliplatin. However, there is an increased risk of febrile neutropenia. Capecitabine should only be offered in the case of mildly disabling dysphagia. Folfox combination: a first-line treatment option.

In HER2-positive cases, trastuzumab[20] is indicated as first-line treatment, combined with chemotherapy.

There are two second-line treatment options if the patient's general condition allows: taxanes or Folfiri combination.[21] Highly controversial. Take into account the patient's wishes and general condition. Nivolumab has an MA if platinum treatment fails but has not been approved for coverage by the French health insurance system.

Surgery is not appropriate: analgesic or decompressive radiotherapy is an option. Discuss inclusion in therapeutic trials.

- *If patient is not eligible: exclusive supportive care*

Supportive care

Essential nutritional management. Oral route: food supplements if dysphagia permits, enteral feeding: nasogastric probe or feeding jejunostomy (rapid and physiological refeeding, limits the risk of infection and

improves prognosis in the event of surgery[22] or chemo-radiotherapy). Post-operative nutritional management without pre-treatment prehabilitation is not enough to prevent post-operative sarcopenia in older patients[23,24] and determines their subsequent survival[25,26].

Palliative endoscopic procedures: oesophageal dilations, stents, tumour destruction techniques, etc.

Bisphosphonates: in the case of bone metastases. Denosumab can be discussed despite the small number of patients with bone metastases of oesophageal origin in the trial.

Monitoring

Every 6 months for 5 years: clinic + thoracic-abdominal-pelvic scan.

Annual ENT examination for squamous cell cancers and digestive fibroscopy at 2 years.

In the case of exclusive chemoradiotherapy: clinical examination + thoracic-abdominal-pelvic scan every 4 months for a year, then every 6 months for 5 years.[27]

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STOMACH CANCER TREATMENT

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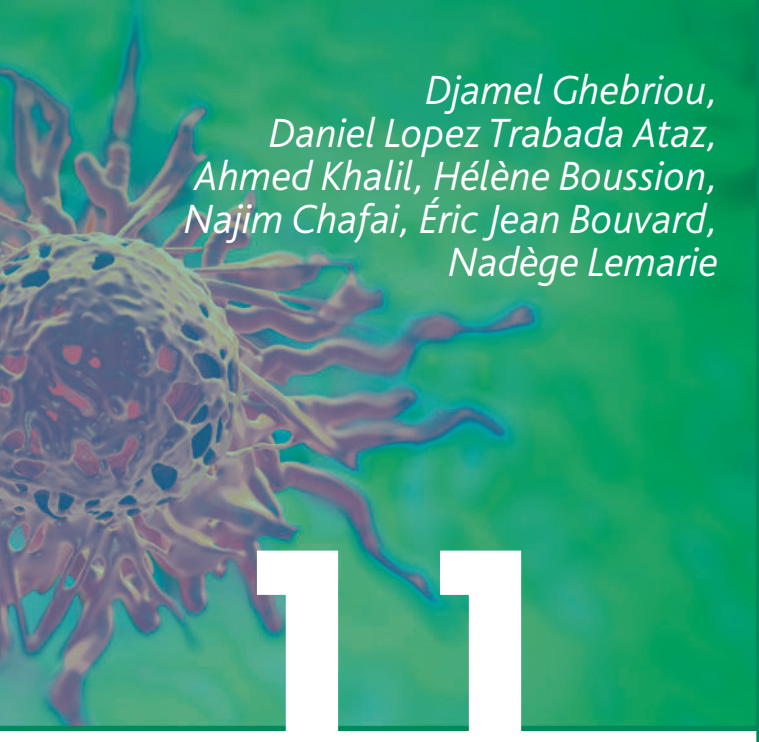

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This chapter includes stomach cancer treatment recommendations from the Thésaurus National de Cancérologie Digestive (French digestive oncology guidelines group), updated in October 2022 (www.tncd.org)[1] and not specific to older patients. In the absence of specific recommendations for this population, the authors have drawn up treatment proposals based on the medical literature.

General information

Gastric cancer is common and is ranked 4th in men and 7th in women in terms of worldwide incidence. It represents the 4th most likely cause of death from cancer in men and the 5th in women.[2]

The incidence of stomach cancer according to 2015 forecasts by the French Public Health Agency - Institute for Public Health Surveillance (INVS) is 6585 cases in the overall population, including 4,106 (62%) in individuals aged over 75. Two-thirds of cases are in men. Overall mortality is 4,362 cases, including 2,259 (52%) in patients aged over 75. Over the past twenty years, there has been a decrease in incidence (mainly due to

Helicobacter pylori eradication enabling better control of risk factors) and mortality caused by stomach cancer.

Treatment of localised forms

There is no specific prospective study of adjuvant or peri-operative treatments in older patients. Subgroup studies in older patients show benefit and feasibility. Peri-operative chemotherapy in resectable forms > IA (T1N0M0) is standard when the patient is in the fit category (no comorbidities, preserved functional independence). A haemorrhagic tumour or significant tumour stenosis (which cannot be removed by a endoprosthesis procedure) requires surgery as first-line treatment.

In patients who are fit to receive triplet chemotherapy, the combination of 5-FU, oxaliplatin and docetaxel (FLOT, 4 courses) pre- and post-operatively is the ***gold standard***. The FLOT regimen is superior to the ECF regimen in terms of complete histological response (16% versus 6%), recurrence-free survival (30 versus 18 months) and overall survival (50 versus 35 months) in a population of patients with an advanced tumour (81% of T3/T4, 80% of N+), 25% of whom were aged over 70 years.[3] This regimen must be administered with growth factors (G-CSF). However, it is difficult to administer the FLOT regimen in older patients other than fit patients in their early seventies due to its toxicity.

In patients who are unfit for the FLOT regimen, so the majority of older patients, but fit for peri-operative treatment: FOLFOX: 4 to 6 cycles before and after surgery.[4,5]

For T2N0œpatients: immediate surgery could be discussed according to the NCCN, given the good prognosis of these tumours (5-year survival rate of 85% without chemotherapy).

Specific cases of localised dMMR/MSIœtumours: the NEONIPIGA study[6] is a phase II trial evaluating the benefit of pre-operative immunotherapy with nivolumab + ipilimumab (6 cycles) and post-operative immunotherapy with nivolumab alone (9 cycles) in patients with stage cT2-T4Nx stomach or GOJ (gastro-oesophageal junction) adenocarcinoma with dMMR/MSI phenotype. In the 29 patients analysed, the complete histological response rate (main objective) was 58.6%. Other studies are underway to confirm the efficacy of this promising

therapeutic strategy (IMHOTEP - NCT04795661 trial). The TNCD (French digestive oncology guidelines) treatment algorithm suggests replacing chemotherapy with immunotherapy for localised dMMR/MSI tumours. However, dual immunotherapy is an ambitious treatment sequence in older patients. More data is required for the older population in order to prevent excessive toxicity from compromising the surgical sequence.

For GOJ cancer, pre-operative chemoradiotherapy treatment may be offered instead of intra-operative chemotherapy.[7] If there is residual tumour in the resection specimen, adjuvant nivolumab treatment must be offered.[8]

- *Post-operative treatment if first-line surgery:*

- adjuvant chemotherapy with FOLFOX for 6 months (if patient is unfit: LV5FU2 or capecitabine, or abstention);
- no benefit of chemoradiotherapy shown over adjuvant chemotherapy when a high quality lymphadenectomy is performed;[9,10]
- however, radiotherapy enhanced by LV5FU2 remains an option for N+ or T3 or R1 resection patients when they have PS 0-1 with good nutritional status (no benefit in the subgroup of women and independent cell adenocarcinomas[11]). The radiotherapy technique must therefore be performed according to the methods published by the French Oncological Radiotherapy Society (Société Française de Radiothérapie Oncologique - SFRO).[12]

D2 lymphadenectomy without splenectomy is recommended and must remove at least 25 lymph nodes. D1 lymphadenectomy is recommended for stage I cancers and for patients at high surgical risk. D1 lymphadenectomy must remove at least 15 lymph nodes.

For non-linitis plastica antrum cancers, a 4/5 gastrectomy is standard.

Total gastrectomy is the standard treatment for linitis plastica, proximal cancers and gastric body cancers. It can be performed in 50% of cases in all age groups. It concerns localised forms. The two prognostic factors after gastrectomy are serous involvement and lymph node involvement. Peri-operative mortality varies from 3% to 10%, with better results in large-volume centres.[13]

The benefit of surgical treatment in older patients with lymph node involvement is debated. However, we do not have any prospective intention-to-treat studies to make a decision about it.

Munich registry data shows that although the patient's general condition allows oncological resection and chemotherapy, the result is comparable across the age groups (50-59, 60-69 and 70-79 years) in terms of 5-year survival (48% to 49.6%).[14]

There is no place for intraperitoneal chemohyperthermia (IPCH) for the over-70 population with limited peritoneal carcinomatosis.

"Aggressive" nutritional management is required in the peri-operative context in older patients to ensure the best outcome.

Metastatic situation

There have been few studies on chemotherapy for gastric adenocarcinomas in older patients.

- *There are several first-line metastatic situations:*
  - *Non-HER2-overexpressing tumour (85% of patients) with PD-L1 CPS < 5:*

- first-line chemotherapy with FOLFOX;[15]
- if the patient is not eligible, discuss palliative care compared with the very modest benefit of optional LV5FU2 monochemotherapy.

A phase III trial in the older population with advanced gastric cancer comparing the standard dose of FOLFOX with two other arms at a reduced dose of 80% and 60% was presented at ASCO 2019.[16] It seems that the lower dose does not reduce the efficacy but increases tolerance.[A24]

- *Non-HER2-overexpressing tumour (85% of patients) with PD-L1 CPS ≥ 5:*

- chemotherapy with FOLFOX-nivolumab or XELOX-nivolumab.

The international CheckMate 649 phase III trial showed that for patients with a PD-L1 CPS ≥ 5 tumour, the addition of nivolumab significantly improved progression-free survival (median: 7.7 vs 6.1 months; HR = 0.69 [0.59-0.80]) and overall survival (median: 14.4 vs 11.1

months; HR = 0.70 [0.60-0.81]). ATTRACTION-4 and ORIENT16 trials confirmed the benefit of adding an anti-PD1 antibody to oxaliplatin-based chemotherapy.[17],[18]

- ***HER2-overexpressing tumour (15% of patients):***

- first-line chemotherapy with 5-FU-cisplatin and trastuzumab,[19] monitoring of left ventricular ejection fraction every 3 months. This regimen will be difficult to administer in older patients and should only be used in fit patients in their early seventies;
- if cisplatin is contraindicated, which will be common in older patients, replace it with oxaliplatin for FOLFOX-trastuzumab or XE-LOX-trastuzumab, as agreed by experts.

- ***If patient is not eligible:*** discuss palliative care compared with the very modest benefit of optional LV5FU2 monochemotherapy.

- ***Second-line chemotherapy: 2 equivalent options:***[20]

- docetaxel monotherapy at a dose of 75 mg/m^2 (GS 5.2 months)[21] or paclitaxel 80 mg/m^2 3 weeks/4;
- irinotecan monotherapy 350 mg/m^2/3 weeks[22] or FOLFIRI;
- the combination of ramucirumab - paclitaxel (GS 9.6 months)[23] is an option but it is not covered by the French health insurance system.

Trastuzumab deruxtecan was evaluated in the DESTINY GASTRIC-02 phase II trial as second-line treatment in patients with a HER2-positive metastatic gastric tumour (IHC3+ or IHC2+/FISH+) confirmed by a new biopsy after progression during chemotherapy with trastuzumab. This trial showed an objective response rate of 38%, and progression-free survival medians of 5.6 and 12.1 months respectively.[24] The international DESTINY GASTRIC 04 - NCT04704934 phase III trial is currently underway to validate these results.

- ***For immunotherapy-naive patients with a dMMR/MSI gastric tumour:*** there is an MA for second-line treatment with pembrolizumab (not covered by the French health insurance system).

- ***If patient is not eligible:*** palliative care.

• *Third-line chemotherapy:*

- trifluridine/tipiracil (TAS102) demonstrated superiority over versus supportive care in terms of overall survival (5.7 vs 3.6 months; HR = 0.69; p < 0.001) in patients pretreated with at least two lines of chemotherapy;[25]
- treatment with taxane or irinotecan/FOLFIRI can be discussed if not used in second-line treatment;
- trastuzumab deruxtecan does not have a European MA for third-line treatment but has an early access authorisation in France for adult patients with HER2-positive, locally advanced or metastatic stomach or GOJ (gastro-oesophageal junction) adenocarcinoma who have previously received at least two lines of treatment including trastuzumab. This authorisation is based on the DESTINY GASTRIC-01 phase II trial showing an objective response rate of 51% in the Asian population in the T-DXd arm (42.9% after central review) versus 14% in the chemotherapy arm (p < 0.0001). Overall survival was also significantly improved (median: 12.5 vs 8.3 months).[26]

• *If patient is not eligible:* palliative care.

Palliative stomach surgery must only be performed for symptomatic tumours (dysphagia, bleeding, perforation) in patients in good general condition (life expectancy of over 6 months).

Screening of first-degree relatives:
- under the age of 40-45 years: *Helicobacter pylori* 13C labelled urea breath test or serology test;
- above the age of 45 years: endoscopy + biopsies.

NB : As 5-FU and capecitabine are very commonly used to treat gastric cancer, phenotype testing to **detect DPD deficiency** (uracil level) must be carried out in order to adjust the doses of 5-FU and capecitabine if there is a partial deficiency. 5-FU and capecitabine are contraindicated if there is a complete deficiency.

Monitoring after curative treatment

No standard. An expert agreement suggests:
- a clinical examination every 6 months for at least 5 years;
- biological assessment: the possibility of complete post-gastrectomy anaemia justifies the monitoring of counts once a year;

- an abdominal ultrasound every 6 months for 3 years then every year, and a frontal chest radiograph every year for 3 years. The latter two options may be replaced by a thoracic-abdominal spiral scan every 6 months for 3 years, followed by clinical monitoring and abdominal ultrasound as described above;
- in the case of partial gastrectomy, gastric stump monitoring must commence 10 years after surgery and involve a high digestive endoscopy every 2 years with systematic biopsies (professional agreement);
- endoscopic ultrasound monitoring of perianastomotic recurrence (after total gastrectomy) in selected patients at high risk of anastomotic recurrence;
- in the case of splenectomy: flu vaccination every year and update vaccination schedule;
- in the case of total gastrectomy: vitamin B12 1 mg IM/3 after 12 months +/- folate.

Only patients eligible for recurrence treatment must be monitored.

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PANCREATIC CANCER TREATMENT

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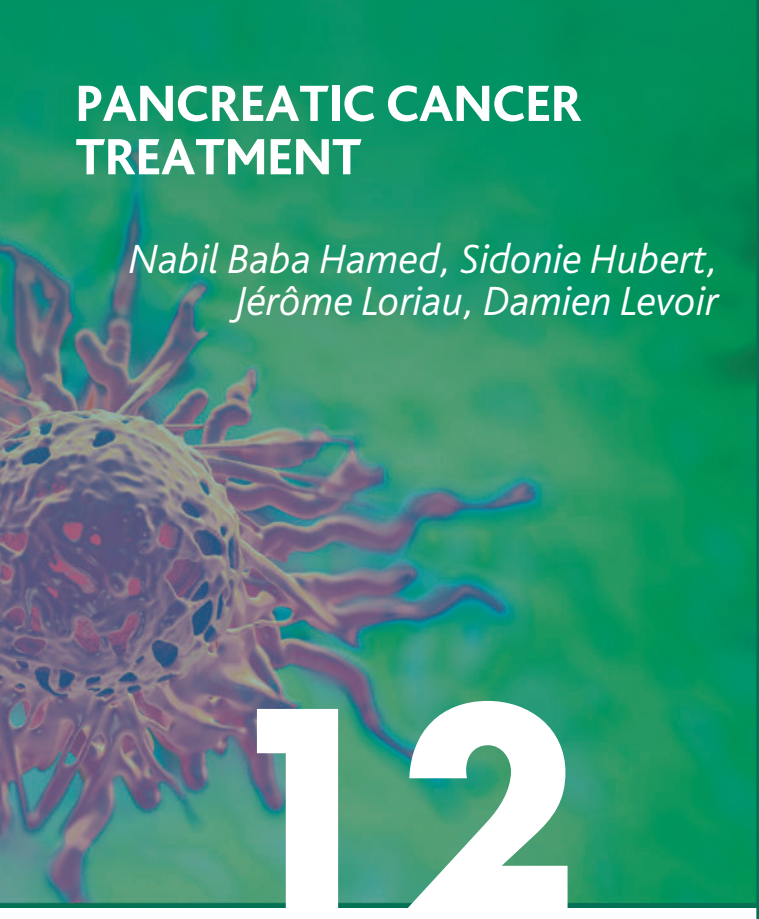

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The main characteristics of pancreatic cancer are early deterioration of general condition (asthenia, anorexia and weight loss), locoregional invasion by the primary tumour responsible for arterial and venous vascular sheathing, as well as thromboses, nerve damage (pain), duodenal damage (high occlusion with gastric dilatation), biliary damage (jaundice) and peritoneal damage (occlusion and ascites). None of these is age specific but the impact of cancer complications may restrict the treatment options, particularly in older patients with other comorbidities.[1]

Initial assessment

The first problem is often obtaining an anatomopathological diagnosis via an endoscopic or transcutaneous biopsy. The primary tumour is often accompanied by a significant desmoplastic component and low cellularity.

The next step is an operability assessment which includes a CA19.9 test, a thoracic-abdominal-pelvic CT scan and a pancreas MRI if no metastases are detected on the CT scan.

• *Tumour staging*

Synchronous hepatic or peritoneal ***metastases*** are frequent and if visible on initial imaging, contraindicate surgery.

Vascular spread: invasion of the superior mesenteric artery, hepatic artery or coeliac trunk strictly contraindicates resection. The same applies for invasion of the superior mesenteric vein or portal vein if it involves more than half of the venous system, if the proximal part of the superior mesenteric vein is concerned (convergence of jejunal and ileocolic veins) or if there are clear signs of segmental portal hypertension.

Lymph node involvement: the metastatic spread of lymph nodes in the pancreatic area is not a criterion for curative unresectability. However, documented distant lymph node invasion (liver hile, mesenteric root, retroperitoneal or interaortocaval) is a criterion for curative unresectability as it is prognostically equivalent to a metastatic situation.

• *Overall assessment*

Detection of comorbidities with a risk of post-operative organ failure (cardiac, pulmonary, renal, proven cirrhosis with signs of portal hypertension, etc.) may result in surgery being denied if the probability of post-operative mortality is higher than 10%.[2]

Deterioration of general condition, poorly controlled pain, significant weight loss with malnutrition and the existence of comorbidities are potential obstacles to carrying out medical treatments and sometimes temporarily or permanently contraindicate chemotherapy.

Thrombosis detection

Treatment decision

A multidisciplinary team (MDTM) discussion is required to define the options and the therapeutic strategy. In much older patients (> 85 years) with loss of independence and/or one or more comorbidities, a geriatric oncology assessment is strongly recommended to assess the risk-benefit ratio of anti-cancer therapy before making any final decisions.

• *Managing tumour disease complications*

Prehabilitation or rehabilitation relating to several elements is a key part of treating patients:
- nutritional status must be taken into account from the outset;
- pain must also be rapidly controlled;
- thrombosis must be detected and treated.

Biliary drainage in the case of jaundice and unresectable tumour, surgical double bypass or metal biliary stent(s). For patients with a life expectancy of 6 months or more (no visceral metastasis or carcinomatosis), surgical double bypass (possibly with alcohol coeliac plexus block for pain control) can be discussed.[3-5] For patients with a life expectancy of less than 6 months, endoscopic treatment of biliary or duodenal obstructions with metal stent(s) is preferable. Biliary drainage can be considered in the case of cholangitis, a long delay before the procedure, bilirubin ≥ 350 micromole/l (6,150 mg/l) and/or symptomatic patient, e.g. pruritus.[6,7] It must not be systematic at the pre-operative stage.

A duodenal stent can be inserted if there is tumour invasion or compression resulting in high obstruction.

In some patients with impaired general condition, early palliative care may be indicated at an early stage.

Treatment of tumour disease

• *Surgical resection*

Surgical resection of the primary tumour can only be performed in less than 20% of patients and either involves cephalic duodenopancreatectomy when the tumour is in the head of the pancreas, or distal pancreatectomy and splenectomy if the tumour is in the body or tail of the pancreas (without extended lymphadenectomy).

The benefit of offering secondary resection of tumours initially considered to be borderline for resection or of "locally advanced" non-metastatic tumours only to patients with a tumour that is shrinking or remaining stable due to neoadjuvant treatment compared with continuing with medical treatment alone must be discussed, even if the benefit remains to be established by prospective studies.

• *Chemotherapy*

Adjuvant chemotherapy improves overall survival (OS) and recurrence-free survival (RFS) and is indicated regardless of the tumour stage. The regimen of 6 cycles of gemcitabine (1,000 mg/m^2 in 30 min D1, D8, D15; D1 = D28)[8,9] has recently been replaced by the modified Folfirinox regimen (oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2, folinic acid 400 mg/m^2 and a continuous infusion of 5-FU 2.4 g/m^2 over 46 h)[10] due to its significantly improved OS and RFS, but the latter is rarely used in older patients due to its toxicity. The GemCap regimen (gemcitabine 1,000 mg/m^2 D1, D8, D15; D1 = D28 combined with oral capecitabine 1,660 mg/m^2 D1 to D21, then 7 rest days) increases overall survival compared with gemcitabine alone but comes at the cost of increased capecitabine-related toxicity, although this does remain manageable.[11]

• *Chemotherapy for inoperable forms (locally advanced or metastatic)*

• *Locally advanced forms*

A phase 3 trial recently presented at ESMO 2022 confirmed the superiority of FOLFIRINOX (which the majority of centres treating pancreatic tumours were already using) over gemcitabine in terms of progression-free survival (main criterion).[12]

• *Metastatic forms*

Folfirinox is used as first-line treatment in patients in good general condition. It is administered with systematic G-CSF: oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, folinic acid 400 mg/m^2, bolus 5-FU 400 mg/m^2, followed by a continuous infusion of 5-FU 2.4 g/m^2 over 46 h.[13] This treatment must be reserved for WHO 0 or 1 patients without coronary artery disease and with a normal or subnormal bilirubin level (< 1.5N). The first study "only" included subjects up to the age of 75 in good general condition and with a normal liver function test. However, several SIOG abstracts have shown the feasibility of the treatment provided that patients are selected based on a geriatric assessment and that doses are adapted if required.

The combination of gemcitabine and nab-paclitaxel is also indicated as first-line treatment. Trial with broader

inclusion criteria than Folfirinox, making it an interesting option if Folfirinox cannot be administered, but nab-paclitaxel is not covered by the French health insurance system, which limits its use.[14]

Gemcitabine monotherapy can be used as first-line treatment in patients in poor general condition. 30-minute infusion of gemcitabine 1,000 mg/m^2 on D1 every week, 7 out of 8 weeks then 3 out of 4 weeks (Burris regimen).[15]

A French trial in progress (GEMFOX) is comparing a FOLFOX regimen with Gemcitabine monochemotherapy as first-line treatment in frail patients who are not eligible for FOLFIRINOX.

There is no treatment standard for second-line chemotherapy in this situation. However, some patients who remain in good general condition may benefit from a second line of chemotherapy.

The GEMPAX combination (gemcitabine 1,000 mg/m^2 + paclitaxel 80 mg/m^2 D1, D8 and D15 then D28) compared with gemcitabine alone improves progression-free survival and has a better objective tumour response but does not impact overall survival.[16]

Liposomal irinotecan is available on the US market as second-line treatment but is not yet available in France.

After first-line Folfirinox: gemcitabine alone or combined with paclitaxel.[17] After first-line gemcitabine: Folfox combination of folinic acid, 5-FU and oxaliplatin or LV5FU.

- *Radiotherapy*

There is no proven benefit in locally advanced tumours (T4),[18] but it may be indicated to relieve symptoms (pain control) in some cases. It is used in many centres in borderline tumours after induction by chemotherapy with a view to surgery but this role remains to be proven by prospective studies. Studies are underway concerning radiation techniques in stereotactic conditions in localised, inoperable tumours, allowing larger doses of radiation to be delivered than in conventional regimens.

• *Other therapies*

Oral maintenance treatment with olaparib PARP inhibitors (poly ADP-ribose polymerase) in a small subgroup of advanced pancreatic tumours with germline BRCA1/2 gene mutation (around 4% to 5% of cases) and controlled after first-line platinum salt-based chemotherapy showed a benefit of a twofold increase in recurrence-free survival (main evaluation criterion),[18] but did not impact overall survival (secondary criterion) despite a hazard ratio of 0.66 in favour of olaparib.[19] This drug has a European MA. How this mutation is detected remains to be defined.

Monitoring

After curative treatment (surgical resection): clinical examination every 3 to 6 months. Paraclinical examinations (abdominal ultrasound + thorax X-ray or thoracic-abdominal-pelvic scan, biological assessment including CA19-9 test) will be requested either according to symptoms or systematically every 6 months (no consensus).

After palliative treatment: paraclinical examinations will be requested according to symptoms or according to therapeutic trial protocols and/or to assess the efficacy of radiotherapy and/or chemotherapy treatment.

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CHOLANGIOCARCINOMA TREATMENT

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General information

Bile duct cancers (BDC) are a heterogeneous group of adenocarcinomas developed from the bile duct epithelium. They have the second highest incidence among primitive liver tumours, after hepatocellular carcinoma.[1] The anatomical location is used to differentiate four subtypes: (1) intrahepatic cholangiocarcinoma (ICC), developed in the hepatic parenchyma; (2) perihilar ICC, between the second-order bile ducts and the cystic duct, previously known as Klatskinœtumours; (3) distant extrahepatic ICC, in the main bile duct below the cystic ductœbifurcation; and (4) gallbladder adenocarcinoma.[2]

BDCs are rare tumours, with an incidence of around 2,000 to 4,000 new cases a year in France.[3,4] The incidence, which varies throughout the world and is higher in Asia, is increasing, mainly for intrahepatic ICC.[5] The main risk factors are chronic inflammatory bile duct diseases (including primary sclerosing cholangitis), parasitic infections (flukes in Asia), chronic alcohol consumption, hepatitis B and C virus infections, metabolic syndrome and cirrhosis in particular (relative risk: 20).[6] BDC prognosis is bleak, with a 5-year overall survival rate (OS) of less than 20%, usually due to late diagnosis

at an advanced stage, owing to initial symptoms not being very specific.[7]

BDCs affect older patients, with an average age of diagnosis of 71 years (± 12.4 years) in all locations, more specifically for perihilar (73 ± 12.5 years) and distal (76 ± 9.7 years) forms than for intrahepatic ICCs (68 ± 12.5 years).[8]

Cholangiocarcinoma treatment

• *General principles*

There is no specific data or recommendations relating to ICC in older patients. The treatment proposals are taken from the French digestive oncology guidelines (Thésaurus National de Cancérologie Digestive). The latest recommendations for the treatment of bile duct cancers were issued in 2022[9] and the AFEF 2022 recommendations are in the process of being published.

• *Localised stage*

Only 30-40% of ICCs are resectable when diagnosed due to their remote locations, vascular involvement, and/or extent of liver invasion making it impossible to retain a sufficient volume of healthy liver parenchyma.[1]

Surgical treatment

Surgical resection, the only treatment that allows longer survival, must be considered wherever possible and discussed by a multidisciplinary team with experience in hepatobiliary surgery.[2,10,11] The objective of the surgery is to achieve complete resection (R0 margins) of the tumour and a lymphadenectomy.[2,10,11]

Patients must be selected for surgery based on a thorough analysis of pre-operative imaging (hepatic MRI with cholangio-MRI, thoracic-abdominal-pelvic contrast scan) carried out prior to any biliary procedures, and an operability assessment (age, general condition, comorbidities).[2,10,11]

An exploratory laparoscopy can change the surgical indication by detecting metastases not seen on the images (in the peritoneum in particular). This must be discussed, particularly before considering major pre-hepatectomy treatment.[12-14]

Surgery has special features according to the location of the primary tumour (intra-hepatic, perihilar, distal and gallbladder). Morbidity and mortality relating to major hepatectomies can be reduced by pre-operative biliary drainage of the future remaining liver in case of jaundice followed by, if required, pre-operative portal vein embolisation of the liver to be resected in order to create hypertrophy in the future remaining liver if its volume is lower than the CT volume (< 30% without cirrhosis, < 40% with cirrhosis).[2,10,11,15,16] Biliary drainage may be complex and must be carried out by experienced teams.

Microscopic resection margin invasion (R1 status) (5-year OS < 10%), lymph node invasion (5-year OS < 5%) and vascular invasion are the main poor prognosis factors, along with tumour size, multifocality for intrahepatic ICCs and differentiation grade.[17-20]

Post-operative recurrences are frequent and the 5-year OS after surgery is no higher than 25-35%.[1] These results question the benefit of peri-operative treatments.

Neoadjuvant therapy

There is no data from prospective randomised trials (i.e. pre-operative chemotherapy and/or radiotherapy).[2,10,11] A chemoradiotherapy (CRT) followed by liver transplant protocol was drawn up by *Mayo Clinic* for patients with locally advanced perihilar ICC but has not become a treatment standard.[21] This multidisciplinary strategy was evaluated versus a standard surgical approach in patients with a resectable tumour in a phase III study (TRANSPHIL, NCT02232932 study), which was stopped early. It was reserved for younger patients (≤ 68 years). In France, the SIROCHO (NCT05265208) study is evaluating neoadjuvant treatment with capecitabine combined with selective internal radiation versus immediate surgery for resectable intrahepatic ICCs.

Adjuvant chemotherapy[2]

Until 2017, the level of proof was too low to systematically recommend adjuvant therapy in patients having had BDC surgery.[2,10,11] Most centres offered adjuvant chemotherapy, particularly in the case of R1 resection or lymph node invasion, based on the low level of proof.[22,23] The French phase III PRODIGE 12-ACCORD 18 study, which compared 6 months of GEMOX (gemcitabine and oxaliplatin) adjuvant chemotherapy with

monitoring, did not achieve its main objective (recurrence-free survival [RFS]).[24] On the other hand, the English phase III BILCAP study, which evaluated adjuvant chemotherapy with capecitabine (according to a standard regimen of 1250 mg/m^2, twice a day, 14 out of 21 days, for 6 months) versus monitoring, despite not achieving its main objective (OS in the intention-to-treat population: 51.1 vs 36.4 months, Hazard Ratio [HR] = 0.81, p = 0.097), showed a significant improvement in OS in the *per-protocol* population (HR = 0.75, p = 0.028) and after adjustment according to sex, grade and lymph node status (HR = 0.71, $p < 0.01$), and of RFS with capecitabine.[25] Despite the insignificance of the study, due to the 15-month survival increase and favourable tolerance, adjuvant therapy with capecitabine for 6 months is considered to be a new standard, including in older patients in good overall condition (PS 0-1) and without major comorbidity.

Inclusions in the study were possible up to 16 weeks after surgery so it would seem reasonable to wait until the patient has recovered from surgery to commence treatment, and possibly to start with a 1,000 mg/m^2 dose x 2/day (after using phenotype testing to check that there is no dihydropyrimidine dehydrogenase) in the first cycle in older/frail patients to assess tolerance. As capecitabine is renally eliminated, specific attention must be paid to renal function.

The results of the phase III ACTICCA-1 trial (CISGEM versus adjuvant capecitabine, NCT02170090) are pending. In France, the PRODIGE IMMUNOBIL-Adj study, starting in 2022, will evaluate adjuvant therapy with capecitabine alone or combined with durvalumab.

- *Advanced stages*

The vast majority of BDCs (70%-80%) are diagnosed at an advanced stage and treated with comfort care (including pain, pruritus, psychosocial and nutritional management as well as adapted physical activity and management of adverse events relating to the treatment and thromboembolic complications) and chemotherapy when possible.[2,10,11] The median OS of patients at this stage of the disease varies from 3 to 12 months depending on the study and whether or not chemotherapy is administered, with the latter proving its superiority over comfort care alone.[26,27]

Biliary drainage

Biliary drainage is the main palliative therapeutic measure for unresectable tumours or inoperable patients.[2,10,11] It must be performed before commencing chemotherapy.[2,10,11]

Incomplete biliary drainage negatively impacts survival and is a source of morbidity (cholangitis, jaundice, pruritus). Drainage must be as complete as possible, focusing on functional areas and minimising iatrogenic risk (drainage of all opaque areas, antibiotic treatment).[28,29] For complex tumours, biliary drainage must be performed by an expert centre with endoscopy (ERCP and endoscopic ultrasound) and interventional radiology experience. These procedures must be carried out frequently and successively or simultaneously.[2,10,11] In this situation, cholangio-MRI is the preferred examination for planning prosthesis placement in order to limit the risk of post-procedural cholangitis.

The percutaneous transhepatic route is required if endoscopic drainage fails or is impossible.[2,10,11] External drains which negatively impact quality of life should be avoided as far as possible. Metallic biliary prostheses, which are permeable for longer, are preferable to plastic prostheses in patients with a life expectancy of over 3 months.[2,10,11] Most patients will need iterative drainage procedures during the progression of their disease. This must be taken into consideration when positioning prostheses.[2,10,11]

Chemotherapy

The objective of chemotherapy is to increase OS but also, in particular, to maintain or improve quality of life and manage symptoms (jaundice, pruritus, pain).[2,10,11]

CISGEM (gemcitabine and cisplatin) chemotherapy has been the first-line standard treatment in advanced BDC since 2010, based on the English phase III randomised ABC-02 trial which showed the superiority of this doublet over gemcitabine alone in terms of OS (median: 11.7 vs 8.1 months, $p < 0.001$) and progression-free survival (PFS) (median: 8.0 vs 5.0 months, $p < 0.001$).[30] In older patients in particular, cisplatin requires the monitoring of hearing and renal function, but the small doses used in the CISGEM regimen (25 mg/m^2) do not require IV hyperhydration or hospitalisation. Monotherapy with gemcitabine

may be offered to frail patients or those with PS 2 or contraindications to cisplatin (e.g. renal failure).

Up until the late 2010s, some centres, particularly in France, widely used the GEMOX doublet, considered to be an equivalent alternative to CISGEM.[31] This practice declined in favour of CISGEM following FOLFOX (5-FU and oxaliplatin) chemotherapy being positioned as second-line therapy.[32]

The phase II/III randomised PRODIGE 38-AME- BICA (NCT02591030) trial did not show that modified FOLFIRINOX (5-FU, folinic acid, oxaliplatin and irinotecan) demonstrated superiority over CISGEM and the FOLFIRINOX combination in patients with advanced BDC.[33] Phase II trials with other molecules (nal-IRI, nab-paclitaxel) showed interesting activity results but these need to be confirmed in phase III.

Until recently, there was no second-line standard treatment.[2] The ABC-06 trial, presented at ASCO in 2019, showed the superiority of modified FOLFOX (5-FU, folinic acid, oxaliplatin) over supportive care alone after first-line CISGEM failure (median OS: 6.2 vs 5.3 months, HR = 0.69, $p = 0.031$).[32] Special attention must be paid to older patients with oxaliplatin-induced cumulative peripheral neuropathy which can cause impaired walking and balance and increase the risk of falling. Other chemotherapies (particularly with the standard form of irinotecan or nal-IRI) were evaluated but only in phase II.

Targeted therapies

"Standard" targeted therapies (mainly anti-EGFR and antiangiogenic) failed to provide a survival benefit when treating BDCs in unselected patient populations.[34,35] Comparative genomic studies between intrahepatic CC, extrahepatic CC and gallbladder adenocarcinoma revealed the molecular heterogeneity of these tumours and identified certain genetic abnormalities specifically present in certain locations.[34,36-40] These BDC molecular classifications paved the way for bio-guided treatments.[41] *IDH* and *FGFR* mutations, each identified in around 10%-20% of intrahepatic CCs, are the two main "modern" therapeutic targets in BDCs with the most advanced clinical development programme. The phase III ClarIDHy trial showed the superiority of mutant IDH inhibitor ivosidenib over the placebo in patients with pretreated *IDH1* mutant BDCs (PFS: HR = 0.37,

$p < 0.001$).[42] Positive phase II trials were also presented with FGFR inhibitors in patients with tumours with *FGFR2* translocation (e.g. pemigatinib, infigratinib, futibatinib[43]), and phase III trials with these molecules are underway. Other molecules are available to target HER2 amplifications (trastuzumab plus pertuzumab, zanidatamab), which are more frequent in extrahepatic CCs and gallbladder cancers, BRAF V600E mutations (dabrafenib plus trametinib), TRK fusions (larotrectinib) or microsatellite instability (MSI/dMMR, pembrolizumab), mutations considered as "actionable" based on the ESMO scale.[44] As the status of the molecules changes quickly, I would offer something more generic: "Many of these molecules are accessible through compassionate or early access programmes." These therapeutic developments justify systematic early use (as first-line treatment, with targeted therapies able to be offered as second-line treatment) of NGS molecular profiling to identify IDH1 and BRAF (DNA or RNA) mutations and FGFR2 and NTRK (RNA) fusions, as well as an HER2 and MMR status in immunohistochemistry testing (INCa-ACABi consensus, March 2022) in all patients with advanced BDC and ECOG PS 0-1. The PRODIGE SAFIR ABC- 10 study, scheduled to start in 2023, will aim to validate this precision medicine as maintenance treatment for advanced BDC after induction chemotherapy with CISGEM.

In addition, phase II trials evaluated immunotherapy strategies, including the French PRODIGE 57-IMMUNOBIL study (second-line durvalumab plus tremelimumab ± paclitaxel, NCT03704480). The intermediate analysis of the phase III TOPAZ-1 trial, presented at ASCO GI 2022[45], showed a benefit in terms of response rate, progression-free survival and overall survival with durvalumab compared with a placebo combined with first-line CISGEM chemotherapy in patients with advanced BDC in good general condition (ECOG PS 0-1). The extent of this benefit was however moderate or modest. In a subgroup analysis, the benefit seemed minor in non-Asian patients and in patients with gallbladder cancer. Anti-PD-L1 immunolabelling did not seem able to identify a population with the best response to immunotherapy, including and particularly for high scores. Adding durvalumab to the chemotherapy did not increase the toxicity risk. If approved by our regulatory authorities and accessible, CISGEM plus durvalumab treatment should become the new standard first-line treatment for

advanced BDC. The results of another international randomised controlled phase III (KEYNOTE-966) trial are not yet available.

Locoregional therapies

Extrahepatic CCs are anatomically and biologically similar to pancreatic cancers and are commonly poorly vascularised tumours whereas intrahepatic CCs are often hypervascular in the arterial phase.[46,47] Hepatic intra-arterial treatments (chemotherapy, Yttrium 90 radioembolisation, conventional hepatic intra-arterial chemoembolisation, and selective embolisation with chemotherapy-loaded microspheres) were studied for the treatment of locally advanced intrahepatic CCs (unresectable, non-metastatic) in some centres.[48,49] The effects of selective internal radiotherapy with Yttrium-90 microspheres were analysed in a systematic review of 12 studies in 298 patients with unresectable intrahepatic CCs: the median OS was 15.5 months, a partial tumour response was observed in 28% of patients, and stability in 54%.[50] It is considered as an option in locally advanced intrahepatic CCs and may, in combination with systemic "induction" chemotherapy, achieve tumour downstaging in some patients and allow secondary resection to be considered.[51] External radiotherapy (e.g. stereotactic) may also be offered for this indication, and may be discussed at an MDTM as an alternative to surgery in frail/inoperable patients.[52-54] Due to the rarity of BDCs, none of the locoregional approaches has been evaluated in randomised clinical trials.[55]

Conclusion

All in all, BDCs are:
- rare tumours with a poor prognosis;
- heterogeneous from an anatomical, epidemiological and therapeutic point of view;
- treated with a multidisciplinary approach (surgeons, endoscopists, digestive oncologists, radiotherapists, interventional radiologists and anatomical pathologists) using expert centres (surgery, locoregional therapies and, more recently, genomic platforms);
- the treatment for which has changed in recent years (standardisation of adjuvant and first- and second-line treatments, development of personalised medicine and immunotherapies);
- and for which there is little data specific to older patients.

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HEPATOCELLULAR CARCINOMA TREATMENT

Alix Durroux, Mohamed Bouattour, François Cauchy, Marco Dioguardi Burgio, Charlotte Fernet

14

In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature.

Hepatocellular carcinoma (HCC) is a heterogeneous tumour which develops in patients with cirrhosis or chronic liver disease in over 90% of cases. Treatment is multidisciplinary and takes three important parameters into account: (i) the stage of the cancer, (ii) the condition of the subjacent liver and (iii) the patient's comorbidities. Current national and international recommendations and decision trees do not take into account the age of patients with HCC.

Early stages: tumours meeting "small HCC" Milan criteria without extrahepatic vascular invasion and/or metastasis.

- *First-line treatment: partial hepatectomy*

Surgical resection in older patients is mainly discussed for single tumours without tumour macrovascular invasion or signs of clinically significant portal hypertension (portacaval gradient of over 10 mmHg) (*Child-Pugh* A, MELD 5-6 cirrhosis).[1] The principles of hepatic resection in older patients are the same as those for younger

patients and favour anatomical resection (resection of the tumour and liver parenchyma with secondary tumour portal vascularisation from the lesion) or non-anatomical resection with 2 cm margins, intra-operative blood loss limitation using intermittent pedicle clamping, and careful tumour manipulation to limit the risk of tumour cell rupture and blood circulation.[2] In the case of major resection (more than 2 segments), the volume of the future remaining liver must represent between 30% (normal subjacent liver) and 40% (cirrhotic subjacent liver) of the total hepatic volume depending on the nature of the subjacent hepatic parenchyma. In specialist surgical centres, the risk of mortality or morbidity resulting from hepatectomies, even major ones, does not seem to increase with age due to a stricter selection of older patients and the fact that the regenerative capacity of the liver does not change significantly with age.[3-5] In the same way as for younger patients, the risk of complications is, however, higher in cases of cirrhosis. Where possible, a minimally invasive approach (laparoscopic or robot-assisted) should be used, which seems to provide a benefit in terms of post-operative complications, particularly where post-operative delirium is concerned.[6] The surgical indication must, of course, be discussed at a multidisciplinary team meeting (MDTM). Patients must be well selected, with an appropriate surgical risk assessment for this population, the adaptation of any procedures, nutritional and possibly rehabilitation programmes, and an assessment of the expected benefit in terms of survival.[6,8,9]

Liver transplant is not generally performed in patients over the age of 70 due to (i) vascular ageing (difficulty performing vascular anastomoses, risk of ischemic complications, (ii) the increased rate of other comorbidities in older patients resulting in a higher risk of complications, and (iii) available stock of transplant organs, with twice as many patients joining the list as patients receiving transplants each year.

- *If patient is not eligible for surgery: percutaneous destruction*

Percutaneous thermal ablation using radiofrequency or microwaves is indicated in patients with compensated cirrhosis (Child-Pugh A/B7) with small (≤ 3 cm), unifocal or ≤3 HCCs.[1] The procedure is performed under

general anaesthetic and lasts an average of 20 minutes. Patients are in hospital for an average of 24 hours. Major complications relating to percutaneous ablation (such as digestive perforation, hepatic abscess, biliary complications, thromboses or haemorrhagic events) are rare, even in older patients.[10,11] The benefit of percutaneous ablation in terms of survival in older patients is disputed in the literature. Some studies find comparable overall survival and recurrence-free survival rates in patients aged over 75 and younger patients.[12,13] In other studies, the benefit has not been clearly observed.[11,14] Therefore, the indication for HCC percutaneous destruction in older patients must first of all be assessed at an MDTM then by the interventional radiologist and anaesthetist to select the best candidates and minimise mortality and morbidities relating to the procedure.[7]

Intermediate stage: locally advanced tumour which is inaccessible for surgical treatment and/or percutaneous destruction, with no extrahepatic spread.

- *As first-line treatment: transarterial chemoembolisation (TACE) (when there is no extrahepatic vascular invasion or metastases)*

TACE consists of a local injection of chemotherapy (doxorubicin, idarubicin or less often cisplatin) combined with possibly selective embolisation of the artery supplying the tumour. TACE is recommended for Child-Pugh A/B7 patients with HCC who are ineligible for local ablation or resection treatment. **Tumours may be single or multiple but without vascular invasion or extrahepatic spread.**[1] Older patients were not initially considered to be good candidates for TACE.[15] However, due to technical advances, it is now recognised that older patients can benefit from this approach.[16] Several studies have shown that TACE significantly improves overall survival in older patients.[12,17,18] TACE is performed under local anaesthetic, requiring an average hospital stay of 2 to 3 days. Complications may be general and directly related to the chemotherapy, or local and related to the procedure with bruising at the puncture site. The rates of serious complications and mortality directly relating to the procedure remain low. [12,17,18]

- *If patient is not eligible (presence of vascular invasion without extrahepatic metastasis)*

The standard treatment is systemic atezolizumab plus bevacizumab therapy (see below).

Radioembolisation (RE): this consists of a hepatic intra-arterial injection of radioactive Yttrium-90 microspheres to perform selective internal radiation. RE showed interesting results in terms of tolerance and increased survival in older patients in an Italian and a French cohort.[19,20] A French randomised controlled multicentre study (SARAH trial) evaluating RE versus sorafenib in patients with locally advanced HCC did not show improved survival compared with sorafenib.[21] However, RE showed better local control of the disease as well as better tolerance and quality of life.[21,22] One of the benefits of this technique would be to maintain quality of life and avoid systemic toxicities in older patients.[22] The indication of RE must be approved at an MDTM in specialist centres for patients with locally advanced HCC.

Advanced stage: tumour with vascular invasion and/or extrahepatic metastases

- *As first-line treatment: a combination of immunotherapy and an antiangiogenic drug*

Recently, the combination of systemic atezolizumab treatment [a humanised immunoglobin G1 monoclonal antibody, anti-Programmed Death-Ligand 1 (PD-L1)] and bevacizumab [an anti-VEGF (Vascular Endothelial Growth Factor) antibody] showed significant improvement in overall survival in advanced-stage HCC.[23] The randomised phase 3 IMbrave 150 trial compared intravenous atezolizumab plus bevacizumab every 3 weeks with oral sorafenib in 501 Child-Pugh A patients in good general condition (PS 0-1) with advanced HCC. After 15.6 months of median follow-up, the combination of atezolizumab and bevacizumab showed a significant improvement in overall survival of 19.2 months (CI 95% 17.0-23.7) compared with 13.4 months with sorafenib (hazard ratio 0.66; CI 95% 0.52-0.85; $p < 0.001$).[23,24] It should be noted that in the IMbrave 150 trial, the median age of patients treated with atezolizumab plus bevacizumab was 64 years (extremes: 56-71 years). There is, therefore, little data currently available relating to older patients. The treatment tolerance is good and the

combination would enable the quality of life of the treated patients to be maintained.[25] Specific attention must be paid to the risk of haemorrhage with bevacizumab and a high digestive endoscopy is recommended prior to treatment. In addition, there is a risk of sometimes severe arterial hypertension, meaning that regular monitoring is required to detect cardiovascular complications. It is worth noting that if immunotherapy is commenced, independence must be regularly reassessed. Older patients are more likely to experience suddenly impaired functional status, which can result in delaying treatment, increasing home support and setting up or strengthening support and comfort care.

- *If patient is not eligible for systemic treatment: symptomatic treatment*

If atezolizumab and bevacizumab are contraindicated: targeted molecular therapies

Sorafenib, an antiangiogenic molecule, can be discussed if atezolizumab and bevacizumab are contraindicated in Child-Pugh A/B patients with advanced HCC and maintained general condition (PS 0-2).[1,26] Several studies reported comparable results in older and younger patients in terms of the safety and efficacy of sorafenib.[10,27] Regular monitoring and specific attention to side effects are required due to the higher number of comorbidities (particularly cardiovascular) in this population, resulting in a higher treatment discontinuation rate.[28,29]

Lenvatinib, a second antiangiogenic molecule, recently demonstrated similar efficacy to sorafenib in a non-inferiority trial.[30] Lenvatinib is not covered by the French health insurance system for HCC.

- *As second-line treatment: targeted molecular therapies*

No molecule has been evaluated following first-line atezolizumab plus bevacizumab treatment. The treatments will be discussed based on the available data after sorafenib failure or intolerance.[31]

Regorafenib demonstrated efficacy and an acceptable tolerance profile in patients with HCC progressing after sorafenib but having tolerated it well.[32] Regorafenib

must be evaluated in older patients with HCC to evaluate its efficacy and tolerance in this population.

Cabozantinib recently demonstrated a significant increase in overall survival as 2nd- and 3rd-line treatment compared with the placebo, in patients with advanced HCC.[33] Cabozantinib has not been specifically evaluated in older patients.

Several phase IV studies are currently in progress, evaluating these new antiangiogenic molecules in real life (REFINE for regorafenib, CLEARENCE for cabozantinib). These studies should determine the tolerance profile and efficacy in the older patient subgroup.

- *If patient is not eligible for systemic treatment: symptomatic treatment*

In the case of decompensated cirrhosis or impaired general condition

Symptomatic treatments and comfort care: ascites treatment, symptomatic portal hypertension treatment, nutritional management and analgesic treatments, etc.

Monitoring

There is no data in the literature enabling optimal monitoring to be recommended either in terms of methods or duration.

The monitoring methods are decided according to the treatment. This monitoring may be stopped if no treatment options are offered for recurrence.

- *After surgical resection or percutaneous destruction:*

- clinic, hepatic and AFP tests every 3 months for 2 years followed by every 6 months;
- hepatic and thoracic MRI and CT scan every 3 months for 2 years followed by every 6 months.

- *After TACE treatment:*

- clinic, hepatic and AFP tests, hepatic MRI or CT scan after 4-6 weeks;
- then on a case-by-case basis according to the number of sessions and efficacy.

• *Systemic treatments:*

- clinical monitoring, hepatic and AFP tests every month;
- hepatic and thoracic MRI and CT scan every 3 months;
- ADL and iADL every 3 months.

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ANAL CANAL CANCER TREATMENT

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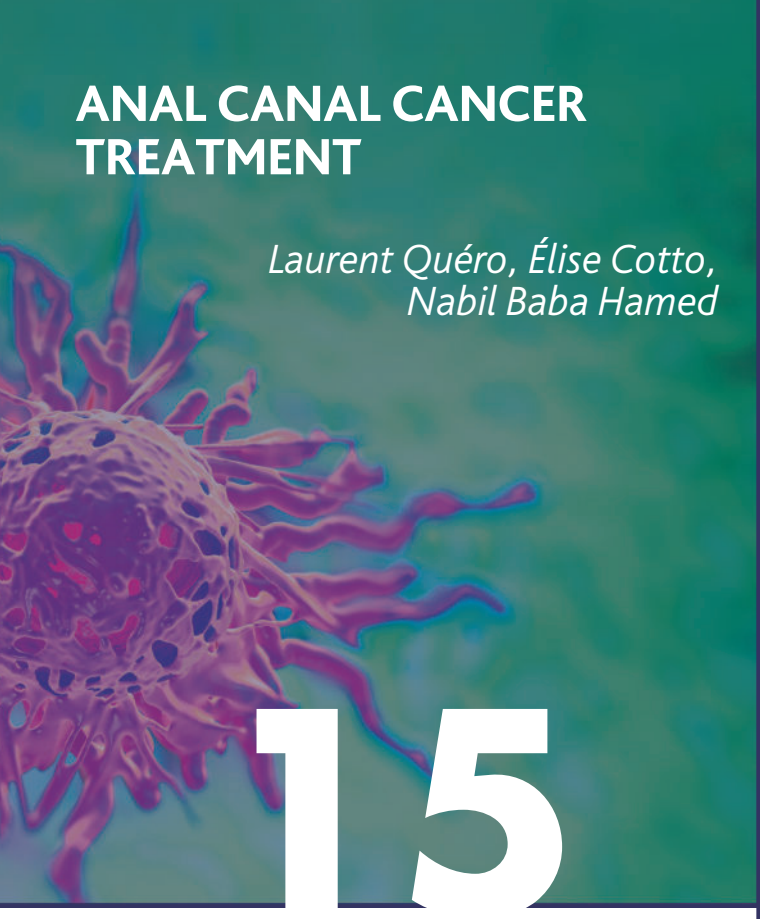

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In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature.

The standard treatment for anal invasive squamous cell cancer (T2 ≥ 3 cm, T3-T4 and/or metastatic lymph node involvement) is a concomitant combination of radiotherapy and chemotherapy (CRT) with 5-fluorouracil (5-FU) and mitomycin C (MMC). It has a 1A recommendation by the American Society of Colon and Rectal Surgeons (ASCRS).[1]

UICC classification (8th edition):[2]
- T1 - tumour ≤ 2 cm at maximum diameter;
- T2 - tumour > 2 cm but ≤ 5 cm at maximum diameter;
- T3 - tumour > 5 cm at maximum diameter;
- T4 - tumour invading adjacent structure(s).

Stage I: Tumour ≤ 2 cm = T1N0

- ***First-line treatment***

Exclusive radiotherapy involving external irradiation of the tumour and mesorectum.

• *If patient is not eligible*

Treatment involves exclusive hypofractionated radiotherapy, interstitial brachytherapy if the tumour occupies less than 2/3 of the anal canal circumference and measures less than 5 cm.

• *Radiotherapy*

This is usually carried out in two phases. The first phase involves locoregional external radiation at a dose of 45 Gray (Gy), delivered in 5 sessions (fractions) of 1.8 Gy a week, followed by a break in some cases, and modulated according to acute cutaneous mucosal or digestive tolerance. The pause must be as short as possible or eliminated. Next, a radiation boost is delivered to the macroscopic tumour volume using 15 Gy external radiation or interstitial brachytherapy at a dose of 15/20 Gy.

• *Another radiation regimen*

Another option, recommended by the EORTC, is an initial series of radiation delivering a dose of 36 Gy followed by an additional dose of 23.4 Gy.[3] The dose delivered by the boost will depend on the initial tumour size and also on the tumour response to the first series of radiation. The benefit of using brachytherapy for the radiation boost is still being assessed.[4]. An intensity-modulated radiotherapy technique (IMRT, tomotherapy or dynamic arc therapy) is recommended in order to minimise the dose delivered to nearby organs, thus reducing acute cutaneous, digestive and haematological toxicities which are responsible for treatment interruptions that may compromise its efficacy.[5-7]

Stage II: Tumour > 2 cm = T2 T3 N0

Chemoradiotherapy has proven its superiority over radiotherapy alone for locally advanced tumours.[8,9] Cisplatin chemotherapy has not proven its superiority over MMC. When combined with MMC, 5-FU chemotherapy can be replaced by oral capecitabine.[10]

For a tumour over 3 cm, inguinal lymph node areas will be included in the radiation volume. Tumours smaller than 3 cm have a low risk of inguinal metastatic lymph node involvement, around 5% synchronously, unlike

tumours measuring over 5 cm which have a risk of over 20%.[11]

• *First-line treatment*

Chemoradiotherapy combining external irradiation of the tumour, mesorectum and pelvic and inguinal lymph node areas in concomitant combination with 5-FU and MMC chemotherapy.[12,13]

• *If patient is not eligible*

The treatment involves reduced-dose radiotherapy delivering 30 Gy in concomitant combination with a cycle of 5-FU and MMC chemotherapy. This regimen showed its efficacy in the first study by Norman Nigro in the 1970s including 21 patients with a complete histological response rate of 57%.[14] A pilot study by the same team including 45 patients showed a disease-free survival rate of 89%.[15] Another study confirmed the efficacy of this protocol, particularly for tumours under 5 cm, with a disease-free survival rate of 90%.[16] Patients with a T3 or T4 tumour had a disease-free survival rate of 38% in this study. Other teams suggested reducing radiation volumes to the tumour and involved lymph node regions without prophylactic lymph node irradiation, limiting the side effects of the treatment and improving compliance.[17]

Stage III: Tumour which has spread to nearby organs or is invading lymph node areas = T1-T3 N1a-N1c;T4 N0-N1c

• *First-line treatment*

Chemoradiotherapy combining external irradiation of the tumour, mesorectum and pelvic and inguinal lymph node areas in concomitant combination with 5-FU and MMC chemotherapy.

If nearby organs are involved (T4 tumour) or there is anal incontinence due to the destruction of the anal sphincter apparatus by the tumour, abdominoperineal amputation surgery following an initial series of radiation must be discussed.

• *If patient is not eligible*

The treatment involves reduced-dose radiotherapy delivering 30 Gy in concomitant combination with a cycle of 5-FU and MMC chemotherapy. Reduction of radiation volumes to the tumour and involved lymph node areas without prophylactic lymph node irradiation.

A subgroup analysis based on the French ANABASE cohort (multicentre prospective cohort examining the treatment of localised anal canal cancer France between 2015 and 2020) involving subjects ≥ 75 years (19.9% = 202 patients) showed that efficacy in terms of complete response, overall survival, recurrence-free survival and colostomy-free survival, as well as tolerance profiles, were similar to in the group of subjects < 75 years.[18]. It is therefore important to offer the best treatment to older patients with a favourable geriatric oncology assessment.

Stage IV: Distant metastatic involvement

• *First-line treatment*

The modified DCF combination (docetaxel, cisplatin, 5-FU) according to a simplified bimonthly regimen is currently considered to be a French national standard due to the highly encouraging results of the phase II non-randomised EPITOPE HPV02 trial.[19] A 5-day course of primary G-CSF prophylaxis will be prescribed due to the haematotoxicity of this combination.

• *If patient is not eligible*

There is no standard chemotherapy treatment. The phase II randomised InterAACT trial showed the superiority of a weekly regimen of carboplatin and paclitaxel over the former standard CF (cisplatin, 5-FU) polychemotherapy in terms of objective response rate and overall survival, and may be suitable for older patients who are not eligible for mDCF.[20]

Recurrence

• *First-line treatment*

Abdominoperineal amputation salvage surgery with permanent colostomy must be offered in the case of histologically proven local recurrence or lack of

response after radiotherapy or chemoradiotherapy treatment.

Treatment side effects and sequelae

- *Acute toxicity*

Resulting from chemotherapy: asthenia, nausea, MMC-related haematological toxicity (25% of grade 2-3 in patients > 74 years, probably due to the more frequent reduction in chemotherapy dosage in patients aged over 69).[21,22] Cardiac toxicity and stomatitis, diarrhoea linked to 5-FU.

Resulting from radiotherapy: cutaneous (epithelitis), digestive (haematochezia, tenesmus, diarrhoea), urinary (pollakiuria, cystitis). These toxicities usually decline within 3 months of the end of radiotherapy treatment. Sequelae may persist in 3% to 20% of cases, and may not become apparent for some time, sometimes several years after treatment.

- *Delayed radiotherapy-related toxicity*

Cutaneous and subcutaneous: subcutaneous fibrosis or sclerosis, permanent hair loss, telangiectasia.

Digestive: radiation proctitis (haematochezia, diarrhoea, tenesmus, pain), stenosis or faecal incontinence, radiation enteritis (diarrhoea, malabsorption syndrome).

Gynaecological, urological: vaginal stenosis, radiation cystitis (intermittent episodes of cystitis, haematuria), urinary incontinence, urethral stricture.

Bone: fractures, osteonecrosis of the femoral head. Some publications mention an increased risk of pelvic fractures, including femoral neck fractures, in irradiated anal cancer, but the low numbers make any assessment of the real incidence rate impossible.[23-26] In addition, the impact of the associated chemotherapy is not known. However, particularly in older women, it is necessary to check that irradiating inguinal and iliac lymph node regions is appropriate through efficient initial staging including positron emission tomography-tomodensitometry (PET-CT). Intensity-modulated conformal radiotherapy is likely to reduce this risk.

Smoking and therapeutic impact

Continued smoking has a clear negative effect during CRT.[26,27] This factor does not explicitly appear to any extent in studies dedicated to older patients.

Prognosis

5-year overall survival for all stages using this strategy is around 65-75%, with local control of around 60%. The 5-year colostomy rate is close to 25%.

Monitoring

Weekly clinical monitoring and varying degrees of biological monitoring during treatment with management of any treatment side effects.

3/4-month assessment: clinical examination = digital anorectal, palpation of inguinal lymph node areas, SCC (squamous cell carcinoma antigen) test if this was raised prior to treatment, anorectal endoscopic ultrasound (AEU) or MRI, abdominal-pelvic CT + thorax X-ray?

For 2 years: clinical examination every 3 months, SCC, AEU or MRI, abdominal-pelvic CT + thorax X-ray every 6 months.

Then for the following 3 years: clinical examination every 6 months, SCC, AEU or MRI once a year.

Then after 5 years: clinical monitoring only.

During monitoring: a PET-CT scan needs to be carried out in the case of non-normalised or re-ascended SCC or abnormal lesions in the monitoring examinations.

Anal biopsies will only be performed in the case of highly suspicious and/or persistent lesions (risk of local necrosis or fistula). There will be a delay of 3 to 6 months after initial treatment due to the possibility of delayed responses to treatment, which could occur up to 6 months after it has ended.

Conclusion

Squamous cell cancer of the anus is relatively rare but its incidence is increasing. It is associated with human papillomavirus (HPV) and the risk is increased by smoking. When diagnosed, the patient needs to be checked for

associated HIV infection. The main decision-making factor relating to treatment in older patients is the existence of associated comorbidities rather than chronological age. Patients aged over 69/74 without any severe associated comorbidity must be treated in the same way as younger patients but with more supportive treatments.

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PROSTATE CANCER TREATMENT

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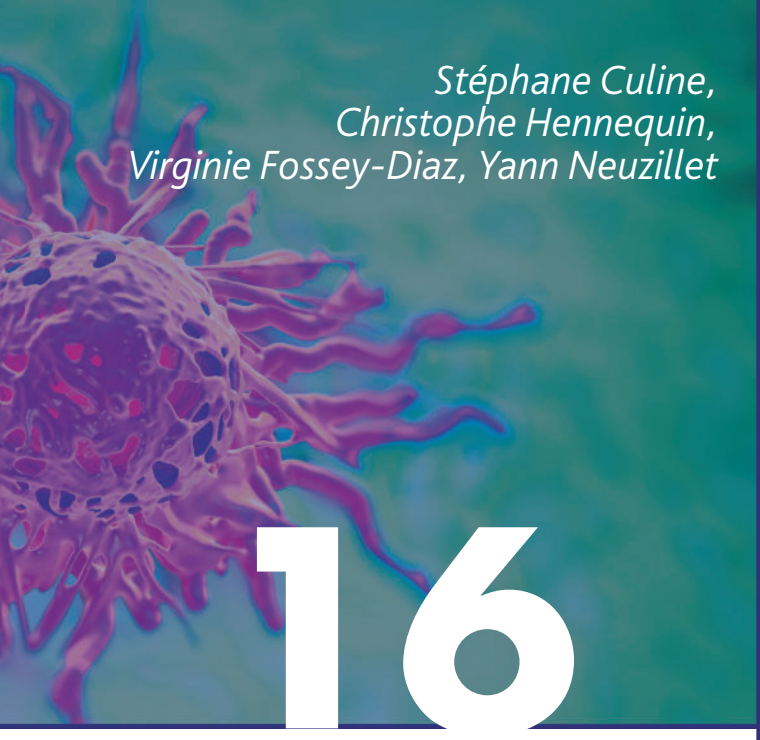

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Prostate cancer treatment in older patients must take into account both the patient's history and condition (following the geriatric oncology assessment) and the clinical-biological characteristics of the prostate tumour.

Localised prostate cancer must be evaluated according to its risk of progression. 3 risk groups are identified based on the serum PSA value, Gleason score on prostate biopsies and tumour stage. The preferred method is currently the ISUP grading system.

Low risk	PSA > 10 ng/ml; and ISUP 1; and clinical stage T1c or T2a.
Intermediate risk	PSA between 10 and 20 ng/ml; or ISUP 2 (favourable intermediate); or ISUP 3 (unfavourable intermediate); or clinical stage T2.
High risk	PSA > 20 ng/ml; or ISUP 4-5; or clinical stage T3-T4.

A very-low-risk group can be added to these three groups (PSA < 10 ng/ml, ISUP 1 and < 2 positive biopsies). A multiparametric prostate MRI with PI-RADS 4-5 abnormality is useful for classifying patients in this group. The risk of death relating to prostate cancer is lower than 5% to 10% in this very-low-risk group.

Localised stages

Low-risk group: active surveillance is the preferred option.

Favourable-intermediate-risk group (ISUP 2): active surveillance can be offered along with strict monitoring and particularly if the grade 4 percentage is ≤ 20%. This is not, however, recommended if there is a cribriform or intraductal component.

Unfavourable-intermediate-risk or high-risk group (ISUP 3): if the patient is in good general condition and considered to be fit with a life expectancy ≥ 5 or 10 years, curative treatment is proposed.

- *Recommendations for local treatment*

If it is justified, a prostatectomy can be proposed. However, post-operative recovery, based on the patient's functional status, decreases with age. As a result, the risk of urinary incontinence is higher than in younger patients. The incontinence rate (> 1 pad/day) is less than 15% before the age of 60 and 38% after the age of 70.[1]

Pelvic lymphadenectomy is indicated for intermediate-risk cancers combining the criteria distinguishing them from low-risk cancers (PSA of 10 to 20 ng/ml, ISUP score of 2-3 and clinical stage T2b), as well as for high-risk cancers. The complication rate of extended lymphadenectomy as recommended is around 20%.

HIFU (*High-Intensity Focused Ultrasound*) was evaluated by an observational clinical study (HIFI study) of patients aged over 70 with an at least 7-year probability of survival, a T1-T2 N0, M0 tumour with an ISUP score of ≤ 2 in a maximum of 4/6 biopsied prostate zones, with PSA < 15 ng/ml and a prostate volume < 50 cc. Recruitment closed on 30 September 2019 and the results are pending.

Radiotherapy is a particularly interesting treatment option in older patients. Its results both in localised and locally advanced stages are identical to those of surgery. Its complications have clearly reduced in terms of frequency and intensity with the use of new techniques, particularly intensity modulation. In particular, it does not cause urinary incontinence.

The occurrence of complications is not directly linked to age but to the existence of comorbidities such as diabetes or the use of anticoagulants or antiaggregants. Like in younger patients, compliance with dose constraints for organs at risk (rectum, bladder) ensures the quality of radiation. If the patient has pre-existing voiding dysfunction, local urological procedures (transurethral resection) may be necessary and must be performed before radiation treatment. Erectile function may be impaired, especially in older patients or those with diabetes.

Several randomised trials have shown the equivalence of hypofractionated regimens, with fewer sessions. A regimen which has become standard is 60 Gy in 20 fractions, but this requires optimal equipment (intensity modulation, image-guided radiotherapy). The reduced number of sessions is a major advantage in older patients. Stereotactic radiotherapy (5 sessions) appears to have similar results in several prospective studies, despite its equivalence with current regimens not being demonstrated. It could, however, be offered to older patients who have difficulty moving around.

In low-risk forms, brachytherapy can be an alternative if the prostate volume (60 cc maximum, without median lobe) allows and if there is no voiding dysfunction or history of endoscopic prostate resection.

- *Should hormone therapy be used as well?*

Trials in younger patients have shown, depending on the tumour groups, a benefit to adding hormone therapy to radiation in intermediate- and high-risk groups. In the "unfavourable"-intermediate-risk group, short-term hormone therapy (6 months) is recommended. In the high-risk group, long-term hormone therapy (at least 18 months) is recommended. For very-high-risks forms, the addition of abiraterone acetate significantly improves survival.

Hormone therapy alone is not recommended in low-risk patients or those with a localised or locally advanced form.

Focal therapy has no indication outside of clinical trials.

Biochemical recurrence

- *Local post-prostatectomy treatment if possible: salvage radiotherapy*

After surgery, local biochemical recurrence is characterised by PSA rising to ≥ 0.20 ng/ml. Recurrence is most likely only local when PSA was temporarily undetectable and increases with slow kinetics, and in cases of positive surgical margin and pT stage > 3a.

Ideally, in patients in very good general condition, a locoregional assessment can be carried out including a PSMA PET scan and MRI of the anastomotic area. Urinary continence should ideally be recovered before commencing radiation therapy.

After assessing the patient's general condition, taking into account comorbidities and life expectancy, localised locoregional radiation therapy can be offered. The recommendation is prostate bed radiation including the anastomotic area.

Short-term hormone therapy can be added if there are poor prognosis factors.

- *General treatment if local treatment is not possible or indicated*

It has been clearly demonstrated that androgen deprivation alone shows worse results than when it is combined with radiotherapy. If local treatment is not possible, the treatment will not be curative and will just delay the onset of symptoms.

The decision to use hormone therapy must be properly considered, weighing up the side effects (asthenia, metabolic disorders, etc.) against the risk of progression of the disease. It must only be commenced in patients with a rapidly progressing disease (PSA doubling time < 12 months).

Intermittent androgen deprivation with:
- LH-RH agonist, or
- LH-RH antagonist.

Monitoring

PSA, testosterone levels.

Bone focus:
- calcium and vitamin D supplements;
- pre-treatment osteodensitometry if long-term hormone therapy (< 12 months);
- 4 mg IV zoledronic acid or 60 mg SC denosumab every 6 months if osteoporosis.

Metabolic (weight, blood pressure, waist circumference and blood sugar, cholesterol and triglyceride levels) and cardiovascular monitoring.
Recommendation for regular physical exercise, if possible.
Monitoring of anxiety-depressive disorders caused by androgen deprivation.

Stages which are metastatic at diagnosis

• *Treatments*

The standard treatment is based on the combination of androgen deprivation and new-generation hormone therapy.

Androgen deprivation can be performed with an LH-RH agonist, an LH-RH antagonist or a pulpectomy.

Second-generation hormone therapies are abiraterone (androgen synthesis enzyme inhibitor), enzalutamide and apalutamide (androgen receptor inhibitors).

These treatments must be administered continuously. The combination achieves longer survival than castration alone. Data in patients aged over 75 is, however, restricted due to the low representation of this age category in studies. The decision between castration only and the combination must be made based on the patient's history and condition and the expected toxicities.

At this stage, there is no indication for:
- anti-androgen monotherapy;
- bone-targeted antiresorptive therapies.

• *Monitoring (see above)*

PSA every 3 months, testosterone levels to check castration has been achieved (< 50 ng/dL).

Bone focus:
- calcium and vitamin D supplements;

- pre-treatment osteodensitometry if osteopenia risk factors;
- 4 mg IV zoledronic acid or 60 mg SC denosumab every 6 months if osteoporosis.

Metabolic (weight, waist circumference and blood sugar, cholesterol and triglyceride levels) and cardiovascular monitoring.

Recommendation for regular physical exercise, if possible.

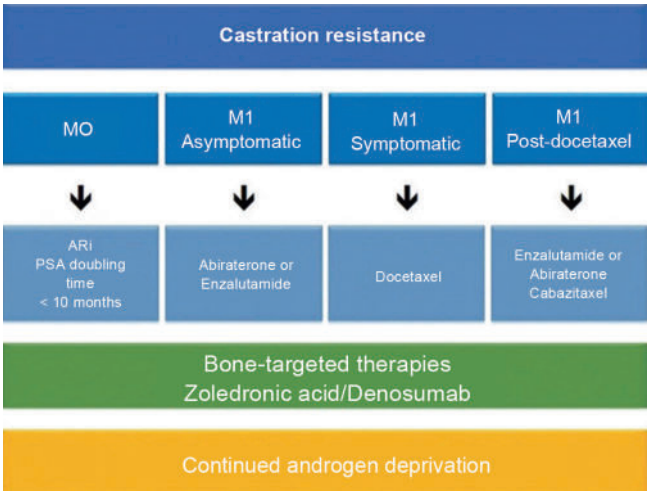
Monitoring of anxiety-depressive disorders caused by androgen deprivation.

Castration resistance

• *Treatments*

The definition of castration resistance is based on a castration testosterone level of < 50 ng/dl or 1.7 nmol/l, biochemical progression (three PSA rises resulting in two 50% rises above the nadir with PSA > 2 ng/ml) or radiographic progression (defined by the appearance of at least two new lesions on the bone scintigraphy or progression of a lesion which is measurable according to RECIST criteria).

The castration resistance phase can be divided into **4 stages** defined by the symptomatic nature of the disease and previously received treatment (Figure).



Abbreviations: M: metastasis; M0: no detectable metastasis: M1: metastasis; ARi: androgen receptor inhibitors (apalutamide or darolutamide or enzalutamide).

The pre-treatment biological assessment must include PSA and testosterone level testing, full blood count (FBC), renal function test (creatinine, FDG), electrolyte panel, liver function tests with alkaline phosphatase test and lactate dehydrogenase (LDH) and albumin tests.

The available treatments are used sequentially:

- Second-generation hormone therapies are used as first-line treatment if they have not already been administered. Generally speaking, doses of second-generation hormone treatments do not need to be adapted for older patients. Abiraterone acetate needs to be supplemented with cortisone, which can sometimes be a problem in older patients. Enzalutamide may cause asthenia, which needs to be monitored, requiring the dosage to be lowered. Apalutamide may cause skin rashes. Potential drug interactions must be anticipated and monitored.

- The standard dosage of docetaxel is 75 mg/m^2/3 weeks. In vulnerable patients, the alternative is 50 mg/m^2/2 weeks.

- The standard dosage of cabazitaxel is 20 mg/m^2/3 weeks. In vulnerable patients, the alternative is 16 mg/m^2/2 weeks.

- All chemotherapy regimens must include the use of G-CSF primary prophylaxis.

- Monthly doses of zoledronic acid must be adapted to renal function.

- Two new therapeutic classes will soon be usable during the castration resistance phase after at least one line of chemotherapy:

- PARP inhibitors for patients with a constitutional or somatic BRCA1 or BRCA2 gene mutation (around 10% of patients);

- Lutetium PSMA, metabolic radiotherapy.

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METASTATIC RENAL CANCER TREATMENT

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Treating metastatic renal cancer in older patients raises the twofold question of treatment efficacy and tolerance. The treatment of advanced renal cancer should not be different in older patients. However, certain considerations concerning the assessment of comorbidities and the renal failure and drug interaction risk, as well as extremely thorough monitoring and therapeutic education, must be taken into account as the treatment and poorly controlled toxicities may have serious consequences for these patients. After a geriatric assessment, decisions must be made at multidisciplinary meetings to ensure the consistency of the therapeutic choice.

Active surveillance, non-surgical ablative techniques (cryotherapy, radiofrequency) and partial laparoscopic or robotic surgeries are now well established for the treatment of localised forms.

In metastatic forms, although phase III registration trials for antiangiogenics, mTOR inhibitors and immune checkpoint inhibitors (ICIs), **and more recently for combinations of ICIs and antiangiogenics/ICIs**, had no age limit in their inclusion criteria, very few detailed results were specifically reported for patients aged over 75. A performance status (PS evaluated by the ECOG score, usually required to be < 2) was an inclusion

criterion in the studies, creating a real-world results reproducibility problem for patients with impaired performance status.

Overall, for these new treatments, no difference was reported in efficacy in older patients. No dosage modification is recommended as tolerance is usually acceptable. However, comorbidities, drug interactions in often polymedicated patients and the decrease in renal function with age can make it more complicated to introduce antiangiogenic or mTOR inhibitor treatment, immunotherapy or combination therapy.

There are prognostic scores for metastatic forms which determine the therapeutic indications. The first was the MSKCC (Memorial Sloan-Kettering Cancer Center) score. The IMDC (International mRCC Database Consortium) score or Heng score is now used.[1] With 0 factors, the patient is classed as having a good prognosis, with 1 or 2 factors, an intermediate prognosis and 3 factors or more, a poor prognosis (Table 1).

Table 1: *Metastatic renal cancer. IMDC prognostic score (Heng).*

Karnofsky index (*Performance status*)	Lower than 80%
Interval between diagnosis and systemic treatment	Under one year
Haemoglobin level	Lower than normal
Corrected serum calcium	Higher than normal
Platelet count	Higher than normal
Neutrophil count	Higher than normal

0 factors: good prognosis

- 1 or 2 factors: intermediate prognosis.

- 3 or more factors: poor prognosis.

In the era of VEGF-targeted therapies, the respective median survival times for these 3 groups were 43 months, 23 months and 8 months.

Sunitinib[2] and sorafenib[3] were registered in 2006, everolimus in 2009[4], pazopanib in 2010[5], axitinib in 2012[6] and cabozantinib in 2016[7].

As first-line treatment, in the COMPARZ[8] trial, pazopanib showed comparable efficacy with sunitinib with a median overall survival (OS) of 28.4 months vs 29.3 months (HR: 0.908 (95% CI: 0.762-1.082, $p = 0.275$). Sunitinib is responsible for more asthenia, hand-foot syndrome, altered taste and thrombocytopenia whereas pazopanib causes more diarrhoea, arterial hypertension, elevated transaminases and hair depigmentation. In the PISCES preference trial[9] in which patients acted as their own controls, sunitinib and pazopanib were delivered successively for two 3-month periods with patient and doctor blinded. Very strong patient-doctor concordance was observed for the choice of pazopanib.

To optimise sunitinib tolerance, alternative regimens of 2 out of 3 weeks instead of 4 out of 6 weeks were developed, increasing tolerance with similar efficacy.[10]

The efficacy of sunitinib and sorafenib was specifically analysed in older patients being treated for metastatic renal cancer.[11-15] Data from the main first-line trials with antiangiogenics according to age did not reveal any difference in efficacy. A large-scale study based on the IDMC international database[16] including 1381 patients, 144 (10%) of whom were aged over 75, showed that an age > 75 was not associated with a difference in overall survival (16.8 months vs 19.7 months, HR = 1.02; CI 95%: 0.78-1.28) or treatment time (HR = 1.01; CI 95%: 0.82-1.25) compared with young adults.

In the AXIS registration trial, second-line axitinib demonstrated superiority over sorafenib in terms of progression-free survival (PFS) with no difference in overall survival. Miyake reported reassuring efficacy and tolerance data in the older population.[17]

Cabozantinib is a new-generation tyrosine kinase inhibitor which inhibits several tyrosine kinase activity receptors (VEGFR-1, VEGFR-2, VEGFR-3, MET and AXL).

Table 2: *COMPARZ trial. Most common adverse events.*

Adverse events*%	Pazopanib (n = 554)		Sunitinib (n = 548)	
	All grades	Grade 3/4	All grades	Grade 3/4
Any event	> 99	59/15	> 99	57/17
Diarrhoea	63	9/0	57	7/< 1
Fatigue	55	10/< 1	63	17/< 1
High blood pressure	46	15/< 1	41	15/< 1
Nausea	45	2/0	46	2/0
Anorexia	37	1/0	37	3/0
Increased ALAT	31	10/2	18	2/< 1
Change in hair colour	30	0/0	10	< 1/0
Hand-foot syndrome	29	6/0	50	11/< 1
Loss of sense of taste	26	< 1/0	36	0/0
Thrombocytopenia	10	2/< 1	34	12/4

It demonstrated superiority over everolimus in the phase III METEOR trial both in terms of progression-free survival (7.4 months vs 3.9 months, HR: 0.51, CI 95%: 0.41-0.62, *p*: 0.0001) and overall survival (21.4 months vs 16.5 months, HR: 0.66, CI 95%: 0.53-0.83, *p*: 0.00026) establishing itself as a standard second-line treatment. It is particularly effective in patients with MET genomic alterations. The results of the CABOREAL early access programme in France provided reassuring real-world tolerance data in France.[18] Age does not impact the prognosis (median overall survival of 14.6 months in patients ≤ 75, and 13.3 months in patients over 75. Some recommend starting older patients on a lower dose and gradually increasing it if tolerated.

The use of everolimus has become minimal, including in older patients, since the arrival in recent years of ICIs, which have dramatically changed the way metastatic renal cancers are treated. The dose can be reduced from 10 mg to 5 mg per day if it is poorly tolerated.[19-21] ICIs targeting the PD1 axis have become first- and second-line standards of care when alone or combined with another ICI or VEGFR inhibitor.[22-24] The main side effects of these systemic immunotherapies are fatigue (when not related to hypothyroidism and adrenal insufficiency), skin problems (rashes, pruritus), digestive problems (diarrhoea), interstitial pneumonia, hepatitis, thyroid dysfunction and blood disorders.

In the CHECKMATE 025 trial,[25] second-line nivolumab demonstrated superiority over everolimus in terms of overall survival, the main evaluation criterion (HR = 0.73, CI 95%: 0.57-0.9). The NIVO-REN trial of 729 patients treated in France as part of the ATU programme confirmed the efficacy and good tolerance of nivolumab in a less selected, real-world population.[26] In terms of efficacy, the overall response rate was 18.5% and median PFS was 4.0 months (CI_{95}: 2.9-4.6). Median OS reached 18.6 months (CI_{95}: 16.0-18.6), and the OS rate was 81.7% (CI_{95}: 78.1-84.8) at 6 months and 66.3% (61.6-70.5) at 1 year.

As first-line metastatic treatment, 4 phase III trials demonstrated the superiority of ICI combination therapy over sunitinib in terms of overall survival:

- The CHECKMATE 214 trial (1096 patients) evaluated the nivolumab plus ipilimumab combination versus sunitinib in intermediate- or high-risk metastatic renal cancer (HR = 068, CI 95%: 0.49-0.95, $p = 0.0003$) with a particularly marked benefit in cases of PD-L1 expression (HR = 0.48, CI 95%: 0.28-0.82, $p = 0.0003$). Where age is concerned, the subgroup analysis did not show a significant benefit for patients aged over 65.[27]

- The KEYNOTE-426 trial (861 patients, median age of 62 years) compared pembrolizumab plus axitinib with sunitinib in all prognostic groups (HR = 0.53 (CI 95%: 0.38-0.74), $p< 0.0001$). The subgroup analysis showed a similar benefit for patients under 65 and patients aged 65 and over.[28]

- The JAVELIN RENAL 101 trial (886 patients, median age of 62 years) compared avelumab plus axitinib with

sunitinib. The subgroup analysis showed a similar benefit for patients aged under 65 and patients aged 65 and over.[29]

- The phase III CHECKMATE 9ER trial,[30] which included 651 patients, showed that as first-line treatment in advanced or metastatic forms, the combination of nivolumab + cabozantinib is superior to sunitinib. It doubles the median time until progression (16.6 vs 8.3 months, $p < 0.0001$), but also the OR rate (55.7% vs 27.1%) as well as improving OS ($p = 0.001$). In addition, tolerance is acceptable and the treatment discontinuation rate is low.

Older patients only represented a low proportion (29-40%) of these 4 main phase III trials, contrasting with SEER (Surveillance, Epidemiology and End Results Program) data in which the incidence of patients aged over 65 was 65%. This under-representation in trials is a major obstacle in oncology research in terms of issuing recommendations in this population of older patients, bearing in mind that immunosenescence is reported, which may reduce the impact of ICIs.

The efficacy of ICI inhibitors in older patients treated for metastatic renal cancer was evaluated based on international IDMC data.[31] This trial evaluated the efficacy of ICIs in 397 patients aged > 70 (28% of a total of 1,427 patients) treated for metastatic renal cancer between 2009 and 2019. The median age was 74 years (vs 60 years in the population aged under 70) with a higher incidence of liver metastases (23% vs 18%, $p = 0.047$) but lower incidence of brain metastases (3% vs 7%). In terms of treatment, fewer older patients received first-line ICI (32% vs 43%, $p < 0.001$). In a univariate analysis, the median overall survival was 25.1 months vs 30.8 months in younger patients ($p < 0.01$). The difference was mainly due to patients receiving first-line ICI treatment: 28.5 months *vs* 41.4 months ($p = 0.01$).

The median overall survival was not statistically different in second- or third-line treatment with medians of 23.8 months vs 25.9 months respectively ($p = 0.3$). In a multivariate analysis, older age was not associated with decreased survival (HR = 1.02, CI 95% = 0.80-1.30, $p = 0.08$).

Other studies confirmed the efficacy and acceptable tolerance of ICIs in older patients.[32-35]

Before the CARMENA trial,[36] cytoreductive nephrectomy (CN) was the standard treatment for renal cancers which were metastatic at diagnosis. CARMENA is a phase III (1:1) non-inferiority trial comparing initial medical treatment with sunitinib (50 mg/d 4/6 weeks) [arm B] with CN followed by sunitinib (arm A) in CRcc with intermediate or poor prognosis. In arm A, CN was performed within 28 days of randomisation. In arm B, sunitinib was commenced within 21 days of randomisation. The main evaluation criterion was OS and the secondary criteria were PFS, OR rate, clinical benefit and tolerance. The trial was stratified according to the MSKCC prognostic group. In total, 450 patients were included between September 2009 and September 2017. After median follow-up of 50.9 months, the results show the non-inferiority of the sunitinib alone arm (HR = 0.89; CI_{95}: 0.71-1.10, non-inferiority upper limit set to 1.2). The median OS was 18.4 months in the sunitinib alone arm versus 13.9 months in the CN followed by sunitinib arm.

Conclusion

The treatment of metastatic forms is identical to in younger patients. No dose adaptation is recommended for VEGFR and mTOR inhibitors although caution is required in patients who are frail or of a very advanced age.

However, for sunitinib, in practice, the dose is frequently reduced and 2 out of 3 weeks dosing regimens can be offered.[60]

The importance of therapeutic education and close monitoring must be stressed to older patients.

Numerous services have set up systematic regular telephone contact to tackle the issue of older patients failing to take action, particularly relating to digestive problems, mucositis and loss of thirst perception which can lead to severe dehydration and renal failure.

Drug metabolism must be taken into account. Sunitinib, pazopanib, axitinib, cabozantinib and mTOR inhibitors are metabolised by the liver. Sorafenib has been widely evaluated in the case of liver function test abnormalities relating to hepatocellular carcinoma and no dose reduction is recommended in the case of moderate abnormalities (Child-Pugh A-B). Sunitinib is metabolised by cytochrome P450-3A4. Renal elimination is

only 16%. Cabozantinib is also metabolised by cytochrome 3A4. Everolimus is metabolised in the liver by cytochrome P45-3A4, 5% in urine. Strong CYP3A4 inducers carry a risk of enhancing tyrosine kinase inhibitors by reducing their metabolism. Conversely, CYP3A4 inhibitors increase the metabolism of tyrosine kinases, reducing their efficacy.

Generally speaking, the tolerance and efficacy of ICIs seem comparable to those in younger patients but the data is limited and prospective data and dedicated studies are required. There are currently no specific recommendations concerning medical treatments for metastatic renal cancer in older patients apart from the need for geriatric assessment and a multidisciplinary team meeting to decide on treatment[37].

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BLADDER CANCER TREATMENT

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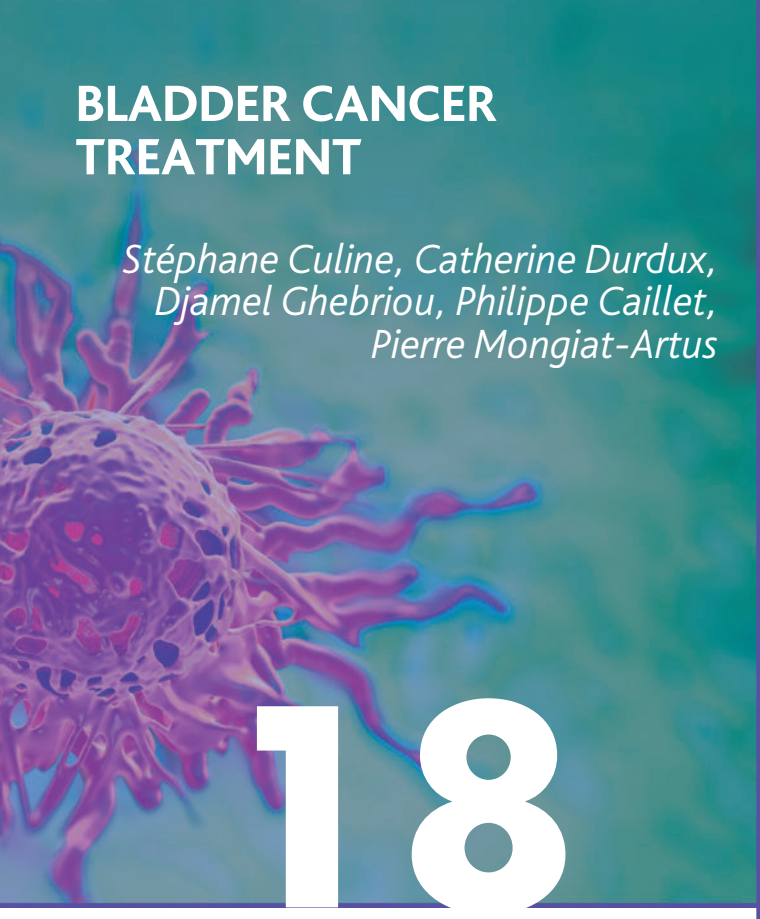

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This chapter includes AFU (French urology association) 2020 recommendations for the treatment of muscle-invasive bladder tumours (MIBC) not specific to older patients and the AFU 2019 report on uro-oncology in older patients.[1]

Localised MIBC (T2-T3 N0 M0)

The standard curative treatment for invasive cancers is based on radical cystectomy with ilio-obturator lymphadenectomy, achieving over 80% local control. However, 30% to 50% of patients are rejected for surgery mainly due to cardiovascular comorbidities, particularly in older patients. In practice, although surgery continues to be recommended by treatment guidelines, three-quarters of patients aged over 75 are treated with a conservative approach[2,3] or with exclusive supportive care after geriatric assessment.[4]

- *In fit patients (PS 0-1 and GFR > 60 mL/mn/1.73 m^2 according to MDRD or CKD-EPI and no geriatric frailty)*

Cystectomy with lymphadenectomy, which is the standard curative treatment, preceded by neoadjuvant

chemotherapy. Non-continent urinary diversion (Bricker) is preferred and a minimally invasive approach should be discussed. Post-operative morbidity and mortality (up to 15% at 3 months in patients in their eighties)[5,6] increase with age. Older patients seem to derive the same benefit from neoadjuvant chemotherapy as younger patients.[5,7,8] A peri-operative treatment optimisation protocol is recommended (*see Peri-operative geriatric procedure in Volume 1*).

The standard neoadjuvant chemotherapy is dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin). This protocol has higher haematological and digestive toxicity than gemcitabine plus cisplatin (GC) but achieves better local control and, in particular, improved progression-free survival.[9,10] There is no reason to exclude patients in their eighties considered fit after geriatric assessment from cisplatin-based neoadjuvant chemotherapy.[11] The number of cycles must be limited to 4. In case of poor tolerance, neoadjuvant chemotherapy must be suspended to avoid compromising local treatment. Current data does not enable carboplatin to be offered as a replacement for cisplatin in this situation. The use of post-operative chemotherapy (if not administered pre-operatively) is still debated. It will be offered for tumours with a high risk of recurrence according to anatomopathological data: pT3 or pT4, N+, positive surgical margins. This adjuvant chemotherapy must not be administered if renal function is impaired (clearance < 60 mL/min) or if the patient's general condition does not allow it (which will usually be the case in older patients in common practice).

- *In unfit patients*

If the patient is unfit for neoadjuvant gemcitabine and cisplatin chemotherapy, immediately perform a cystectomy with lymphadenectomy.

Nivolumab is now available in early access for patients who have undergone a cystectomy for a bladder cancer after complete excision, whose tumor cells express PD-L1 at the threshold ≥ 1%:

- having received neoadjuvant chemotherapy;
- or having not received neoadjuvant chemotherapy and not eligible/or having refused adjuvant cisplatin-based chemotherapy.

If the patient is unfit for cystectomy, perform conformal chemoradiotherapy, ideally with cisplatin, or 5-FU combined with mitomycin C if there is significant renal function impairment meaning platinum salts cannot be used.[12] Moderate hypofractionation (55 Gy in 20 fractions) is not inferior to standard fractionation so would seem particularly indicated in older patients.[13] Lymph node area treatment is not recommended in patients with a cN0 tumour.[14] Conformal intensity-modulated radiotherapy reducing acute toxicity is being increasingly used but is not recommended by the HAS (French National Authority for Health). This treatment could be preceded by neoadjuvant chemotherapy if the patient is eligible, without prohibitive toxicity in correctly selected patients aged over 70 with comparable survival results to in younger patients.[13]

If the patient is unfit for cystectomy and chemoradiotherapy with a localised bladder tumour: exclusive palliative radiotherapy in the case of pain or haematuria or iterative TURBT failure.

A reminder of the prognostic factors for failed concomitant chemoradiotherapy: T4 or multifocal tumour, macroscopically incomplete resection during TURBT, N+ status, ureterohydronephrosis or presence of an extensive carcinoma in situ.

Although a geriatric assessment must be offered when there is a G8 score of 14 or under, the writers consider that the invasive nature of the proposed treatments may justify a systematic geriatric assessment, particular in patients in their eighties.

MBIC with lymph node invasion (T2-T4 N + M0)

Patients with initial pelvic lymph node involvement in the staging assessment (cN+) have a much more reserved prognosis. Induction chemotherapy using the same methods as neoadjuvant chemotherapy (dose-dense MVAC or GC) is the first therapeutic step. For patients with a complete radiological response, a cystectomy or radiotherapy must be offered. Other patients have a similar prognosis to metastatic patients and must therefore be considered as such for treatment and follow-up (grade C).

Treatment of metastatic MIBC (T2-T4 M+)

• *First-line treatment*

- The strategy involves delivering platinum salt-based chemotherapy (gemcitabine and cisplatin in fit patients, gemcitabine and carboplatin in unfit patients) followed by maintenance avelumab immunotherapy in patients whose disease did not progress during chemotherapy. This maintenance treatment increases median survival by over 6 months (14.3 months vs 21.4 months).[15]

- If there is significant deterioration in general condition (PS > 2), palliative care is recommended.

• *Second-line treatment*

- In patients who have not received immunotherapy beforehand, pembrolizumab provides a clinical benefit in 25% of patients and a 3-month increase in median survival compared with standard chemotherapy (10.3 months vs 7.4 months).[16]

- In patients who have not received immunotherapy beforehand, the standard treatment is the antibody-drug conjugate enfortumab vedotin due to a 4-month increase in median survival compared with conventional chemotherapy (9 months vs 13 months).[17] There is an MA application in progress in France for this treatment, which must be used very cautiously in older patients due to noticeable side effects (digestive problems, peripheral neuropathy, skin rashes, blood sugar imbalance, etc.) and the lack of evaluation in older/frail patients. A weekly administration regimen of paclitaxel is used off label by numerous teams.

- If there is significant deterioration in general condition (PS > 2), palliative care is recommended.

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NON-SMALL CELL LUNG CANCER TREATMENT

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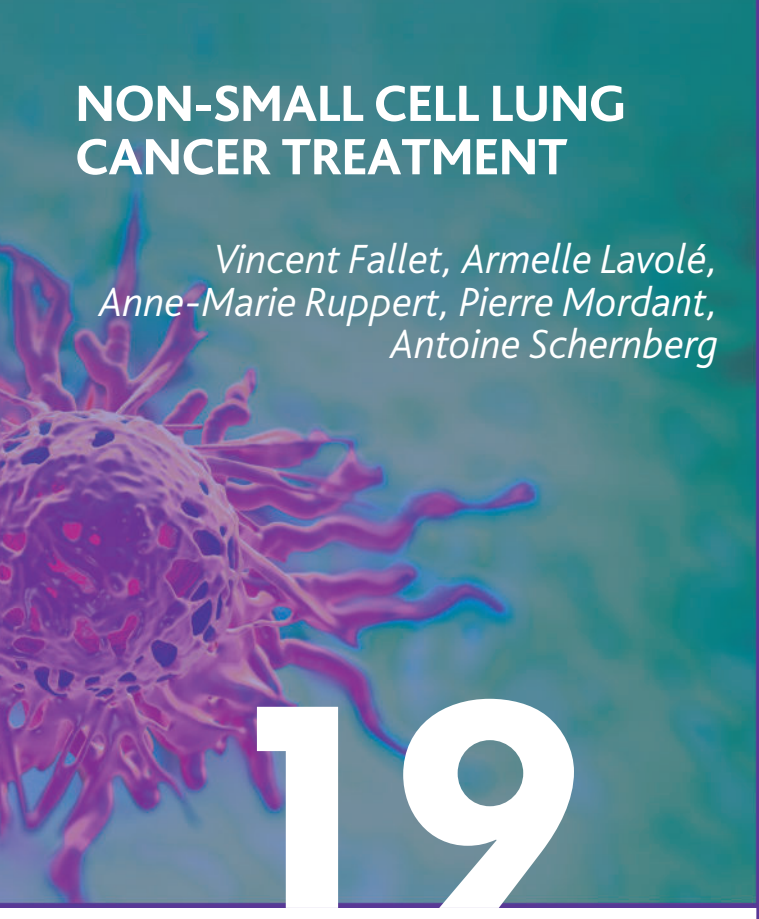

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Stage I

First-line treatment is surgery, subject to the geriatric assessment and respiratory and cardiac reserve. The standard procedure is lobectomy with lymphadenectomy. The approach can involve a thoracotomy or video-assisted thoracoscopy which seems to be associated with decreased morbidity in older patients. The addition of robotic assistance to video-assisted thoracoscopy appears to reduce the risk of conversion to thoracotomy. The use of infra-lobar resections (atypical resection, segmentectomy) must be discussed at an MDTM and reserved for peripheral tumours of less than 2 cm. A Japanese randomised trial found a benefit to segmentectomy over lobectomy in peripheral tumours of less than 2 cm, but the benefit in very long-term survival comes at the cost of higher early morbidity. Pneumonectomy must be used on an occasional basis in highly selected patients.

After the anatomopathological examination of the surgical specimen, the tumour usually remains stage I and adjuvant chemotherapy is not recommended. In the case of N1 upstaging (pathological stage II, 5-10% of cases) or N2 upstaging (pathological stage III, 5-10% of

cases), the benefit of adjuvant chemotherapy is discussed at an MDTM. For an EGFR-mutated stage II or III tumour, adjuvant therapy with osimertinib for 3 years is recommended, whether or not adjuvant chemotherapy is administered.

If the patient refuses or is not eligible for surgery, the treatment options are:
- stereotactic radiotherapy with fractionation adapted to the tumour location;
- radiofrequency thermal ablation subject to the tumour location and whether general anaesthesia can be used;
- other local endobronchial treatment methods (cryotherapy, brachytherapy) are uncommon.

The choice between these different methods is made according to the accessibility of techniques for each centre and the teams' usual practices. One of the questions frequently raised is administering the treatment in the (frequent) absence of histological evidence, which requires the formal approval of the MDTM.

Stage II

First-line treatment: surgery, the same as for stage 1. Adjuvant chemotherapy is recommended for younger patients but there is no consensus regarding its use in older patients. For an EGFR-mutated tumour, 3 years of adjuvant therapy with osimertinib is recommended, whether or not adjuvant chemotherapy is administered.

If the patient refuses or is not eligible for surgery:
- if N0: radiotherapy in stereotactic conditions or standard conformal radiotherapy;
- if N1: standard conformal radiotherapy.

Stage III

First-line treatment is a combination of sequential radio- and chemotherapy: chemotherapy then consolidation radiotherapy on the residual volume.

Cisplatin-based doublets are rarely used in older patients. Carboplatin is most commonly prescribed. It will usually be combined with taxol, etoposide or vinorelbine, or pemetrexed in the case of non-squamous cell tumours (but in the absence of an MA).

The optimal number of cycles to carry out before commencing radiation treatment is not defined. Common practice, if tolerance permits, is to carry out 4 cycles of chemotherapy.

Radiation is delivered in conventional fractionation (2 Gy per day, 5 days a week) up to a dose of 66 Gy, or in a moderately hypofractionated scheme (55 Gy in 20 sessions of 2.75 Gy).

Durvalumab immunotherapy as maintenance therapy for 12 months following chemoradiotherapy, and in the absence of morphological progression in an early CT assessment, provides a benefit in terms of survival and recurrence-free survival (PACIFIC trial), including in the subgroup of patients > 70 years.

Radiotherapy alone is delivered to patients who are not eligible for chemotherapy.

Studies are in progress to assess the benefit of maintenance immunotherapy after exclusive hypofractionated radiotherapy in frail older patients.

Stage IV: first-line

- ***Without oncogenic addiction***

Before the introduction of immunotherapy:

The IFCT0501 phase III trial involving 451 patients with an average age of 77, PS 0 to 2, showed that the weekly carboplatin-paclitaxel doublet (4 courses) increased overall survival compared with monochemotherapy with gemcitabine or vinorelbine (overall survival of 10.3 vs 6.2 months, regardless of the histological type, despite greater toxicity [febrile neutropenia 9.4% vs 2.7%]). It therefore became the standard in France in this population (AURA and ONCORIF guidelines). The carboplatin pemetrexed combination is an option for non-squamous cell tumours.

The IFCT1201 MODEL trial evaluated the benefit of switch maintenance with pemetrexed or gemcitabine. It involved 328 patients (with an average age of 76) with stable disease or response after 4 cycles of carboplatin and paclitaxel. Switch maintenance increases toxicity and does not improve overall survival so is not recommended in this population.

Finally, adding bevacizumab in subgroup studies showed increased toxicity in people aged over 70 with no benefit in overall survival. It will be prescribed on a case-by-case basis at an MDTM.

Since the introduction of immunotherapy:

PD-L1 > 49%

Recommendations for the general population are either pembrolizumab or a combination of chemotherapy and pembrolizumab (platinum and pemetrexed in non-squamous cell tumours, carboplatin and paclitaxel in squamous cell tumours). There are no studies dedicated to people aged over 75 but pooled analyses from KN-010, KN-024 and KN-042 trials showed that in 149 patients > 75 years, overall survival was superior in the pembrolizumab group compared with chemotherapy, and toxicity was no greater than in people aged under 75. Pembrolizumab monotherapy can therefore be used as first-line treatment.

PD-L1 < 50%

Recommendations for the general population are also either pembrolizumab or a combination of chemotherapy and pembrolizumab (platinum and pemetrexed in non-squamous cell tumours, carboplatin and paclitaxel in squamous cell tumours). There is not enough data in the older population so the decision will be made on a case-by-case basis at an MDTM. It is recommended that patients be included in therapeutic trials. The IFCT1805 ELDERLY trial is in progress, comparing carboplatin paclitaxel with carboplatin paclitaxel + atezolizumab.

- *With oncogenic addiction*

Be aware of the specific case of tumours with molecular alterations which can be treated orally. The particularity of these oral treatments is their high efficacy and good tolerance, even in older patients. Therefore, osimertinib 80 mg/d is delivered as first-line treatment for cancers with activating EGFR mutations, regardless of the PD-L1 status. In the case of ALK translocation, first-line treatment is alectinib (600 mg x 2/d) or brigatinib (180 mg/d). Crizotinib (250 mg x 2/d) is proposed in the case of ROS1 rearrangement. In the case of progression with targeted therapies, the recommendation is to

determine the resistance mechanism by detecting resistance mutations via circulating tumour DNA and/or repeat biopsy. Metastatic patients must be seen every 3 months. It is important to combine cancer monitoring with geriatric assessment to provide the most appropriate comprehensive care.

In some cases, supportive treatment alone may be offered to the patient due to their general condition or impaired cognitive function.

Monitoring

For patients having undergone surgery, the common approach is six-monthly assessments for two years, followed by annual monitoring.

In patients having received radiation treatment, monitoring is on a four-monthly basis for two years then according to clinical progression.

Metastatic patients must be seen every 3 months. It is important to combine cancer monitoring with ongoing geriatric assessment to provide the most appropriate comprehensive care.

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SMALL CELL LUNG CANCER TREATMENT

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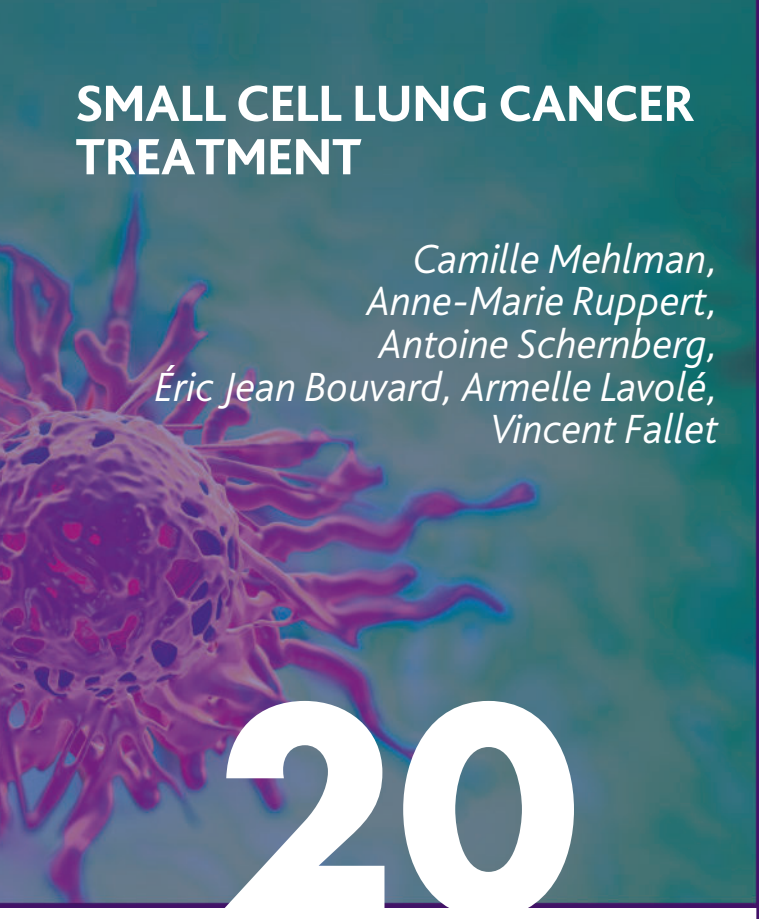

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In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature.

Small cell lung cancer is usually highly chemo- and radiosensitive.

Stage I to III – Chemoradiotherapy

The treatment consists of concomitant chemoradiotherapy in patients in good general condition.[1,2] Chemotherapy combines AUC5 carboplatin (Calvert formula) D1 and etoposide 100 mg/m^2 D1 to D3 every 21 days. The doses can be reduced by 20% in combination with radiotherapy.

Radiotherapy delivers a dose of 60 to 66 Gy in conventional fractionation of 2 Gy per session, and must commence in the 6th week of treatment at the latest (in the second cycle of chemotherapy).[3]

In the frailest patients (PS = 2), the administration regimen can be sequential. Compared with a concomitant regimen, the sequential regimen reduces haematological complications without changing the frequency of

severe esophagitis, and with reduced efficacy on overall survival.[4]

In the case of complete response, prophylactic cranial irradiation (PCI) (25 Gy in 10 fractions) is discussed for patients aged under 75, PS 0 to 2.[5]

Surgery is uncommon for stage I-II tumours and must be accompanied by chemotherapy (platinum-etoposide) and possibly thoracic radiotherapy.

Stage IV

• First-line

Care involves chemotherapy combined with immunotherapy in PS 0 or 1 patients. The relevance of immunotherapy is not demonstrated for PS > 1 patients. Treatment therefore combines platinum salt (AUC5 carboplatin or cisplatin) D1, etoposide (100 mg/m^2) D1 D2 D3, and immunotherapy (atezolizumab (1,200 mg) or durvalumab (1,500 mg)) D1. After 4 cycles, maintenance immunotherapy is continued according to the tolerance and control of the disease.[6,7] Toxicity remains acceptable in older patients provided haematopoietic growth factors are used during chemotherapy treatment. Thrombocytopenia appears to be a limiting factor. Supportive care plays a key role throughout the process.

Additional thoracic irradiation, commenced within 6 weeks following chemotherapy, must be discussed at an MDTM on a case-by-case basis for PS 0-1 patients in case of partial thoracic response after chemotherapy, and if there are fewer than 3 metastatic sites at diagnosis. It will deliver a dose of 30 Gy in 10 x 3 Gy fractions. This radiation is generally well tolerated, and is associated with a benefit in terms of overall survival and progression-free survival.[8]

• Second-line treatment

Patients are classed according to the time between the end of treatment and tumour recurrence (nearly always systematic):

- "refractory" in the case of progression during treatment;
- "resistant" in the case of relapse before 3 months;
- "sensitive" between 3 and 6 months;

- or "highly sensitive" if the relapse occurs over 6 months after stopping first-line chemotherapy.

In "highly sensitive" and "sensitive" patients, the combination of carboplatin and etoposide can be offered again.

In resistant patients, new chemotherapy can be offered (topotecan 1.5 mg/m^2 D1 to D5 every 21 days or lurbinectedin available in early access in France at the time of writing this chapter). Topotecan treatment is responsible for grade 3-4 haematological toxicity in over 60% of cases, justifying the administration of a haematopoietic growth factor. Weekly topotecan administration (3 to 4 mg/m^2 D1 D8 D15 and D28) can be an alternative in the frailest patients.

In the case of relapse, brain radiotherapy *(encephalon in toto)* (30 Gy in 10 fractions of 3 Gy) is systematically considered.

Stereotactic radiotherapy is an option in the case of brain oligometastatic relapse (≤ asymptomatic 4 brain lesions < 3 cm) in a patient without extracerebral spread during systemic treatment.

Monitoring

Relapses are frequent and early. Secondary cancers are frequent, mainly occurring after 3 years. Continued smoking is associated with the risk of relapse and secondary cancer. Smoking cessation support must be offered to the patient. A thoracic-abdominal-pelvic-skull scan every 3 months is recommended.

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SKIN CANCER TREATMENT

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Basal cell carcinoma

In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature.

Basal cell carcinomas are classified according to their size, location and extension based on AJCC staging used for cutaneous squamous cell carcinomas, classifying basal cell carcinomas with good, intermediate or poor prognosis, which guides their treatment.

Operable basal cell carcinoma

First-line treatment: **resection surgery,** 3 mm to 5-10 mm margin according to the tumour characteristics, usually under local anaesthetic.

If patient is not eligible:

- Radiotherapy can be offered;

- The following can be offered for superficial basal cell carcinoma:

- topical treatment with imiquimod for small tumours. It must be applied 5 times a week for 6 weeks and left in contact with the skin for around eight hours;

- photodynamic therapy: a topical photosensitising agent such as 5-aminolevulinic acid is applied to the tumour, followed by exposure to a particular type of light. The photosensitising agent reacts with oxygen, destroying the tumour cells. This treatment is painful and it may be necessary to repeat the sessions. It is indicated for non-recurrent superficial basal cell carcinoma on the trunk, limbs and neck. Lesions must be confirmed by biopsy beforehand. The treated lesions must be assessed 3 months after the first session and, if required, two additional sessions may be carried out one week apart.

Given the relatively slow and local progression of this type of tumour, the patient's comorbidities and life expectancy must be taken into account when deciding whether surgery is appropriate. The geriatric assessment can also help to decide whether surgery should be performed under local or general anaesthetic in patients with cognitive impairment.

Locally advanced, inoperable or metastatic basal cell carcinoma

• *First-line treatment: sonic hedgehog pathway inhibitors*

There are two molecule options:

- vismodegib can be administered in patients with symptomatic or locally advanced metastatic basal cell carcinoma for whom surgical treatment or radiotherapy does not seem possible. The dose is 150 mg per day. In the pivotal phase II ERIVANCE trial, the response rate was 60% for locally advanced basal cell carcinomas and 48% for those in the metastatic stage. The median response duration is 20 months. Treatment was, however, interrupted in 80% of patients due to toxicity (dysgeusia, alopecia, cramps, asthenia, weight loss). There is no specific dose adaptation required for older patients;
- sonidegib is also approved. A phase II trial evaluated sonidegib in 194 patients with locally advanced disease and 39 patients with a metastatic tumour at 2 different doses (200 mg/d and 800 mg/d). The response rate, at a dose of 200 mg, was 47% in patients with a locally advanced tumour versus 15.4% in patients with a metastatic tumour. The MA for sonidegib at a dose of 200 mg/d was only granted to patients

with a locally advanced basal cell carcinoma. The most frequently reported grade 3-4 adverse events relating to sonidegib 200 mg were: increased serum CPK, increased lipase (6.3% each), asthenia (3.8%), weight loss, cramps, hypertension and hypotension (2.5% each).

If patient is not eligible: the main alternatives to targeted therapy are radiotherapy, anti-PD-1s which are approved in the USA (since February 2021) and Europe (since May 2021) as second-line treatment.[1] However, cemiplimab is not yet covered by the French health insurance system for this indication. Cisplatin chemotherapy can also be offered as salvage treatment.

Monitoring

Annual skin monitoring for life. For patients having received radiation treatment, annual monitoring by a radiation oncologist is required for 5 years following treatment.

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Squamous cell carcinomas

In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature.

Table 1: *AJCC 2010 staging of cutaneous squamous cell carcinomas and risk factors identified by this staging (AJCC Cancer staging manual, 2010).*

TX	Primary tumour cannot be evaluated
T0	No primary tumour
Tis	Carcinoma in situ
T1	Tumour ≥ 2 cm and fewer than 2 risk factors
T2	Tumour > 2 cm or tumour of any size with at least 2 high risk factors
T3	Tumour with invasion of the maxilla, mandible, temporal bone or eye socket
T4	Tumour with bone invasion (axial skeleton or limbs) or perineural invasion of the skull base
Nx	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Single metastasis in ipsilateral lymph node area, diameter ≤ 3 cm
N2	Single lymph node metastasis in ipsilateral lymph node area, diameter > 3 cm or ≤ 6 cm; or multiple ipsilateral lymph node metastases, largest dimension ≤ 6 cm; or multiple bilateral or contralateral lymph node metastases, largest diameter ≤ 6 cm
N2a	Single lymph node metastasis in ipsilateral lymph node area, diameter > 3 cm or largest dimension ≤ 6 cm
N2b	Multiple ipsilateral lymph node metastases, diameter ≤ 6 cm
N2c	Multiple bilateral or contralateral lymph node metastases, diameter ≤ 6 cm
N3	Lymph node metastasis, diameter > 6 cm
Mx	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis or metastases

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Tx	N3	M0
	T4	Tx	M0
	Tx	Tx	M1

Primary tumour (Stage I-III) (TxN0M0)

- *First-line treatment:*

Operable tumour:

Resection surgery, with 5 mm margins for stage T1 and 6-10 mm for stage T2 or T3.

The sentinel lymph node procedure can be offered as an option. If the sentinel lymph node is involved, regional lymphadenectomy is offered.

Adjuvant radiotherapy must be discussed in the case of histological signs of severity (particularly in the case of neurotropism) or a recurrent tumour. A study evaluating neoadjuvant cemiplimab 350 mg IV, 2 cycles (6-week treatment duration), in 20 patients with operable stage III or IV CSCC with a performance status of 0 or 1 showed that the major histological response rate (less than 10% residual tumour) was 75%. So far, none of the patients with histological response has relapsed.

Adjuvant trials are also in progress.

If resection is incomplete, revision surgery can be offered.

If this is not possible, adjuvant radiotherapy is offered.

- *Inoperable tumour*

Medical treatment such as first-line immunotherapy, second-line anti-EGFR or neoadjuvant chemotherapy with the aim of reducing the tumour mass is discussed before considering a surgical procedure followed by radiotherapy or, as second-line treatment, radiotherapy alone.

Immunotherapy treatment (cemiplimab IV 350 mg every 3 weeks for 30 min) for patients with an ECOG score of 0 or 1 is only currently available in France as second-line treatment, or as first-line treatment in patients who cannot be treated with platinum salts.[2] The decision is discussed at an MDTM as well as with the patient, taking comorbidities into account.

Another alternative to be discussed for an inoperable tumour located on a limb is limb perfusion chemotherapy (as second-line treatment).

Regional lymph node involvement (Stage III)

- *First-line treatment: surgery and adjuvant radiotherapy*

In the case of palpable lymph node involvement, adenomectomy with histological verification and lymphadenectomy will be offered, if possible during the same operation. Adjuvant radiotherapy to the regional lymph node area is then offered. Trials evaluating anti-PD-1s as adjuvant or neoadjuvant therapy[1] could impact treatment of stage III with lymph node involvement.

- *If patient is inoperable*

First-line alternatives are a first line of immunotherapy followed by a second line with anti-EGFR drugs if necessary, or neoadjuvant chemotherapy followed by a combination of surgery and radiotherapy, or radiotherapy alone. The decision is discussed at an MDTM as well as with the patient, taking comorbidities into account. Immunotherapy treatment (cemiplimab IV 350 mg/3 weeks) for patients with an ECOG score of 0 or 1 is only currently available in France as second-line

treatment, or as first-line treatment in patients who cannot be treated with platinum salts.

Distant metastases (Stage IV)

- *First-line treatment*

If single metastasis: resection surgery; if multiple or inoperable metastases: medical treatment.

- *Immunotherapy (first-line)*

Immunotherapy treatment (cemiplimab) for patients with an ECOG score of 0 or 1 is approved in Europe and, according to European and American recommendations, should be administered as first-line treatment. However, immunotherapy treatment (cemiplimab) is only currently available in France as second-line treatment, or as first-line treatment in patients who cannot be treated with platinum salts.

- *Conventional chemotherapy (second-line)*

The usual regimen combines the administration of cisplatin and 5-fluorouracil but, in older patients, cisplatin is often replaced by carboplatin, which is better tolerated and does not require hyperhydration. Like for ENT squamous cell carcinomas, the other alternatives are mainly the administration of taxanes or methotrexate.

- *Targeted therapy (second-line)*

A phase II trial suggested the benefit of cetuximab monotherapy in older patients with inoperable squamous cell carcinomas, with a response rate of 28% and acceptable tolerance.[3] But no phase III trial has been carried out. Cetuximab can be prescribed in combination with chemotherapy or radiotherapy and the benefit of combining it with anti-PD-1s was shown by P. Bossi at ASCO 2022 in the I-TACKLE trial combining cetuximab with an anti-PD-1 after anti-PD-1 failure with a response rate of 38%.

In practice, in older patients, immunotherapy must be prescribed as first-line treatment according to current recommendations and due to platinum salts being frequently contraindicated.

Monitoring

- *Stage T1 tumour*

Six-monthly skin monitoring is offered.

- *T2 and T3 tumours*

Quarterly skin monitoring for 2 years is offered. Imaging monitoring is often also offered for tumours with a high risk of recurrence.

In the long term, annual skin monitoring must be continued for life.

For patients having received radiation treatment, annual monitoring by a radiation oncologist is required for 5 years following treatment.

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Cutaneous melanoma

In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature.

Stage I primary melanoma

• First-line treatment

Melanoma resection surgery with margins adapted to the melanoma thickness (Table 2) (SOR 2005 recommendations).

In general, limited melanoma resection is carried out first, then revision surgery is offered according to the Breslow index. In the specific case of Dubreuilh melanoma in situ, margins of 10 mm if possible and 5 mm if not are proposed according to French 2005 recommendations.[1]

• Indications for sentinel lymph node procedure

Sentinel lymph node biopsy is recommended in France[1] in patients with primary melanoma with a Breslow index > 1 mm) and a negative regional and distant imaging and clinical assessment. It is optional in patients with a stage T1b melanoma (Breslow 0.8 to 1 mm melanomas and ulcerated melanomas of less than 0.8 mm). This recommendation is independent of age but must take the patient's comorbidities and life expectancy into account. It is only beneficial if the patient has understood and accepted the principle of adjuvant therapy in the case of positive sentinel lymph node (see adjuvant therapy chapter). This procedure is generally well tolerated but it requires general anaesthesia and can be complicated by lymphoedema, which is usually moderate.

Indications for the sentinel lymph node procedure will change as a European authorisation like in the USA for stage IIB and IIC adjuvant therapy with pembrolizumab is expected in the next few months. This means that some of the patients who were previously eligible for the sentinel lymph node procedure could directly benefit from adjuvant therapy.

Table 1: *AJCC 2017 staging according to Gershenwald et al.*

STAGE T	Breslow	With or without ulceration
TX: the thickness of the primary melanoma cannot be evaluated (e.g. diagnosis by curettage)	Not applicable	Not applicable
T0: no primary tumour (e.g. unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma in situ)	Not applicable	Not applicable
T1	≤ 1.0 mm	Unknown or not specified
T1a	< 0.8 mm	Without ulceration
T1b	< 0.8 mm	With ulceration
	0.8-1.0 mm	With or without ulceration
T2	> 1.0-2.0 mm	Unknown or not specified
T2a	> 1.0-2.0 mm	Without ulceration
T2b	> 1.0-2.0 mm	With ulceration
T3	> 2.0-4.0 mm	Unknown or not specified
T3a	> 2.0-4.0 mm	Without ulceration
T3b	> 2.0-4.0 mm	With ulceration
T4	> 4.0 mm	Unknown or not specified
T4a	> 4.0 mm	Without ulceration
T4b	> 4.0 mm	With ulceration

Table 2: *Primary melanoma resection margins according to the Breslow index*

Breslow index	Safety margin
0	0.5 cm (but 1 cm for Dubreuilh melanoma)
0.1 to 1 mm	1 cm
1.1 to 2 mm	1-2 cm
> 2 mm	2 cm

- *If patient is not eligible*

After being approved and recorded by an MDTM after examining the patient, attentive monitoring will commence, guided by the patient's general condition and comorbidities.

Lymph node involvement and/or presence of in-transit metastases (stage III)

Table 3: *AJCC stage III staging.*

Staging	No. of lymph nodes	Status
N1	0-1 lymph node	a: 1 clinically occult lymph node[1], no in-transit/satellite metastases b: 1 clinically detected lymph node, no in-transit/satellite metastases c: 0 lymph nodes, with in-transit/satellite metastasis

N2	1-3 lymph nodes	a: 2-3 clinically occult lymph nodes, no in-transit/satellite metastases b: 2-3 lymph nodes, at least one of which was clinically detected, no in-transit/satellite metastases c: 1 clinically detected or occult lymph node, in-transit/satellite metastasis
N3	> 2 lymph nodes	a: ≥ 4 clinically occult lymph nodes, no in-transit/satellite metastases b: ≥ 4 lymph nodes, at least 1 clinically detected lymph node/lymph node cluster, no in-transit/satellite metastases c: ≥ 2 clinically detected or occult lymph nodes or lymph node cluster, in-transit/satellite metastasis

Source: EZ Keung, JE Gershenwald, Expert Rev Anticancer Ther 2018; 18: 775-84.

Lymph nodes are clinically detected if they are identified in the clinical examination or imaging and histologically confirmed after analysis.

- *Microscopic lymph node involvement*

First-line treatment: immunotherapy or adjuvant targeted therapy.

Several studies published in the *New England* show a benefit in terms of relapse-free survival in patients undergoing adjuvant therapy either by targeted dual therapy or anti-PD-1. We do not yet have enough data

suggesting a survival benefit in these studies apart from a study comparing high-dose ipilimumab with a placebo. All adjuvant therapies administered for a year are currently covered by the French health insurance system including nivolumab and pembrolizumab regardless of the BRAF status, and the dabrafenib-trametinib combination in the case of BRAF mutation (see adjuvant therapy chapter).

The benefit of additional regional lymphadenectomy in the case of microscopic lymph node involvement was dismissed.

- *Macroscopic lymph node involvement*

First-line treatment: regional lymphadenectomy then immunotherapy or adjuvant targeted therapy.

In the case of palpable lymph node involvement, regional lymphadenectomy will be carried out after adenomectomy and histological verification of lymph node metastasis diagnosis, if possible in the same operation with the aid of frozen section examination. This treatment will be followed by adjuvant immunotherapy or targeted therapy according to the BRAF status. The benefit of adjuvant radiotherapy combined with adjuvant medical therapy has not currently been established.

If patient is inoperable: medical treatment with targeted therapy or immunotherapy, or a combination as part of a therapeutic trial, will be considered. Adjuvant radiotherapy of involved lymph node regions (N+) will be discussed if medical treatment fails.

In-transit metastases

If there are few metastases, resection surgery with 1 cm margins must be offered, followed by adjuvant targeted therapy or immunotherapy (see adjuvant therapy paragraph).

If there are multiple inoperable lesions, immunotherapy or targeted therapy must be used.

Limb perfusion chemotherapy in the case of localised metastases on a limb provides a progression-free survival benefit but no survival benefit. This type of treatment must only be offered as salvage treatment after

immunotherapy and targeted therapy have failed, and after ruling out distant lesions.

Distant metastases (stage IV)

Table 4: *AJCC stage IV staging.*

Staging	Site	Serum LDH
M1a-d	Distant cutaneous/subcutaneous/lymph node (a), pulmonary (b), other visceral (c), cerebral (d) involvement	Not evaluated
M1a-d(0)	Distant cutaneous/subcutaneous/lymph node (a), pulmonary (b), other visceral (c), cerebral (d) involvement	Normal
M1a-d(1)	Distant cutaneous/subcutaneous/lymph node (a), pulmonary (b), other visceral (c), cerebral (d) involvement	Elevated

Table 5: *AJCC staging.*

Stage	T	N	M
0	Tis	N0	M0
IA	T1a T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b T3a	N0	M0
IIB	T3b T4a	N0	M0
IIC	T4b	N0	M0

IIIA	T1a-b-2a T1-2a	N1a N2a	M0
IIIB	T0 T1 a-b-2a T1 a-b-2a T2b-3a	N1b-c N1b-c N2b N1a-2b	M0
IIIC	T0 T0 T1a-3a T 3b-4a T4b	N2b-c N3b-c N2c-3a-c All N ≥ N1 N1a-2c	M0
IIID	T4b	N3a-c	M0
IV	All T	All N	M1

Source: EZ Keung, JE Gershenwald, Expert Rev Anticancer Ther 2018; 18: 775-84.

- *First-line treatment*

Surgical treatment must be considered in the case of single metastasis. Medical treatment will be offered for multiple or inoperable metastases.

Immunotherapy is now the first-line treatment.

Immunotherapy uses anti-PD-1 and anti-CTLA-4 monoclonal antibodies.

Anti-PD-1s (nivolumab 240 mg every 2 weeks for 30 minutes or 480 mg every 4 weeks for 60 minutes and pembrolizumab 200 mg every 3 weeks, or 400 mg every 6 weeks, for 30 minutes) are associated with response rates ranging from 35% to 45% with longer response durations.

Anti-CTLA-4 ipilimumab has lower efficacy with a response rate of around 15% and causes more toxicity, with mainly diarrhoea and hepatitis observed in over half of patients treated with ipilimumab,[2,3] but has a different action mechanism. A total of 4 doses of 3 mg/kg are administered by intravenous infusion over a 90-minute period every 3 weeks.

For the combination of nivolumab 1 mg/kg and ipilimumab 3 mg/kg, 4 injections then continued with nivolumab which has an MA in Europe. The response rate reached 57% in first-line treatment but with severe toxicities in 55% of subjects.

The DREAMseq study is comparing the following sequences in a randomised trial in patients with advanced inoperable or BRAF-mutated metastatic melanoma: ipilimumab plus nivolumab then continued with nivolumab then dabrafenib plus trametinib, versus dabrafenib plus trametinib with change to ipilimumab plus nivolumab in the case of progression. Preliminary results show that sequential treatment starting with ipilimumab plus nivolumab is associated with significantly better overall survival from the 10th month than treatment starting with targeted therapy.

2-year survival is 72% vs 52% (log-rank p = 0.0095).

According to the results of 2 studies (Checkmate 511 and Keynote 029), a modified regimen of low-dose ipilimumab at 1 mg/kg and anti-PD-1 at the standard dose has the same efficacy and better tolerance.[4]

This is the regimen to use in patients who would benefit from dual immunotherapy but who are a bit less fit in geriatric terms than those who are eligible for the standard regimen. For very frail patients and/or those in which it is difficult to monitor tolerance, mono-immunotherapy is a better option.

In the case of cerebral metastasis, mucosal melanoma or rapid progression, an ipilimumab + anti-PD-1 regimen must be used and discussed.

If there is a threatening lesion or if immunotherapy is contraindicated in patients with a BRAF-mutated lesion, targeted therapy may be offered as first-line treatment.

Targeted therapy

This is reserved for second-line treatment, threatening situations and rare contraindications to immunotherapy in patients with BRAF-mutated melanoma.

Three combinations of a BRAF inhibitor and a MEK inhibitor have an MA in France in the case of V600E or K somatic mutation:

i) vemurafenib (960 mg x 2/day) and cobimetinib (60 mg/day for 3 weeks on and 1 week off);
ii) dabrafenib (150 mg x 2/day) and trametinib (2 mg/day);
iii) encorafenib (450 mg/day) per day and binimetinib (45 mg x 2/day).

These are orally administered products with an MA for first- and second-line treatment. The response rate is around 70% with mainly partial responses which are maintained for over a year on average, but secondary escape is frequent. For BRAF inhibitors, the often moderate toxicities can be cutaneous (rash, hyperkeratosis, papilloma, squamous cell carcinoma) but can include arthralgia, asthenia or fever.[5] MEK inhibitors can cause weight gain, oedema or folliculitis as well as cardiac (hypertension) and ocular toxicities and cramps. Liver function test abnormalities[6] can also occur and rare cases of severe pneumonia can threaten the vital prognosis. Each of these treatments has a variable toxicity profile. If toxicity occurs, another combination can be tried. The first combination is responsible for a very high level of photosensitivity and is currently the least prescribed treatment in France. The main side effect of the dabrafenib plus trametinib combination is fever which usually occurs during the first weeks of treatment. This fever is usually manageable and requires the treatment to be temporarily stopped for a period lasting 24 hours after it is resolved with antipyretics. The encorafenib-binimetinib combination involves more tablets being taken but can be administered at mealtimes. Fever is less frequent.

Chemotherapy

The response rate to dacarbazine, fotemustine or cisplatin is around 10-20%. Responses are usually maintained for 3 to 6 months with some cases of long response. Dacarbazine is the best tolerated chemotherapy and it is currently extremely rare to use other lines of chemotherapy. Chemotherapy is a second-line or more treatment according to the BRAF status.[7] Orally administered temozolomide is not superior to dacarbazine in terms of survival but is administered orally and crosses the brain barrier. Polychemotherapy is not superior to monochemotherapy.

Radiotherapy

Melanoma has a low level of radiosensitivity. Local radiotherapy can be offered in the case of Dubreuilh melanoma in situ after incomplete resection where revision surgery is not possible,[8] in the case of R1 resection of metastases and after resection of high-volume tumours (III, B) if systemic treatment is not possible. A randomised prospective study showed that post-operative lymph node radiotherapy after N+ lymphadenectomy reduced the risk of relapse by around 50%.[9] Radiosurgery combined with immunotherapy seems to improve control of intracerebral disease. Prospective trials are required. Whole brain radiotherapy should be avoided as it does not provide a survival benefit and causes irreversible cognitive impairment.

Palliative radiotherapy is indicated particularly for painful bone, lymph node and soft tissue secondary locations as well as for neurological/epidural compression.

Adjuvant therapy

Three adjuvant therapies are currently covered by the French health insurance system for patients in stage III or **stage IV with completely resected disease.**

- **Nivolumab** 240 mg/2 weeks for 30 min or 480 mg/4 weeks for 60 min.

A phase III trial (Checkmate 238) compared the efficacy of nivolumab at a dose of 3 mg/kg/2 weeks with that of high-dose ipilimumab[10] (10 mg/kg) in patients in stage IIIB, IIIC or IV. The main objective was recurrence-free survival in the population on an intention-to-treat basis. The recurrence-free survival rate at one year was 70.5% vs 60.8% in the nivolumab and ipilimumab arm respectively ($p < 0.001$) and the benefit was observed regardless of the BRAF status. Compared with ipilimumab, there was three times less severe toxicity with nivolumab (10% vs 42%) and treatment discontinuation (9.7% vs 42.6%).

- **Pembrolizumab** (200 mg every 3 weeks).

The Keynote 054 trial compared pembrolizumab with a placebo in patients in stage IIIA to IIIC.[11] In stage IIIA, the lymph node location must be over 1 mm. In-transit metastases are excluded. The main objective was

recurrence-free survival. After one year of monitoring, the risk of relapse was 43% lower in the pembrolizumab arm compared with the placebo arm (HR = 0.57; CI 98.4%, 0.43-0.74; $p < 0.0001$), regardless of the BRAF status. The toxicity profile of pembrolizumab was consistent with the product's tolerance data. The frequency of severe toxicities was 7% with pembrolizumab. One myositis-related death occurred.

The combination of dabrafenib 150 mg twice a day and trametinib 2 mg/day can now be prescribed as an adjuvant in the case of BRAF mutation.

The COMBI-AD double-blind controlled trial studying the administration of dabrafenib 150 mg twice a day and trametinib 2 mg/day versus a placebo in patients with stage IIIA, IIB or IIIC BRAF-mutated melanoma with the primary objective of relapse-free survival and secondary objective of overall survival, showed a benefit in terms of relapse-free survival at 3 years of 58% vs 39% (HR 0.47 [CI 95%, 0.39-0.58]; $p < 0.001$),[12] observed regardless of the stage of the disease. 3-year survival was better in the combination group (86% vs 77%) but the difference was not significant (data is possibly not mature enough).

Available monitoring data for these 3 trials shows maintained benefit over the long term. **Finally, the Keynote 716 trial evaluating pembrolizumab 200 mg/3 weeks vs placebo as adjuvant treatment of stage IIB or IIC** showed a reduced risk of relapse in patients taking pembrolizumab compared with those receiving the placebo with an HR of 0.65 ($p = 0.00658$).[13] There were also fewer distant recurrences in the pembrolizumab arm than in the placebo arm. The frequency of adverse events (AE) relating to the treatment was 96% (pembrolizumab arm) vs 92% (placebo arm). The frequency of severe AEs was 17% (pembrolizumab arm) vs 5% (placebo arm).

This study led to pembrolizumab being approved in Europe in May 2022. It is expected to be covered by the French health insurance system in the coming months.

Monitoring

The monitoring frequency depends on the stage of the melanoma. According to 2016 recommendations, monitoring methods are as follows:

Stages IA and IB: six-monthly clinical skin monitoring for 3 years then annual clinical monitoring.

- **Stage IIA-IIB:** clinical examination 2 to 4 times/year for 3 years then once a year for life; lymph node ultrasound 2 to 4 times/year for 3 years.

- **Stages IIC and IIIA:** quarterly skin monitoring for 3 years then annual. Lymph node ultrasound 2 to 4 times/year for 3 years.

Photoprotection measures and self-examination must be proposed at all stages. In older patients with multiple conditions, geriatric monitoring is closer and must be defined for each specific case.

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Merkel cell carcinoma

In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature.

Merkel cell carcinoma is a rare but aggressive cutaneous neuroendocrine tumour readily occurring in older patients. Immunosuppression and sun exposure are the main risk factors for this disease, which is associated with Merkel cell polyomavirus in 50% to 75% of cases.

Primary tumour: stage I (diameter < 2 cm) and stage II (diameter > 2 cm)

- *First-line treatment: surgery and adjuvant radiotherapy*

Wide resection with 2cm lateral margins is still recommended when possible. If the tumour location does not allow these margins to be maintained, more limited resection with margins of at least one centimetre is

proposed. Revision surgery will be offered in the case of incomplete resection.

Sentinel lymph node technique

Detection with sentinel lymph node resection is recommended in all patients without palpable adenopathy, regardless of the tumour diameter. The sentinel lymph node is involved in 20% to 30% of cases so additional regional dissection will be offered. If sentinel lymph node detection is not carried out or fails, radiotherapy to satellite lymph node areas must be offered.

Adjuvant radiotherapy

Adjuvant radiotherapy of 50 Gy to the tumour bed will be offered, as well as in the case of regional lymph node involvement. Several retrospective studies show that adjuvant radiotherapy improves locoregional control[1] and overall survival[2] compared with surgery alone.

If patient is not eligible

If the tumour is inoperable, neoadjuvant immunotherapy with the objective of reducing the tumour mass before considering surgery then radiotherapy, or radiotherapy alone will be discussed. The decision is discussed at an MDTM as well as with the patient, taking comorbidities into account.

Another alternative in the case of therapeutic failure for an inoperable tumour located on a limb is limb perfusion chemotherapy.

Regional lymph node involvement (stage III)

- *First-line treatment: surgery and adjuvant radiotherapy*

In the case of palpable lymph node involvement, adenomectomy with histological verification and lymphadenectomy will be offered, if possible during the same operation. Adjuvant radiotherapy to the regional lymph node area is then offered.

If patient is inoperable: neoadjuvant immunotherapy followed by surgery and radiotherapy, or radiotherapy alone are discussed at an MDTM.

Distant metastases (stage IV)

First-line treatment: surgery if single operable metastasis, medical treatment if distant inoperable metastases.

- *If patient is not eligible*

Avelumab[3] is associated with a response rate of 62% as first-line treatment and 32% as second-line treatment after chemotherapy. Avelumab can currently only be prescribed as second-line treatment in France. Anti-PD-1s, the efficacy of which has been demonstrated, are not approved in France.

Merkel cell carcinoma is chemosensitive but chemotherapy escape usually occurs quite quickly like in small cell bronchial carcinoma. The most common therapeutic regimen in older patients is the carboplatin + etoposide combination. Objective responses are obtained in around 2/3 of patients but there is no survival benefit.[4] Chemotherapy should now be reserved for second-line treatment.

The administration of Glivec in patients overexpressing c-kit has produced disappointing results. Some responses were reported with somatostatin analogues.

Monitoring

In stages I, II and III: quarterly clinical skin monitoring for 2 years then six-monthly up to 5 years. There is no consensus on paraclinical monitoring but it is usually offered.

For patients having received radiation treatment, annual monitoring by a radiation oncologist is required for 5 years following treatment.

After 5 years, annual skin monitoring is recommended due to the risk of secondary skin cancer.

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ENT CANCER TREATMENT

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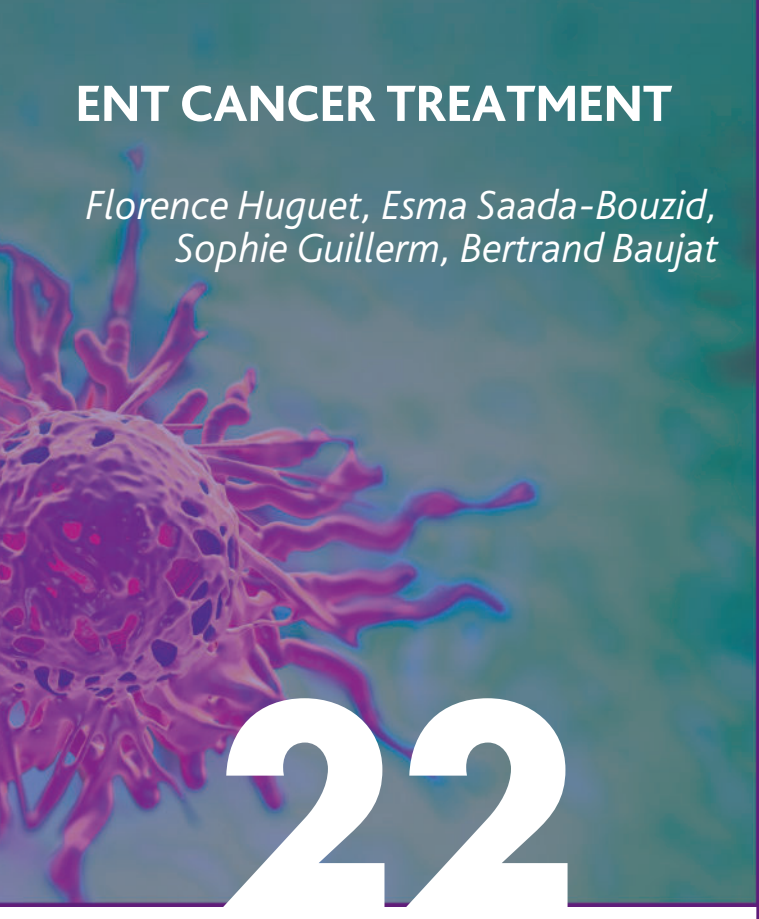

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In the absence of specific recommendations for treating ENT cancers in older patients, the authors have drawn up treatment proposals based on the medical literature.

Stage I and II (T1-T2N0M0)

- *First-line treatment*

After an operability assessment, the standard treatment for stage I and II ENT squamous cell carcinomas is surgical resection of the lesion with associated lymphadenectomy. Lymphadenectomy will be bilateral for medial lesions.

Recently, two randomised equivalence trials showed the non-inferiority of the sentinel lymph node technique compared with lymphadenectomy for T1-T2 tumours in the oral cavity and oropharynx, with a significantly lower morbidity in patients treated with the sentinel lymph node technique, making the technique particularly attractive for older patients.[1,2]

In selected patients aged over 70 in good general condition, surgical complications are not more frequent than in younger patients and survival is comparable.[3]

Dissection is not necessary for T1N0 glottic squamous cell carcinomas. Exclusive irradiation of the glottis at a dose of 66 to 70 Gy is an alternative to surgery for these carcinomas. In older patients, this radiation limited to the glottis will be hypofractionated.[4]

After surgery, post-operative radiotherapy will be offered in the case of incomplete resection (R1), multiple lymph node invasion (3 or more) and/or capsular rupture.

- *If patient is not eligible (inoperable for medical reasons or refusing surgery)*

Exclusive interstitial brachytherapy is offered if the lesion is accessible and has a small volume (T1 in the oral cavity or oropharynx). In other cases, exclusive radiotherapy to the tumour site and draining lymph node areas will be discussed at an MDTM.

Lymph node area irradiation will be ipsilateral for a well-lateralised tumour in order to reduce the severity of radiation-induced xerostomia.

The radiotherapy ballistics must minimise the portion of oral mucosa irradiated in order to improve tolerance, so conformal intensity-modulated radiotherapy (IMRT) will be used.[5]

Nutritional management is essential and must start at the same time as treatment.

Concomitant chemotherapy and radiotherapy is not indicated in patients aged over 71, having not shown a benefit in the MACH-NC meta-analysis.[6] It also increases the toxicity of radiotherapy. It can, however, be discussed in patients in very good general condition without comorbidities after consulting a geriatric expert. Similarly, the addition of cetuximab, an anti-EGFR (Epidermal Growth Factor Receptor) monoclonal antibody, to radiotherapy does not appear to provide a benefit over the age of 65[7,8] but can be discussed on a case-by-case basis.

For patients in poor general condition (unfit), modified fractionation radiotherapy (hypofractionation) can be offered in order to improve treatment compliance.[9-13] The results of the GORTEC ELAN RT trial conclude the non-inferiority of split-course hypofractionated radiotherapy

compared with normofractionated radiation in terms of the rate of patients alive at 6 months with locoregional control of the tumour in this population (35% versus 34%).[14] However, patients in the normofractionated arm had longer overall survival (18.9 months versus 13 months; $p = 0.055$) making this regimen preferable for patients able to receive it.

Stage III (T1N1M0, T2N1M0, T3N0M0, T3N1M0)

- *First-line treatment*

After an operability assessment, the standard treatment is surgical resection of the lesion with associated lymphadenectomy. Dissection will be bilateral for lesions crossing the midline. Post-operative radiotherapy will be offered in the case of incomplete resection (R1), multiple lymph node invasion and/or capsular rupture.

- *If patient is not eligible (inoperable for medical reasons or refusing surgery)*

Exclusive radiotherapy to the tumour site and draining lymph node areas will be discussed at an MDTM (see stages I-II for details). Modified fractionation radiotherapy (accelerated radiotherapy, i.e. dose increased in fractions and shorter treatment time or hypofractionated with several sessions a day) did not show a clear benefit in patients aged over 71 in the Baujat et al. meta-analysis.[15] In the specific case of larynx-preservation strategies, the addition of concomitant chemotherapy to radiotherapy can be discussed according to the patient's general condition and comorbidities.[16]

For patients in poor general condition (unfit), modified fractionation radiotherapy (hypofractionation) can be offered in order to improve treatment compliance and tolerance.[9-13] The results of the GORTEC ELAN RT trial conclude the non-inferiority of split-course hypofractionated radiotherapy compared with normofractionated radiation in terms of the rate of patients alive at 6 months with locoregional control of the tumour in this population (35% versus 34%).[14] However, patients in the normofractionated arm had longer overall survival (18.9 months versus 13 months; $p = 0.055$) making this regimen preferable for patients able to receive it.

Stage IVa (T4, N2, N3, M0)

- *First-line treatment*

For inoperable stage IV tumours or when the risk-benefit balance is not in favour of surgery, the standard treatment is exclusive normofractionated radiotherapy (5 sessions of 2 Gy a week for 7 weeks) to the tumour site and draining lymph node areas. Lymph node area irradiation will be ipsilateral for a well-lateralised tumour in order to reduce the severity of radiation-induced xerostomia. The radiotherapy ballistics must minimise the portion of oral mucosa irradiated in order to improve tolerance, so conformal intensity-modulated radiotherapy (IMRT) will be used.[5] The addition of concomitant chemotherapy to radiotherapy is not indicated in patients aged over 71 as it did not show a benefit in the MACH-NC meta-analysis.[6] It also increases the toxicity of radiotherapy. Also, the addition of cetuximab, an anti-EGFR (Epidermal Growth Factor Receptor) monoclonal antibody, to radiotherapy does not appear to provide a benefit over the age of 65.[7,8]

In the specific case of cT4 laryngeal lesions, the standard treatment is total laryngectomy.

If the patient is inoperable or refuses laryngectomy, radiation can be offered with added concomitant chemotherapy according to the patient's general condition and comorbidities.[16]

- *If patient is not eligible (unfit)*

Modified fractionation radiotherapy (hypofractionation, split course) will be preferable in order to improve treatment compliance.[9-13] Supportive care must be offered in all cases. In older patients refusing total laryngectomy or who are too frail to tolerate it, relatively long survival and acceptable quality of life can be achieved with a small cannula with speaking valve, at the cost of a tracheotomy when breathing becomes difficult. This option must be honestly discussed with the patient and their family (unpublished data).

Metastatic tumours or inoperable locoregional relapse (R/M)

- *First-line treatment*

Up until 2019, the standard first-line R/M treatment in older patients in good general condition was a combination of 5-FU, carboplatin and cetuximab[12] although only 18% of patients included in the EXTREME trial were over 65.[17] The phase II ELAN FIT trial later showed that the combination of carboplatin, 5-FU and cetuximab was indeed associated with efficacy equivalent to that reported in a younger population (median overall survival = 14.7 months) in a cohort of 85 selected older patients (fit).[18]

Since then, immunotherapy has become established in the treatment of R/M ENT squamous cell carcinomas. For first-line R/M treatment, the PD-L1 inhibitor pembrolizumab can be prescribed as monotherapy or in combination with carboplatin-5-FU for PD-L1-expressing tumours (CPS score ≥ 1).[19] As patients aged 68 or over were not included in the registration trial (KEYNOTE 048), vigilance is still required as the tolerance profile and efficacy of this combination were not specifically explored in older patients. As second-line treatment, nivolumab can be prescribed regardless of the PD-L1 expression profile in patients pre-treated with platinum salts. The CHECKMATE 141 trial also showed significantly longer overall survival with second-line treatment when nivolumab was compared with the investigator's choice of methotrexate, weekly docetaxel or cetuximab (7.5 months versus 5.1 months, p = 0.01).[20] The KEYNOTE 040 trial also showed the superiority of pembrolizumab versus the same chemotherapy as second-line treatment (overall survival of 8.4 months versus 6.9 months, p = 0.01) but pembrolizumab is not covered by the French health insurance system for this indication.[21]

Very few older patients were included in the two registration studies (5% of patients in the Checkmate 141 trial were aged over 75 and there were no patients aged over 65 in the KEYNOTE 040 trial). A multicentre retrospective French study showed that, contrary to expectations, the objective response rate is higher in patients aged over 70 when compared with younger patients (23% versus 13%) and that their survival was at least equivalent to that in younger patients receiving immunotherapy (overall survival of 9.7 months versus 8.7 months).[22]

• *If patient is not eligible (unfit)*

If the patient's general condition allows, (PS 0 or 1), immunotherapy (pembrolizumab +/- carboplatin) if CPS ≥ 1 or monochemotherapy with methotrexate or cetuximab can be discussed, following the results of the ELAN UNFIT trial conducted by GORTEC.[18]

For patients in poor general condition (PS 2 or more), exclusive comfort care is recommended as neither immunotherapy nor monochemotherapy showed superiority over exclusive supportive care in this situation.[18,23]

Supportive care is always essential in any situation and must be systematically included in the care provided to these patients.

Monitoring

For UADC squamous cell carcinomas, nearly 90% of relapses occur in the first two years following treatment. Close monitoring is therefore required. Monitoring is based on clinical examination. The French ENT Society (SFORL) recommends a clinical examination every two months in the first year, every three months in the second year, every four months in the third year, and every six months up to 5 years, followed by an annual clinical examination.[24] Standard imaging with MRI or CT scan can be carried out three months after the end of treatment. It will not be systematically repeated, only if there are warning signs. An annual thoracic scan is recommended for patients who smoke.

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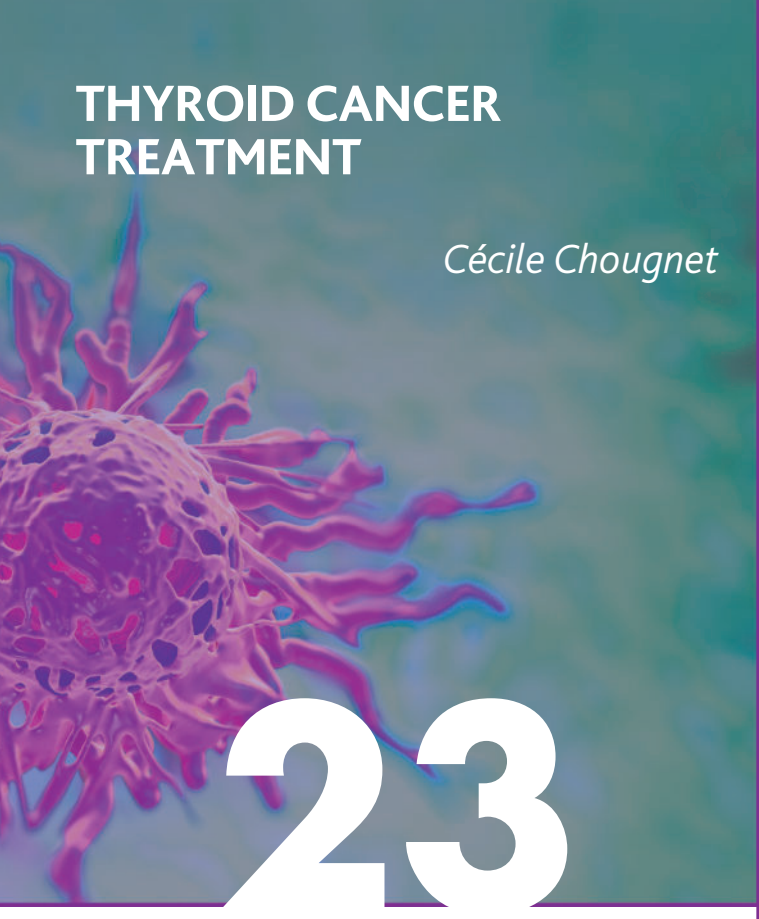
THYROID CANCER TREATMENT

Cécile Chougnet



23

In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature.

Differentiated thyroid cancer (papillary thyroid cancer or follicular cancer)
Stage I: T1 or T2T3a/N0 or Nx/M0

• *First-line treatment*

1. Clinical monitoring is an option if the ultrasound shows the cancer is smaller than 15 mm.

2. Otherwise surgery: preferably thyroid lobo-isthmectomy or discuss total thyroidectomy if contralateral nodules are shown on the ultrasound image, +/- ipsilateral lymph node dissection.

3. +/- Substitution with levothyroxine if necessary -> normal target TSH level 0.5 to 4 mIU/L if test is normal.

Stage II: T1 or T2/N1/M0 or T3b/N0 or N1/M0

- *First-line treatment*

1. Surgery: total thyroidectomy +/- combined with lymph node dissection if an abnormality is detected by ultrasound (central +/- lateral).
2. Substitution with levothyroxine for life: normal target TSH level 0.5 to 4 mIU/L if test is normal.
3. Discuss inpatient radioactive iodine-131 treatment: 1 oral capsule after 2 IM injections of recombinant TSH (thyrotropin) then scintigraphy after treatment.

- *If patient is not eligible:* simple clinical and ultrasound monitoring. Partial thyroid lobectomy surgery can also be considered (not iodine 131).

Stage III: T4a/N0 or N1 or Nx/M0 or poorly differentiated aggressive histological form

- *First-line treatment*

1. Surgery: total thyroidectomy ± combined with lymph node dissection after tumour staging.

2. Substitution with levothyroxine for life, normal target TSH level 0.5 to 4 mIU/L.

3. Inpatient adjuvant radioactive iodine-131 therapy: oral administration of 1 capsule of 3700 MBq iodine-131 after 2 IM injections of recombinant TSH (thyrotropin) then scintigraphy after treatment.

4. If patient is not eligible: simple ultrasound monitoring or partial surgery only.

- *If patient is not eligible:* simple ultrasound monitoring or partial surgery only.

Stage IV: T4b or M1

- *First-line treatment after morbidity and mortality assessment and after consulting a specialist if metastases or locally advanced*

1. Surgery if operable and after complete tumour staging: total thyroidectomy ± combined with lymph node dissection (according to ultrasound and histological type).

2. Post-operative substitution with levothyroxine for life, normal target TSH level 0.5 to 2 mIU/L.

+/- Inpatient adjuvant/therapeutic iodine-131 treatment: oral administration (only after thyroidectomy if this was possible) of 1 capsule of 3700 MBq iodine-131 after discontinuing levothyroxine or after 2 IM injections of recombinant TSH, according to the MDTM decision and general condition.

3. Then scintigraphy after treatment.

- *First-line treatment if inoperable, locally advanced or metastatic on diagnosis*

1. Specific metastasis treatment for functional and analgesic purposes: orthopaedic surgery, neurosurgery, interventional radiology, radiotherapy.

If iodine refractory or can be considered as such (thyroidectomy is impossible): specialist opinion discussion via the TUTHYREF network (regional expert centre), after a biopsy to confirm the histological type.

2. Oral targeted therapy with reduced-dose lenvatinib or sorafenib (MA) or targeted inhibitor or treatment protocol, after geriatric and cardiovascular assessment.

3. In certain inoperable, rapidly progressing, compressive cervical adenopathies: cervical radiotherapy.

- *If patient is not eligible:* palliative care.

- *Notes:*

- AJCC TNM stage used, 8th edition (2017);
- recombinant TSH can be injected via deep subcutaneous route if intramuscular injections are contraindicated;
- target TSH level to be adapted to the patient's cardiac function: be careful of levothyroxine overdose as hyperthyroidism is clearly harmful in older patients (heart rhythm disorder, amyotrophy, bone and psychiatric disorders, etc.).

Non-differentiated thyroid cancer or anaplastic cancer

- different treatment, urgent oncology specialist opinion.

Medullary thyroid cancer

• *First-line treatment*

- surgery: total thyroidectomy ± combined with lymph node dissection after tumour staging;
- after pre-operative calcitonin tumour marker testing, CEA;
- after eliminating possible associated pheochromocytoma.

Specialist opinion for systematic intratumoural RET gene mutation search even with no family history (familial medullary cancer).

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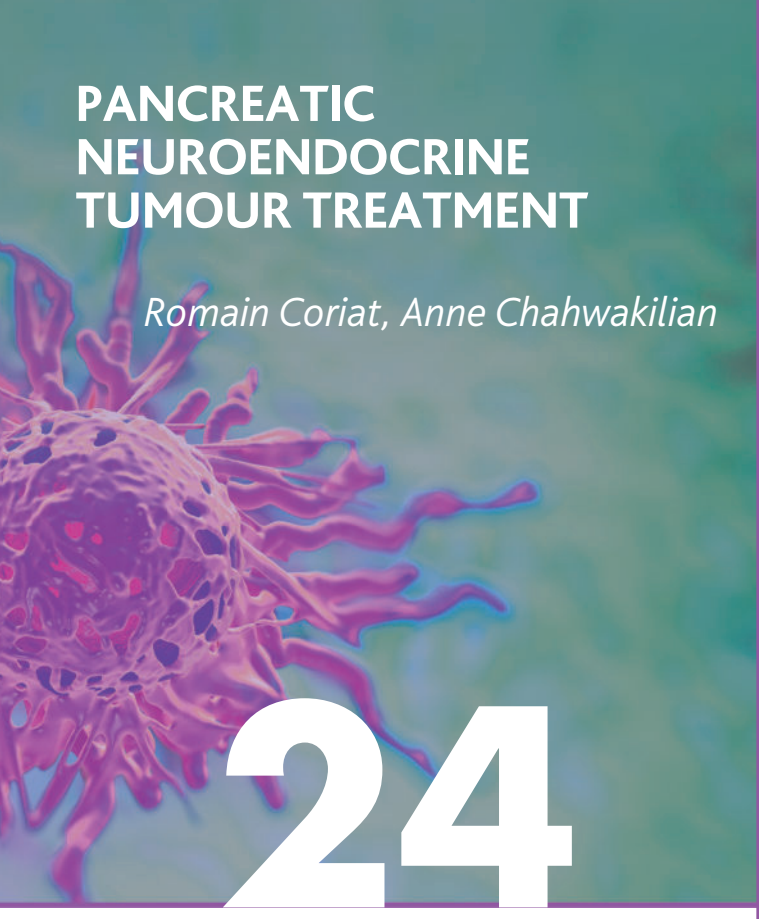
PANCREATIC NEUROENDOCRINE TUMOUR TREATMENT

Romain Coriat, Anne Chahwakilian



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In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature.

Neuroendocrine tumours (NETs) are rare and require complex treatment. Anatomopathological diagnosis standardisation work has been ongoing for several years. It has included the WHO 2010 classification,[1] then the WHO 2017 classification, which is now internationally recognised,[2] and the 2019 update.[3]

All neuroendocrine neoplasms must be classified according to the WHO classification, which is based on histological differentiation (neuroendocrine tumours (NETs) versus neuroendocrine carcinoma (NEC)) and the tumour grade, according to the proliferation index measured by the Ki67 index and the mitotic index. The latest version from 2019 (Table 1) identifies the NET G3 category in all digestive locations (WHO Classification of Tumours. 2019). The other prognostic factors are chromogranin A level (general serum marker considered to be the hormone secretion control), the tumour site and size, and whether it is localised or metastatic.

Table 1: *WHO 2019 classification of Neuroendocrine Neoplasms. Adapted and modified according to the WHO Classification of Tumours. 2019.*

	Ki67*	Mitotic index**
Grade 1 (G1)	< 3%	< 2
Grade 2 (G2)	3-20%	2-20
Grade 3 (G3)	> 20%	> 20
	Grade	Differentiation
NET G1	G1	Well-differentiated
NET G2	G2	Well-differentiated
NET G3	G3	Well-differentiated
NEC***		Poorly differentiated, large-cell or small-cell
MiNEN		Mixed neuroendocrine and non-neuroendocrine neoplasm

NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour.

** The Ki67 proliferation index is determined by counting at least 500 cells in areas of highest marking.*

*** The mitotic index must be expressed as the number of mitoses per 2 mm^2 (equivalent to 10 high-power fields at x40), determined by the count of fifty 0.2 mm^2 fields (so a total area of 10 mm^2). The final grade is based on whichever of the two proliferation indices places the lesion in the highest grade category.*

**** NECs are considered high grade (G3) by definition.*

The most recent TNM classification is the 2017 one (8th Tumour-Node-Metastases (TNM) classification of NETs according to UICC).[4]

The treatment strategy for pancreatic NETs (pNETs) must take these factors into account, as well as, in older patients, treatment-related risks and epidemiological data concerning the natural history of these tumours and their expected life expectancies.

Well-differentiated tumours: functional tumours

- *First-line treatment*

For tumours responsible for symptoms relating to tumour production of peptides or amines, first-line antisecretory treatment must be carried out, with somatostatin analogues (SSAs) and other agents appropriate to the specific syndrome.

The search for multiple endocrine neoplasia type 1 (MEN 1), a genetic disorder which is rare in older patients, must be systematic.

- *Specific case of insulinoma*

Surgical treatment: resection of pNET responsible for hypersecretion of insulin.[5]

Recommended initial treatment: diazoxide.[6]

Second-line treatment is possible if metastases and persistent hypoglycaemia: everolimus,[6,7] potentially effective on glycaemic control.[8]

- *Specific case of gastrinoma and Zollinger Ellison syndrome (ZES)*

Initial treatment: based on high doses of proton pump inhibitors,[9] adapted to the clinical and endoscopic response.[5]

- *Specific case of carcinoid syndrome*

Treatment based on somatostatin analogues:[10] octreotide[JA25] or lanreotide with an objective of fewer than 3 stools and fewer than 3 flushing episodes per day.[5]

- *Specific case of VIPoma and glucagonoma*

Standard treatment: SSA with doses adapted to the symptoms.

- *Somatostatin analogues*

Lanreotide and octreotide bind to somatostatin receptors (SSTR), mainly sst-2 and sst-5, effectively inhibiting hormone secretion and improving symptoms such as vasomotor flushes and diarrhoea.

80% of well-differentiated NETs express SSTR versus just under 50% for poorly differentiated NETs.

There is no difference between the two drugs in terms of symptom control or biochemical response.[11]

A new analogue, pasireotide, which more specifically binds to receptor 5, is an alternative to other analogues for refractory functional NETs.[12]

Well-differentiated non-metastatic tumours

- *First-line treatment*

Surgery remains the standard treatment, whatever the age of the patient, as it is the only one likely to achieve a cure. It must be performed in expert centres, particularly in the case of oncogenetic syndrome. The following are required prior to surgery:[5]

- an expert MDTM discussion of indications and surgical procedures, with a surgical risk assessment;
- control of hormone hypersecretion and its clinical and biological consequences;
- Treatment by an anaesthetist, ideally one with NET surgery experience, including peri-operative antisecretory treatment (high-dose PPI for ZES, SSA for carcinoid syndrome, VIPoma, and glucagonoma) of functional NETs.[5]

Isolated, well-differentiated NETs (G1/G2)

- *Ampullary NETs?*

= Increased risk of lymph node metastasis and shorter survival.

Radical surgery + lymphadenectomy if tumour ≥ 2 cm, to be performed in expert centres.

Option for small tumours < 10-15 mm without suspected adenopathy.

Ampullectomy is an option, particularly in patients with comorbidities who are not good candidates for cephalic duodenopancreatectomy. This surgery must be performed in specialised centres.[5]

- *Low-grade (1 or 2), well-differentiated tumour < 2 cm diameter, without distant metastases, with Ki67 threshold < 5% not precisely defined, asymptomatic, with typical low-grade NET signs in imaging without pancreatic or bile duct dilation in cross-sectional imaging, and without progression on follow-up images*

If the resection requires major surgery, there is the option of not taking action and monitoring the patient via endoscopic ultrasound and MRI or CT scan after 6 months then every year (Recommendations by the European Neuroendocrine Tumor Society, and the TNCD (French digestive oncology guidelines group).[13,14]

However, a recent study recommends surgery, enucleation or partial pancreatectomy for these tumours, with a benefit in terms of risk of death of 75 and 58% respectively,[15] compared with observation. Although promising, there are however limits to this study (including patients undergoing surgery having an average age of 56 to 58 years, and there being no comorbidity information) which justify exploring the alternative further, for example with a randomised prospective study including older patients.

- *Other tumours < 2 cm and tumours ≥ 2 cm*

First-line treatment: surgery. Patients must undergo surgery if possible, even if there is locoregional spread, unless the surgical risk is too high or if there are severe predictable post-operative functional consequences.[5] In the USA, 75% of tumours are < 1 cm and 80% of those > 1 cm and ≤ 2 cm are resected, with longer 5-year survival.[16]

Central or distal pancreatectomy, cephalic duodenopancreatectomy, with systematic lymphadenectomy.

A cholecystectomy must be systematically discussed in patients with pancreatic NET with a high risk of recurrence due to subsequent risks of SSA-related vesicular lithiasis.[17]

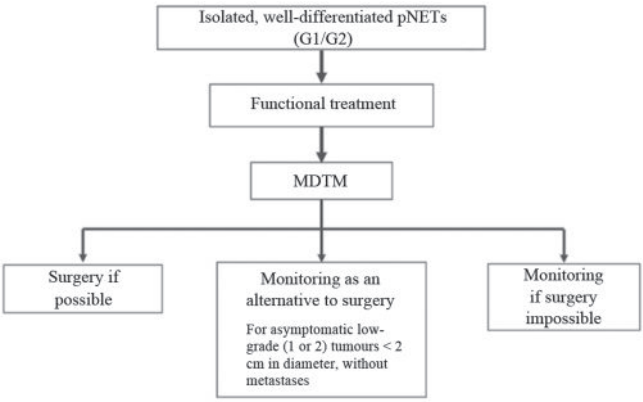
For patients with a reassuring prognosis, sparing pancreatectomy with lymph node picking can be discussed (risk-benefit trade-off). An alternative could be a new technique carried out in some referral centres: pancreatic radiofrequency. This technique, which is currently being developed in some centres and still not routinely

recommended, involves grade 1 (Ki67 < 3%) pNET destruction, including insulinoma destruction, by radiofrequency and is therefore limited to non-metastatic lesions of less than 2 cm.[18,19]

Surgery for patients with NET must be carried out at expert centres.[20] These treatments will need to be discussed at an MDTM, ideally including a standardised geriatric assessment (SGA) and an anaesthesia consultation. Complications are frequent: post-operative (haemorrhage, delayed gastric emptying, pancreatic fistula, death,[21,22] and geriatric (confusion, dehydration, falls and fractures, bed sores, failure to thrive, etc.),[23,24] making few patients eligible, as the average age (50-60 years) of patients in numerous trials suggests. However, studies and meta-analyses have shown that the surgical risks of pancreatic surgery in older patients mainly correlated with their history and condition, and comorbidities in particular, and that careful patient selection could limit these risks.[24-26] Coelioscopic surgery is an interesting alternative,[27] with all studies comparing it with laparotomy surgical techniques showing a low complication rate.[27] But randomised trials are still required, particularly in older patients.[28] Some authors emphasize the need for specialist centres to perform pancreatic cancer surgery in much older patients.[29,30]

- *If surgery is contraindicated*

Clinical monitoring is a viable option, or treatment (not surgery) similar to locally advanced NETs.



Algorithm 1: *Treatment of isolated, well-differentiated pNETs (G1/G2)*

Advanced and/or metastatic, well-differentiated NETs (G1/G2)

All cases must be discussed at an expert MDTM dedicated to NENs (in France, in the RENATEN network).[5]

Points to consider:[5]

- tumour grade and differentiation;
- disease-free interval and/or tumour growth rate;
- SST receptor expression in nuclear imaging;
- FDG-PET uptake;
- tumour volume, particularly the level of hepatic metastatic involvement, which can be classified semi-quantitatively into 4 categories (0-10, 11-25, 26-50 and > 50%);[31]
- extrahepatic metastases (bone and peritoneum in particular);
- resectability of the primary tumour and metastatic disease;
- patients' characteristics (age, comorbidities, general condition);
- previous treatment and cumulative toxicity;
- patient's therapeutic goal, including quality of life. This is particularly important as patients with NET can have prolonged survival (> 5-10 years) even in the case of metastases.

Older patients.

For older patients, particularly those who are much older and/or have comorbidities, the therapeutic strategy must take into account the prognosis and chance of 5-year survival. North American data since 2008 shows median overall survival of 136, 77, and 24 months for pancreatic NETs diagnosed at a localised, locally advanced and metastatic stage respectively.[32] 5-year survival rates for well- or poorly-differentiated pancreatic NETs are 79% and 27% respectively.[32] More recently, a multicentre study showed median overall survival of 6.67 years with a 5-year survival rate of 62% and 10-year survival rate of 34% for all stages.[33] This often slow growth of well-differentiated NETs makes it possible to assess tumour progression over long periods by carrying out thoracic-abdominal-pelvic scans every 6 months.

Fully resectable hepatic tumour and metastases with no or weak progression

Slow progression can be arbitrarily defined by a tumour size increase ≤ 20% (RECIST criteria) in 12 months.[5]

First-line treatment: surgery. Surgical treatment of the primary tumour and hepatic metastases can be offered if considered to be a possibility following the surgical and geriatric assessments[34,35] after approval at the multidisciplinary team meeting.

The surgeon must take into account the extent of the procedure, the predicted remaining hepatic volume and comorbidities. The risk of intrahepatic recurrence and complications may lead to non-indication of surgery in older patients due to the expected morbidity and mortality.

Cholecystectomy is recommended.[5]

Adjuvant anti-tumour therapy is not indicated as it has no demonstrated benefit.

Surgical resection may be reconsidered in the case of initially unresectable metastases objectively responding to anti-tumour treatment. [5]

Duodeno-pancreatic NET associated with unresectable metastases.

Indications for primary tumour resection, duodenopancreatectomy in particular, are rare and do not concern older patients in theory.

- ***Asymptomatic hepatic metastases with hepatic invasion < 50%, Ki67 < 10% and without morphological progression***

First-line treatment: Somatostatin analogue[12]
- Lanreotide[36]
- Octreotide[37]

They have symptomatic action on functional pNETs,[34] and antiproliferative action.[12]

Medium-dose octreotide improves survival in fit older patients.[38]

Much older patients are often excluded from studies, as demonstrated by the average age of ≤ 65 years.

- More recently, pasireotide has been offered, which seems beneficial for patients with functional NETs who did not respond to the other analogues.[12] There is no current data for older patients.

Or simple monitoring if minor disease or low risk of progression.[5]

- *Progressive hepatic and/or symptomatic metastases despite well-conducted treatment, and/or hepatic invasion > 50%, and/or Ki67 > 10%, and/or bone metastases and probably positive FDG-PET when cancer surgery is not possible*

Systemic treatment

First-line chemotherapy

This is the line of treatment after progression with analogues or if aggressiveness criteria are identified (e.g. RECIST progression < 1 year) as the objective response rate is higher than with targeted therapies or somatostatin analogues (only in grade 1 or 2 pancreatic NETs).[39] The protocol must be approved by a multidisciplinary team after geriatric oncology assessment.

The regimens used are:
- streptozocin + 5-FU.[35,40] Its nephrotoxicity can be reduced by close monitoring;[41]
- dacarbazine + LV5FU2;
- temozolomide + capecitabine (oral treatment), beneficial in older patients with a risk of renal or cardiac toxicity.[39] The CAPTEM regimen confirms the benefit of this combination in patients with grade 2 and 3 metastatic NETs, with manageable toxicity;[42]
- other options: FOLFOX (oxaliplatin + 5-FU) or GEMOX (oxaliplatin + gemcitabine).[43] XELOX (capecitabine + oxaliplatin),[44] FOLFIRI (irinotecan + LV5FU).[45]

Surgery can be rediscussed if there is a good response to chemotherapy.

Second-line somatostatin analogues

SSAs at an increased dose and reduced frequency can be used in patients progressing after a prolonged period of stabilisation on first-line SSA.[46]

Second-line targeted therapies

These are indicated for unresectable or metastatic, well-differentiated pancreatic NETs which are progressive on somatostatin analogues or chemotherapy, or if chemotherapy is contraindicated:[34]
- sunitinib, tyrosine kinase inhibitor;[47]
- everolimus, mTOR inhibitor.[48]

The risk of side effects requires a thorough pre-treatment assessment and close clinical-biological monitoring,[47,48]

and can result in treatment interruption. Little is known about tolerance in older patients. This means that a geriatric assessment must be carried out before any treatment decisions are made at the multidisciplinary team meeting, and supportive care must be provided. Studies of these molecules showed, in each case versus a placebo, doubling of survival but without a certain net effect as the response rate on the tumour volume was lower than 10%.[35]

Bevacizumab[JA26], combined with 5-FU + streptozocin, seems promising.[49]

Locoregional therapies

Intra-arterial therapies

- Intrahepatic intra-arterial chemoembolisation

The response rate for this treatment ranges from 52% to 86%.[50] The technique can be used in older patients, with a comparable complication rate to younger patients,[51] but after MDTM assessment of the risk-benefit ratio for the patient. It seems more effective than embolisation alone.[52]

- Radioembolisation

This technique involves intra-arterial delivery of Yttrium-90 microspheres. It achieves an objective tumour response in 40% to 65% of cases.[52] The lack of data in older patients and the quite demanding pre-treatment assessment limit its use in this population, despite the technique seeming to be quite well tolerated.

Radiofrequency

This is a minimally invasive technique for a small metastasis < 5 cm, 3 metastases < 3 cm or a total diameter of < 8 cm.[50] It is an interesting alternative for older patients who are ineligible for surgery[53,54] but who can tolerate general anaesthetic. According to data in the literature, the main indication for PRF is the treatment of pancreatic neuroendocrine tumours of less than 2 cm with Ki67 < 3%.

Internal vectorised radiotherapy (IVR)

Or PRRT (Peptide Receptor Radionuclide Therapy).

This technique consists of targeted irradiation of the tumour and metastases after administering a Lutetium-labelled

somatostatin analogue (^{177}Lu-DOTATATE), which delivers cytotoxic beta radiation.[55]

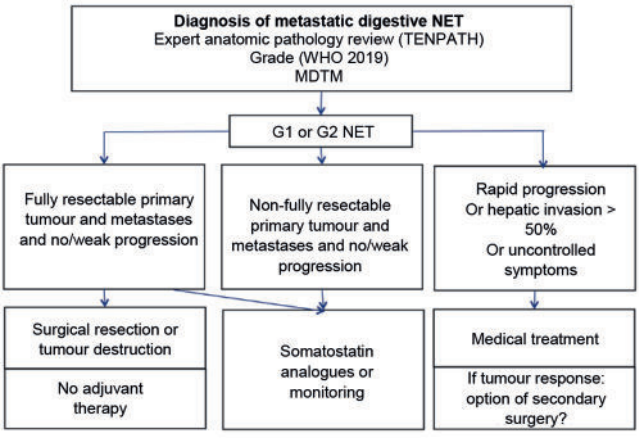
Promising work is being carried out relating to this treatment[56] in pNETs, but is not covered by the French health insurance system despite there being an MA for this indication. Zandee *et al.* retrospectively showed a partial or complete response in 59% of patients and a disease control rate of 78%, with relatively good tolerance. A randomised trial including more patients, particularly much older ones, is therefore required. But this technique would appear to be beneficial as first-line treatment of metastatic functional pNETs in older patients.

An alternative: tumour reduction surgery on hepatic metastases

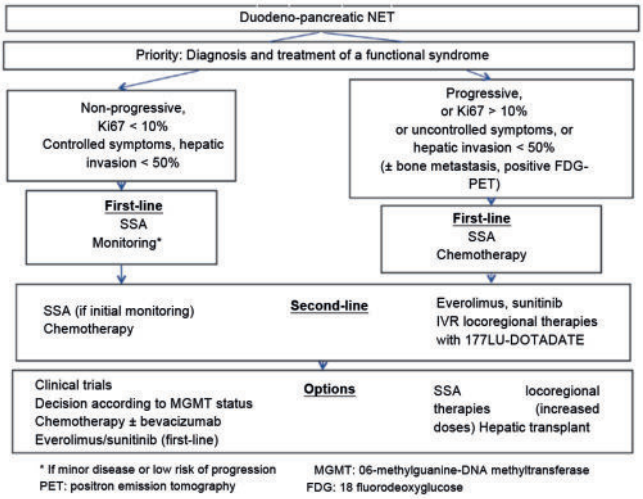
This type of surgery is an alternative to local therapies for a symptomatic functional tumour or slow-growing non-functional tumour with hepatic metastases which are macroscopically resectable or fully destructible. It can be performed in several stages and combined with radiofrequency. The treatment will be considered after approval in the multidisciplinary team meeting, and remains reserved for highly selected situations.[5]

Hepatic transplant

Rare, does not concern older patients.



Algorithm 2: *Treatment algorithm for G1 G2 metastatic digestive NET*
(according to the French digestive oncology guidelines [TNCD], Version 2020)



Algorithm 3: *Treatment for G1 G2 unresectable metastatic digestive NETs*
(according to the French digestive oncology guidelines [TNCD], Version 2020)

Pancreatic neuroendocrine carcinoma (poorly-differentiated grade 3)

These tumours are rare (5 to 10% of pNETs), and still have a poor prognosis.[57] Once the diagnosis has been made, treatment is relatively urgent.

Non-metastatic NECs

- *First-line treatment: surgical resection*[57]

This procedure is only possible in 20% to 30% of cases, for localised tumours and if the patient's general condition is good. Complications are frequent,[21] with mortality and morbidity rates for surgical resection of 5% to 50% respectively according to the type of procedure,[58] and there is a significant risk of recurrence. It is therefore rarely indicated in older patients.

In theory, adjuvant therapy can be considered given the potential aggressiveness of these lesions.

- *Chemotherapy*

Adjuvant. This treatment must be commenced quickly and be adjuvant if the surgical treatment is curative.

The standard recommended protocol combines cisplatin and etoposide.[59,60] The mediocre tolerance of this protocol limits its prescription in older patients due to the renal and cardiac risks.

An alternative, if cisplatin is contraindicated, is the combination of carboplatin and etoposide.

Neoadjuvant. Etoposide + cisplatin (or carboplatin) chemotherapy may be considered as neoadjuvant therapy if surgery is contraindicated or delayed.

- *Other treatments*

There is currently little data concerning the place of treatments such as somatostatin analogues, targeted therapies, chemoembolisation or internal vectorised radiotherapy for grade 3 neuroendocrine tumours.

Metastatic NEC

- *First-line: chemotherapy*

Etoposide + cisplatin (or carboplatin). Response rate of approximately 40-50%, PFS of around 6-9 months, and median overall survival of approximately one year.[61-63]

Chemotherapy efficacy to be assessed/2-3 cycles, for a total of 6 cycles followed by a break if there is no progression:

If progression after a 4- to 6-month break: continue the same chemotherapy.

If progression during the 4- to 6-month break: second-line chemotherapy.

- *Second-line*

No standard second-line treatment.

Options: FOLFIRI64 and FOLFOX65 with objective response rates of < 30% and a median PFS < 5 months. To be reserved for ECOG PS 0-1 or fit patients.

It is worth noting that there is possible effective antitumour activity due to the combination of bevacizumab - FOLFOX or FOLFIRI[66] which needs to be confirmed by therapeutic trials in progress.

Well-differentiated grade 3 pancreatic NET

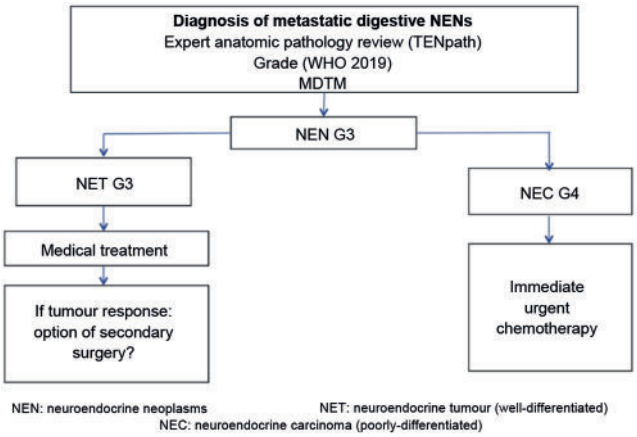
There are not many up-to-date recommendations due to the heterogeneous nature of these tumours.[60] There are well-differentiated grade 3 NETS with mitotic index and/or Ki-67 index > 20%. A review by a member of the TENpath network is essential in all situations. Treatment is based on anatomical pathology (particularly the tumour differentiation character and its histological grade correlated with cell proliferation), and the metastatic status.[5]

- *First-line surgery for localised tumours*[57]

This surgery can also be performed for well-differentiated, grade 3 small pancreatic NETs.

- *Chemotherapy*

The protocol is comparable to those for well-differentiated grade 2 pancreatic NETs for forms with a moderate proliferation grade.[35] A recent study has called into question platinum-based chemotherapies in well-differentiated grade 3 pancreatic pNETs with Ki67 ≤ 55-60%.[67]



Algorithm 4: *Treatment algorithm for G3 metastatic digestive NENs.*
(according to the French digestive oncology guidelines [TNCD], Version 2020)

Monitoring

In all cases, whichever treatment plan is decided upon at the MDTM, the MDTM should be used as an opportunity to draw up a supportive care plan with the geriatrician including nutritional,[68] possible aftercare, close monitoring and quality of life aspects.

Follow-up will be long term due the risk of significantly delayed metachronous metastatic recurrence.[5]

1) If simple monitoring is chosen:

- monitoring must be six-monthly for small, isolated grade 1 or 2 pNETs;
- monitoring must be quarterly or according to progression for other pancreatic NETs.

2) Pre-, peri- and post-operative monitoring:

Non-metastatic NETs with curative surgery:

After 3 to 6 months

Then 6-12 months for 5 years

Then 12-24 months for 10 years

Metastatic NET:

At 3 months then 3-6 months or according to the clinical and/or biological characteristics

3) Somatostatin analogue monitoring

4) Chemotherapy monitoring

5) Late-identified iatrogenic side effects

- renal failure (streptozocin[JA27], IVR);
- heart failure (sunitinib, doxorubicin);
- medullary involvement (IVR, alkylating agents).

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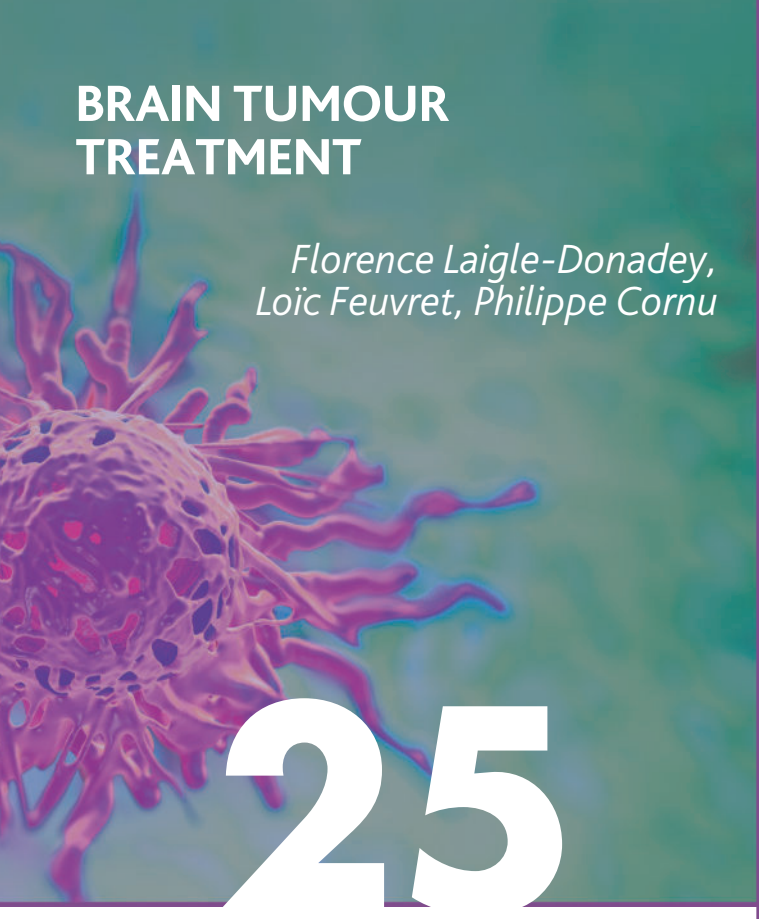
BRAIN TUMOUR TREATMENT

Florence Laigle-Donadey, Loïc Feuvret, Philippe Cornu



25

This chapter includes recommendations for the management of brain tumours specifically in older patients. In the absence of specific recommendations for older patients for certain histological types or phases of the disease, the authors have drawn up treatment proposals based on the medical literature.

Malignant glioma in a patient with KI ≥ 70

- *First-line treatment*

Surgery

Following the results (presented at EANO 2021) of the French prospective randomised "CSA" trial evaluating the impact of "surgery" versus "biopsy" in older patients: if inoperable and no contraindications to anaesthesia, a surgical resection is recommended after neurological and geriatric assessment of the risk-benefit ratio. The trial was unable to demonstrate the benefit of resection surgery on survival but reported a positive impact on quality of life and independence: less severe deterioration of these and significant, although modest, improvement in progression-free survival.

If resection is not chosen: biopsy.

Radiotherapy with concomitant adjuvant temozolomide chemotherapy

Transposition of the "Stupp" regimen to the older population which, since the publication of data from the European and Canadian prospective randomised "EORTC 26062-22061" trial, has become the new standard treatment provided the patient is in good general and functional condition.

Radiotherapy regimen: a "short-course" regimen (40 Gy in 15 fractions over 3 weeks) is preferable to the "standard" regimen of 60 Gy over 6 weeks, which is long and restrictive.

Chemotherapy alone

An alternative to accelerated chemoradiotherapy used on a case-by-case basis, particularly in patients with MGMT promoter methylation status depending on the context, after discussion at MDTM (retrospective data + evaluation by two randomised trials conducted in Nordic countries: "NOA-8" and "NORDIC trial").

- *Treatment of subsequent recurrences*

First recurrence:
a. recurrence operability is checked: another operation if applicable;
b. monthly temozolomide chemotherapy (150-200 mg/m^2 D1-D5) for patients who did not initially receive concomitant adjuvant temozolomide chemotherapy.

Second recurrence:
a. if there are no contraindications: bevacizumab targeted treatment after discussion at an MDTM and patient and family have been informed of the off-label nature of the prescription and the treatment risks, often combined with CCNU chemotherapy beginning with reduced doses;
b. if bevacizumab is contraindicated: CCNU alone;
c. at this stage, supportive care alone can be considered according to the patient's clinical condition and quality of life, and their and/or their family and friends' wishes.

Third recurrence: discussion of possible change to carboplatin chemotherapy versus supportive care alone.

These treatments will only be considered if there are no contraindications and will depend on the patient's

eligibility for treatment. With malignant glioma cases, for which the prognosis is particularly poor at this age, the benefit of treatment in terms of quality of life always needs to be considered, and comfort must be ensured throughout the disease by providing high-quality support.

Malignant glioma in a patient with KI < 70

- *First-line treatment*

Surgery

Biopsy or, in exceptional circumstances where the patient's quality of life is very mediocre and the family wishes to prioritise comfort, and after a multimodal MRI, the decision may be made to carry out treatment without histological proof.

Conversely, if the patient is operable and there are no contraindications to anaesthesia, and the family wants "vigorous" treatment for a patient with a KI of 50% to 70%, based on the results of the "CSA" trial, surgical resection can be discussed with a view to improving quality of life and independence.

Chemotherapy

Isolated temozolomide chemotherapy: an interesting alternative for older patients in poor initial functional condition for whom radiotherapy is not usually indicated, with marked clinical improvement in some cases (1/4 of patients reached a KI ≥ 70 in the ANOCEF "TAG" trial). However, a tailored hyperaccelerated radiotherapy regimen (5 x 5 Gy) could also be an option and is being studied in this population.

- *Treatment of subsequent recurrences*

Given the particularly poor prognosis at this age and in this sub-population, the benefit of second- or third-line treatment (see supratotal) must be given more consideration in terms of quality of life and, depending on the situation, purely palliative care must be chosen.

Monitoring

MRI every 2 months, can be increased to every month if required (if no contraindications to MRI).

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Primary cerebral lymphoma in fit* patients over 65 to 75 years*
- * Fit: KI ≥ 60 and a score of < 6 on the CIRS-G rating scale for geriatrics (without taking into account symptoms directly linked to the PCL)

Due to the rarity of these tumours, there is a national referral MDTM web conference relating to oculocerebral lymphoma (OCL) held on the first and third Tuesday of the month at 5pm (contact: *caroline.houillier@aphp.fr*).

• *First-line treatment*

High-dose methotrexate-based chemotherapy (MTX). The best combination of chemotherapy to associate with MTX is still being debated. A R-MPVA- "Rituximab-Methotrexate-Procarbazine-Vincristine-Aracytine") regimen can be offered.

Consolidation radiotherapy: no longer recommended, particularly when there is a complete response to chemotherapy alone (high risk of neurotoxicity), resulting in it being delayed to relapse or replaced by second-line chemotherapy.

Prophylactic intrathecal chemotherapy **(MTX and/or cytarabine):** not indicated when a high dose of MTX is used intravenously (> 3 g/m^2). However, it can be offered as additional treatment in the case of confirmed meningeal dissemination (positive CSF cytology or suggestive MRI) if, after an initial assessment of IV MTX chemotherapy efficacy, it was not sufficient (LP after two cycles of MTX after one month).

Intensification can be discussed following 8 cycles of MTX, with age-appropriate autograft with "Thiotepa" - BCNU.

• *Treatment of subsequent recurrences*

If there is a relapse after a prolonged response to the first line of chemotherapy, reinduction with high-dose MTX-based chemotherapy may be discussed (R-MPVA or R-MTX/TMZ).

If early relapse or refractory patient:

- second-line chemotherapy is discussed on a case-by-case basis at the MDTM (ifosfamide-carboplatin-

etoposide (ICE), temozolomide alone, PCV, DHAP: cytarabine-cisplatin or ESHAP: cytarabine-VP16; lenalidomide possibly combined with rituximab, ibrutinib and clinical trials).

Primary cerebral lymphoma in patients aged 65 to 75 and unfit or > 75 years

- High-dose methotrexate-based (MTX) chemotherapy alone (for 1 or 2 debulking cycles) followed by a combination of MTX chemotherapy (MPVA - Methotrexate-Procarbazine-Vincristine-Aracytine), without Rituximab.

NB: For all patients aged > 65: MTX doses are adapted.

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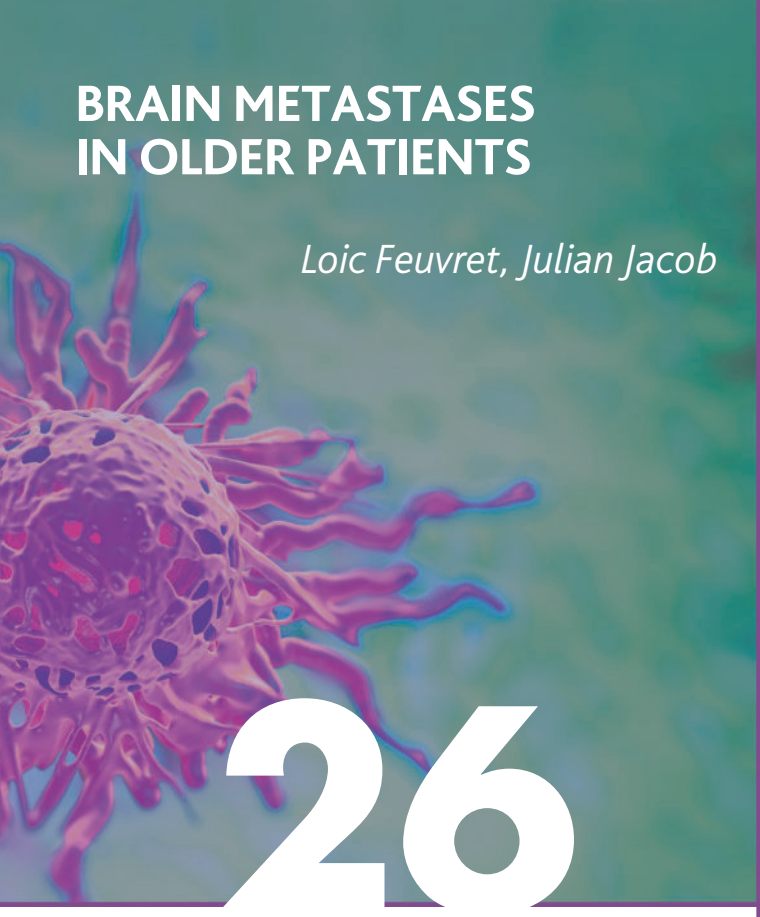
BRAIN METASTASES IN OLDER PATIENTS

Loic Feuvret, Julian Jacob



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Brain metastases treatment in older patients is based on a standard multidisciplinary approach with an additional geriatric oncology assessment to tailor the proposed treatment decisions. Surgery, radiotherapy and systemic treatments are used, like for "younger" patients. The use of a prognostic model recently updated by Sperduto *et al*. is recommended (Diagnosis Specific-Graded Prognosis Assessment) [DS-GPA].[1] In this chapter, we will propose a master plan based on the number of brain metastases diagnosed.[2,3]

Single metastasis

- *Surgery*

Neurosurgical resection is proposed when there are no contraindications to anaesthesia and the patient is in good condition, according to the lesion topography, and in one of the following situations: necessary histological examination, metastasis > 3 cm in diameter, intracranial hypertension, hydrocephalus, and debilitating neurological symptomatology (motor impairments, etc.).

• *Radiotherapy*

Stereotactic radiotherapy of the surgical cavity can be considered according to the results of two randomised trials.[4,5]

Radiotherapy in stereotactic conditions (non- or multi-fractionated according to the lesion volume) is offered in the absence of surgical resection.[6,7]

Multiple metastases

• *Radiotherapy*

Between two and five metastases

Radiotherapy in stereotactic conditions (non- or multi-fractionated according to the lesion volume) is the preferred option in patients with fewer than five metastases. Panencephalic irradiation is poorly tolerated in older patients and has not provided any benefit in terms of overall survival.[8]

More than five metastases

In patients in good general condition, with five to ten brain metastases and a total tumour volume of less than 25 cc, radiotherapy in stereotactic conditions (non- or multi-fractionated according to the lesion volume) is a treatment option.[9,10]

Panencephalic radiotherapy: the standard technique in younger patients (for example, 30 Gy in 10 fractions) but which is poorly tolerated in older patients, particularly those aged over 70. In patients with a significantly impaired general condition, this treatment does not provide any significant benefit in terms of quality of life compared with the best palliative care.[11] If it is absolutely necessary, weaker doses should be used (between 2 and 2.5 Gy).

• *Surgery*

Surgical resection could be discussed in patients in good general condition if there are no contraindications to anaesthesia and in one of the previously described clinical situations.

• *Systemic oncological treatments*

Systemic oncological treatments such as immunotherapy and targeted therapies have shown therapeutic efficacy at the intracranial stage, particularly with regard to asymptomatic infracentimetric metastases.[12] They are a therapeutic option that can be considered according to the overall oncological context.

New brain tumour progression

The different treatment options mentioned above will be discussed if one or more new lesions appear.

When a local recurrence relating to an irradiated metastasis is suspected, the diagnosis of radiation necrosis must be ruled out using various diagnostic approaches (MRI with specific sequences, PET scan or surgical resection).

If there is a confirmed local recurrence, surgery and reirradiation in stereotactic conditions (mono- or multi-fractionated) can be discussed. Panencephalic radiotherapy can only be delivered once. If local treatment is impossible, systemic treatment or exclusive supportive care may be offered according to the primary cancer and general condition.

Monitoring

The first MRI scan should be carried out in the first two months of treatment then every 3 months if there is no intercurrent neurological event. This examination may be brought closer if necessary. Multimodal imaging (MRI with specific sequences, F-DOPA PET) may be recommended if there is diagnostic uncertainty between local recurrence and radiation necrosis.

If MRI is contraindicated, a brain scan, ideally with an injection of iodine-based contrast material, can be used as a pre-treatment and follow-up diagnostic test.

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SOFT TISSUE SARCOMA TREATMENT

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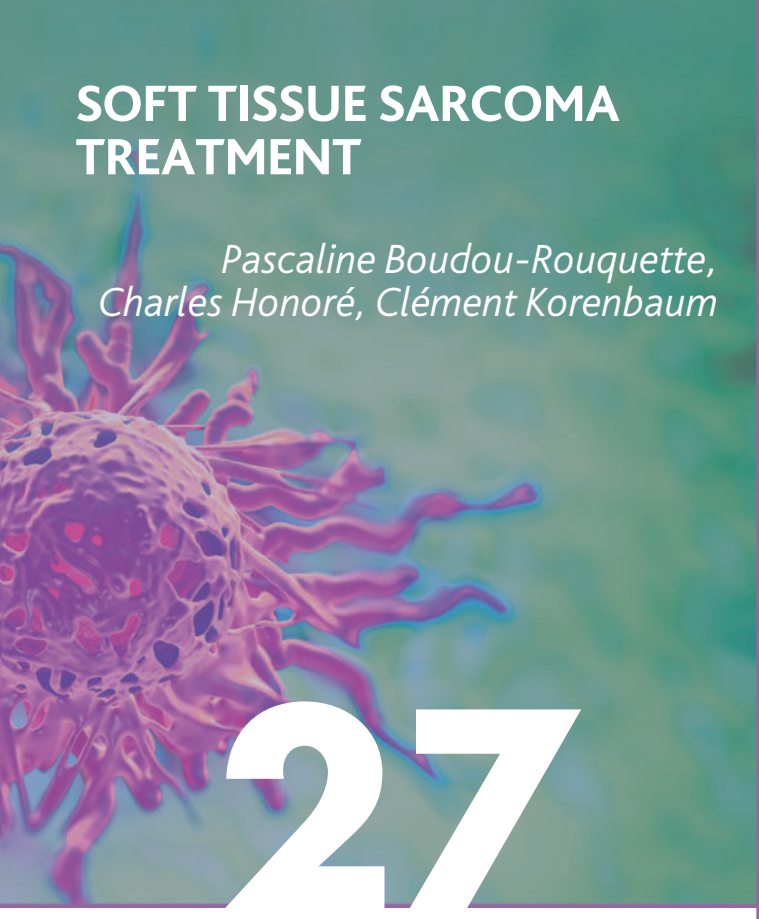

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In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the literature applying to all adult patients.

This chapter does not cover GIST (gastrointestinal stromal tumour) or chordoma treatment.

Introduction

Soft tissue sarcomas (STS) are malignant mesenchymal tumours which can occur in all anatomical locations. They are rare cancers affecting 4,000 people a year in France. 42.8% of cases are in patients aged over 60, 7.6% are in patients aged over 80 and 0.9% are in patients aged over 90. Treatment, which is usually multimodal, must be carried out in a specialist centre in the NETSARC+ reference network.

Diagnostic treatment

All soft tissue masses without an obvious cause which are deep (subgaleal) regardless of their size or superficial and sized ≥ 5 cm must be assessed at a specialist NETSARC+ centre. There are no specific clinical signs

of malignancy and the benign/malignant ratio in these soft tissue tumours is 1/200. The initial diagnostic approach when sarcoma is suspected is independent of the tumour location and is included in recommendations issued by the European Society for Medical Oncology (ESMO, *www.esmo.org*) which are updated every 2 years.

There are four key elements to this approach. In an at-risk population, i.e. unexplained superficial mass of over 5 cm in an adult, regardless of its location, or unexplained deep mass in an adult regardless of its size or location, the following must be completed before considering treatment:
- request appropriate imaging (CT scan and/or MRI);
- perform a coaxial, percutaneous, multiple, large-bore, image-guided (ultrasound or CT scan) pre-treatment biopsy in conjunction with the surgeon (for the biopsy path);
- request a systematic anatomic pathology review by a specialist pathologist (NETSARC+ network) if the biopsy was performed outside the network;
- discuss the case at a specialised multidisciplinary team meeting within the NETSARC+ network.

The imaging assessment will include:
- locoregional MRI staging of soft tissue with axial sections (T1, T2 and STIR) covering a significant area above and below the lesion; axial, coronal or sagittal sections with gadolinium injection and sections including the whole affected compartment for limb, wall and pelvic sarcomas; a thoracic-abdominal-pelvic CT scan for visceral and retroperitoneal sarcomas;
- distant staging via non-contrast thoracic CT scan;
- an additional specific assessment can be requested according to the histology in order to assess lymph node spread (PET scan/epithelioid sarcoma, clear cell sarcoma, Ewing sarcoma), bone spread (thoracic-abdominal-pelvic CT scan and spinal MRI or whole body MRI/myxoid liposarcoma) or brain spread (MRI/angiosarcoma, alveolar soft part sarcoma). Bone scintigraphy is not standard for soft tissue sarcomas.

STS staging is based on elements including general clinical information such as age and tumour location, but also histology reported according to the latest World Health Organization (WHO) classification, the analysis of tumour aggressiveness evaluated by the histological

grade according to the French National Federation of Cancer Centres (FNCLCC) and the assessment of tumour spread summarised by the TNM stage of the American Joint Cancer Committee (AJCC) and the Union for International Cancer Control (UICC). Few anatomic pathologists have exhaustive experience of these tumours, the staging of which is constantly changing, so collegial reviews, immunohistochemistry diagnosis aids and, more recently, molecular biology techniques play an important role. Since January 2010, the French National Cancer Network has required all unexplained soft tissue masses to be reviewed by an anatomical pathologist from the French sarcoma pathology review network (RRePS), which recently merged with the NETSARC+ network.

STS in older patients are often complex genomic sarcomas. The most frequent subtypes include undifferentiated pleomorphic sarcoma (UPS), myxofibrosarcoma, leiomyosarcoma and angiosarcoma. In a study of patients aged over 90 in France, sarcomas in older adults usually had a superficial location and were located on the limbs or in the ENT sphere. When located on the limbs, functional impact, loss of independence and deterioration of general condition are often more pronounced than in younger patients. Older patients with STS have more limited access to multimodal treatments due to the comorbidities that are often present. In a retrospective study involving 11 centres in France and the USA, 34% of patients aged over 75 received supportive care only. A specific additional geriatric assessment is often essential to ensure appropriate treatment is offered.

Treatment

- ***Localised stage, resectable***

The standard treatment is surgery performed by a surgeon trained in the NETSARC+ network ("en bloc" resection with a minimum margin planned according to the histological type, peri-operative treatments, procedure-related morbidity and the presence of anatomical barriers).

Adjuvant radiotherapy is usually recommended in the case of intermediate- or high-grade deep tumour (FNCLCC G2-3). This is discussed at an MDTM on a

case-by-case basis for superficial lesions of over 5 cm, regardless of the grade, and for low-grade deep lesions of any size. Pre-operative radiotherapy has not clearly shown its value in treating retroperitoneal sarcomas, perhaps with the exception of low-grade sarcomas and liposarcomas.

Chemotherapy must be discussed pre-operatively in the case of high-grade (FNCLCC G3) or rapidly progressing tumours to facilitate surgery, and in histological types deemed to be chemosensitive. Adjuvant chemotherapy does not improve overall survival and is not a standard treatment for STS. The sarculator nomogram is an effective tool which can be useful in identifying candidates for neoadjuvant and, in rare cases, adjuvant chemotherapy in patients with a predicted 10-year overall survival probability of lower than 60%. Chemotherapy can be discussed for these patients with a high risk of mortality. This tool should be used with caution in older patients whose 10-year life expectancy may be influenced by numerous factors such as natural life expectancy and comorbidities.

In the case of marginal resection (R1, invaded microscopic margins) which is unplanned or macroscopically incomplete (R2), post-operative treatment is not standardised and must be discussed at a specialised multidisciplinary team meeting within the NETSARC+ network.

- *Localised stage, unresectable tumour (locally advanced)*

Anthracycline-based chemotherapy and/or radiotherapy must be discussed to make surgery possible.

If resection is impossible, treatment will be exclusively chemotherapy and/or radiotherapy based.

- *Metastatic stage*

The standard treatment for metastatic sarcomas is chemotherapy.

Isolated pulmonary metastases can be treated locally (surgery, stereotactic radiotherapy, interventional radiology) whenever possible, after being discussed at an MDTM.

The chemotherapy options are:
- monotherapy with anthracyclines (doxorubicin 75 mg/m^2 D1, D1 = D21 provided there is normal cardiac function), except when a rapid response is required in older patients in excellent general condition, when dual therapy with the addition of ifosfamide (or dacarbazine for leiomyosarcoma) can be discussed;
- first-line pazopanib was assessed as being non-inferior to doxorubicin monotherapy specifically in a population aged over 60;
- some histological subtypes have specific chemosensitivities:
  - weekly taxol for the treatment of angiosarcoma;
  - gemcitabine and dacarbazine for the treatment of leiomyosarcoma;
  - imatinib to treat dermatofibrosarcoma;
  - antiangiogenics to treat alveolar soft part sarcoma.
- second-line and subsequent-line treatment in PS 0-1 patients and extra caution in older patients:
  - ifosfamide (according to renal function);
  - trabectedin (not currently covered by the French health insurance system for this indication);
  - pazopanib (taking into account possible drug interactions and cardiac function);
  - eribulin (liposarcoma);
  - dacarbazine;
  - gemcitabine (angiosarcoma and leiomyosarcoma);
  - oral metronomic cyclophosphamide or etoposide.
- in the case of impaired general condition: palliative treatment.

According to their general condition and the clinical situation, patients will be invited to participate in dedicated clinical trials, such as the GE-RICO-14 trial comparing doxorubicin with cyclophosphamide as first-line metastatic treatment for soft tissue sarcomas in patients aged over 65.

Monitoring

• Localised stage

First 5 years: clinical and imaging every 6 months (thoracic CT scan and primary site CT or MRI scan).

Next 5 years: annual clinical and imaging.

• *Advanced stage*

Clinical and radiological (CT) assessment every 3 to 6 months according to the progression profile.

Specific features of uterine sarcomas and desmoid tumours

• *Specific features of uterine sarcomas*

These include uterine leiomyosarcomas (LMS), endometrial stromal sarcomas (ESS) and undifferentiated endometrial sarcomas (UES).

The treatment of these carcinomas at localised stage involves total hysterectomy without fragmentation. Systematic oophorectomy has not clearly proven its benefit. Lymphadenectomy contributes to morbidity without proven efficacy. It should only be considered for ESS where lymph node involvement may be present in 10% of cases.

Adjuvant radiotherapy is not usually recommended for LMS. The same applies for adjuvant chemotherapy.

ESS are potentially hormone-sensitive cancers. Anti-hormone therapy must be reserved for advanced forms (aromatase inhibitors, LH-RH analogues). Tamoxifen is contraindicated due to its agonist activity in the endometrium, like hormone treatments for menopause.

High-grade SSE and UES are cancers with high metastatic risk which often justify the use of adjuvant chemotherapy despite the lack of level A evidence.

• *Specific features of desmoid tumours*

Non-metastasising tumours with uncertain potential for progression.

These are very rare in older adults and have an unpredictable natural history with spontaneous stabilisations or regressions. When there is no involvement in high-risk locations, initial close monitoring (a "wait & see" approach) is usually offered as absence of progression is common (progression-free survival rate: 50% at 5 years and spontaneous regression rate of 20% to 30%). MRI is the chosen monitoring method. Decisions must be made on a case-by-case basis at the specialised multidisciplinary team meeting, starting with the treatments

with the lowest morbidity: non-steroidal anti-inflammatory drugs (with an increased risk in older adults), anti-hormone therapy, low-dose chemotherapy (methotrexate, vinca alkaloids), VEGFR/PDGFR tyrosine kinase inhibitors (sorafenib, pazopanib), but also radiotherapy or thermal ablation/cryotherapy in interventional radiology. When systemic treatment is indicated, the agents associated with the best response rates are as follows (in decreasing order of response rate): combination of low-dose methotrexate and vinblastine/vinorelbine, pazopanib, sorafenib, imatinib. Desmoid tumour surgery often causes morbidity and must be reserved for patients who are refractory to less invasive treatments.

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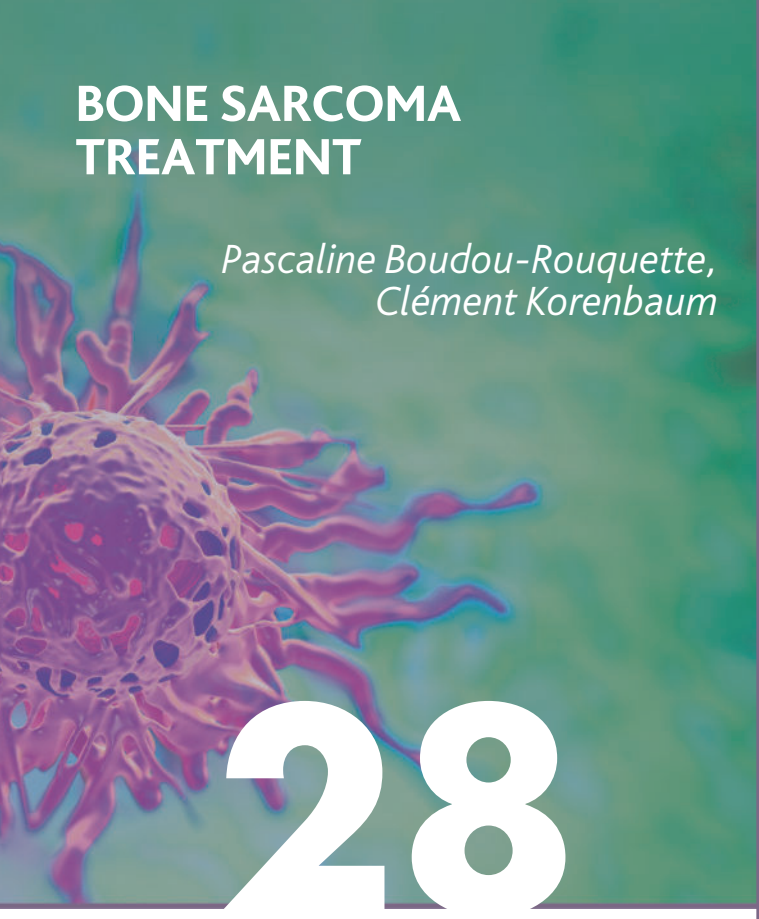
BONE SARCOMA TREATMENT

Pascaline Boudou-Rouquette, Clément Korenbaum



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In the absence of specific recommendations for older patients, the authors have drawn up treatment proposals based on the medical literature and their clinical experience at expert centres.

These are rare tumours and the quality of their initial treatment is a determining factor for prognosis. Best practices involve consulting a multidisciplinary team in a specialist centre at each step, including prior to biopsy.

The most common bone sarcomas in older patients are chondrosarcomas. Osteosarcomas are rarer and Ewing tumours rarer still.

Biopsy, which has serious consequences, is the first procedure discussed at the MDTM. It must be planned taking into consideration the positioning (approach) so as to avoid contaminating nearby important structures, and using a path that enables en bloc removal with the tumour resection.

For osteosarcomas and chondrosarcomas, the initial radiological assessment includes local imaging with standard X-ray, bone MRI/CT of the superjacent and subjacent joint, and bone scintigraphy + thoracic CT scan for staging.

The cornerstone of treatment is "en bloc" cancer surgery performed by an expert surgeon. Except for when the tumour is inaccessible for surgery or surgery is refused, exclusive curative local radiation is not indicated in the first-line treatment of osteosarcoma and chondrosarcoma due to these tumours having a low level of radiosensitivity. Local treatment of Ewing sarcomas involves surgery, radiotherapy or a combination of the two.

At a localised stage, standard treatment for high-grade osteosarcomas and Ewing tumours combines neoadjuvant chemotherapy, surgery (+/- radiotherapy for Ewing tumours) and adjuvant chemotherapy, but this has only been confirmed by phase III trials in younger populations.

Osteosarcomas

Advanced age is an unfavourable prognostic factor in osteosarcomas. In older patients, high-dose methotrexate is not used due to its nephrotoxicity. Protocols combining doxorubicin ± cisplatin ± ifosfamide can be offered to selected fit patients (AP-AI protocol for example). The following can be effective at a metastatic stage, as second- or third-line treatment: ifosfamide ± etoposide, gemcitabine ± docetaxel, celltop-endoxan, metronomic etoposide, endoxan-sirolimus, regorafenib or cabozantinib. Local metastases treatments (surgery, interventional radiology, stereotactic radiotherapy) are discussed on a case-by-case basis.

Dedifferentiated chondrosarcomas

These tumours are less chemosensitive than osteosarcomas and Ewing tumours. In metastatic forms and on a case-by-case basis in localised forms, chemotherapy with doxorubicin ± cisplatin or ± ifosfamide may be indicated.

Ewing tumours

Patients will be offered dual or triple therapy using the most active drugs for this disease (doxorubicin, vincristine, actinomycin, etoposide, ifosfamide, cyclophosphamide).

Other rare bone sarcomas

A recent retrospective study by the French Sarcoma Group showed that in a cohort of 145 patients with rare bone sarcomas (leiomyosarcomas, UPS and sarcomas in the radiation field), being aged over 60 was the only detrimental prognostic factor in terms of disease-free survival, in a univariate analysis. Neo and adjuvant chemotherapy did not improve overall survival but there was a tendency towards better disease-free survival.

One of the key elements in delivering medical treatments to older patients is multidisciplinary expertise in analysing toxicity risks: geriatrician, dietitian, pharmacist, etc.

Monitoring

Monitoring is carried out every 4 months with local imaging and a thoracic CT scan for the first 2 years, then every 6 months until the 5th year, followed by annually up to 10 years.

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CHRONIC LYMPHOCYTIC LEUKAEMIA TREATMENT

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Initial assessment

CLL diagnosis is easy and involves investigating chronic hyperlymphocytosis (> 5000/mm^3 for over 3 months). Simple lymphocyte phenotyping of circulating lymphocytes enables a diagnosis to be made (CD5+, CD23+, FMC7-, low CD79b, low surface immunoglobin expression). CLL is diagnosed if the Matutes score is > 3. Over 30% of patients will not require treatment.

Therapeutic indications

IWCLL 2008 recommendations. Treatment in the presence of at least one active disease criterion:[1]

- bone marrow failure with increased anaemia/thrombocytopenia;
- bulky (> 6 cm below the costal margin) or progressive or symptomatic splenomegaly;
- bulky (> 10 cm) or progressive or symptomatic adenopathy;
- lymphocyte count increase of > 50% in 2 months or lymphocyte doubling time < 6 months;
- anaemia/immune thrombocytopenia not responding adequately to corticosteroids;

- general signs: weight loss of > 10% in 6 months, asthenia with ECOG PS ≥ 2, fever > 38° for over 2 weeks with no signs of infection, night sweats > 1 month with no signs of infection.

• Pre-treatment assessment only in the case of therapeutic indication:

- haemolysis test, detection of hypogammaglobulinemia, viral serologies for hepatitis B in particular, creatinine level, LFT;
- thoracic-abdominal-pelvic scan;
- detection of p53 mutation using FISH and molecular biology (CLLs with p53 abnormality do not respond to chemotherapy);
- definition of IGHV mutational status (patients with p53 abnormality respond well to chemotherapy).

• Treatment stratification according to 3 parameters (FILO group 2021 recommendations):

- presence or absence of 17p deletion or TP53 mutation (resistance to immunochemotherapy);
- eligibility or ineligibility for FCR (Fludarabine Cyclophosphamide Rituximab) chemotherapy;
- unfavourable genetic factors (complex karyotype and 11q deletion);
- note the disappearance of treatment stratification according to the CIRS comorbidity score used to identify FIT and UNFIT patients.

Current treatments and future directions: disappearance of chemotherapy

• First-line treatments in patients eligible for FCR chemotherapy with no 17p deletion or TP53 mutation

The standard treatment (FC-R) combining fludarabine, cyclophosphamide and rituximab has inferior progression-free survival and overall survival to the rituximab-Ibrutinib combination apart from in mutated CLLs.[3] This combination is the beginning of the end for chemotherapy apart from in patients without an unfavourable genetic factor who can still benefit from FCR chemotherapy.

- *First-line treatments in patients ineligible for FCR chemotherapy with no 17p deletion or TP53 mutation*

The bendamustine plus rituximab combination is inferior in terms of progression-free survival to the ibrutinib-rituximab combination, which has the same progression-free survival as ibrutinib. This suggests that it is not necessary to combine rituximab and ibrutinib.[4]

In unfit (CIRS > 6) patients, the standard treatment of GA101 or obinutuzumab combined with chlorambucil was previously inferior in terms of progression-free survival to obinutuzumab-ibrutinib[5] and the obinutuzumab-acalabrutinib combination.[6]

Finally, the obinutuzumab-venetoclax combination for a fixed period of 1 year also showed its superiority over the obinutuzumab-chlorambucil combination.[7]

Like in younger patients, this data puts an end to chemotherapy.

Therefore, if there are no unfavourable genetic factors, the FILO group recommends either chemotherapy-free protocols (ibrutinib or acalabrutinib or obinutuzumab [JA28]venetoclax pending the opinion of the French transparency commission) or immunochemotherapy (o-chlorambucil or bendamustine-rituximab). Use chemo-free protocols in patients with unfavourable genetics.

Long-term data on ibrutinib use is reassuring, with results not previously achieved. In the Resonate 2 study (comparing ibrutinib with chlorambucil), after 5 years of median follow-up, 58% of patients are still undergoing treatment and 70% are experiencing progression-free survival.[8] In much older patients, the dose often has to be reduced from 420 mg to 280 mg due to toxicities (infections, arthralgia, bleeding, diarrhoea, AF, haematological toxicities) but this does not seem to affect the results.[9] The cardiovascular tolerance profile of acalabrutinib compared with ibrutinib (less hypertension and arrhythmia) could favour the use of acalabrutinib in patients at risk of this type of complications.[10]

- *Treatment in cases of 17p deletion or TP53 mutation:*

- ibrutinib (420 mg per day).

In case of contraindication to ibrutinib:
- acalabrutinib (100 mg x 2/d) or R-idelalisib[JA29] (150 mg twice a day) or venetoclax (introduced at 20 mg/d then a gradual weekly increase to 400 mg in the 5th week).

• *Relapse treatment*[9]

3 parameters need to be considered:
- patient's general condition: Fit or Unfit;
- the type of treatment and the response to first-line treatment;
- response to first-line treatment > or < 3 years (refractory patients);
- 17p deletion or TP53 mutation.

Patients with 17p deletion or TP53 mutation will be offered the following solutions:
- ibrutinib: BTK (Bruton's Tyrosine Kinase) inhibitor. As monotherapy at a dose of 420 mg/d, 71% of patients are responsive (68% if 17p deletion). At 26 months, 75% of patients have not progressed;[11]
- acalabrutinib: same efficacy as ibrutinib as relapse treatment but a better cardiovascular tolerance profile (less hypertension and arrhythmia);[10]
- venetoclax (introduced at 20 mg/d then a gradual weekly increase to 400 mg in the 5th week).[12] The Murano trial, also evaluating venetoclax as relapse treatment but combined with rituximab and for a fixed treatment period of 24 months, showed its superiority over R-bendamustine;[13]
- idelalisib[JA30]: PI3K inhibitor. Combined with R for 6 cycles then continuously until progression. Superiority over R + placebo in a phase III trial including CLLs having progressed less than 24 months after the last treatment and which cannot receive other chemotherapies for one of the following reasons: clearance < 60 ml/mn, CIRS > 6, severe cytopenias. The overall response rate is 81%. At 2 years, 93% of patients have not progressed.[14]

Conventional chemotherapy has almost disappeared as first-line and relapse treatment. The choice will be made according to the comorbidities, particularly cardiovascular ones, (avoid BTK inhibitors) and the patient's preference: a fixed duration with obinutuzumab venetoclax (12 months as first-line treatment, 24 months as relapse

treatment) versus continuous treatment for BTK inhibitors.

Combinations of venetoclax-BTK inhibitors +/- anti-CD20 antibodies with a fixed duration according to the residual disease are currently being evaluated.

- *Associated treatments*

PCP and herpes virus and VZV reactivation prevention must be prescribed if immunochemotherapy is used. Prescribe intravenous polyvalent immunoglobulins in the case of recurrent infections and hypogammaglobulinemia.

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MYELODYSPLASTIC SYNDROME TREATMENT

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MDS diagnosis

A myelogram and a karyotype are required for MDS diagnosis and prognosis.

MDS classification

The WHO 2016[1] classification is currently used (Table 1).

Table 1: *MDS classification according to the WHO.*

WHO CATEGORY	BLOOD	BONE MARROW
Refractory cytopenia with unilineage dysplasia (RCUD): refractory anaemia (RA), refractory neutropenia (RN), refractory thrombocytopenia (TR)	Anaemia < 1% blasts	Dyserythropoiesis only < 5% blasts < 15% sideroblasts

RARS: refractory anaemia with ring sideroblasts	Cytopenia (2 or 3) < 1% blasts, no Auer rods	Dyserythropoiesis only < 5% blasts > 15% sideroblasts or ≥ 5% if SF3B1 mutation present
RCMD: refractory cytopenia with multilineage dysplasia: in at least 2 lineages	Cytopenia (2 or 3) < 1% blasts, no Auer rods	Dysplasia in more than 2 myeloid lineages < 5% blasts, no Auer rods, < 15% sideroblasts
RAEB-1: refractory anaemia with excess blasts-1	2-4% circulating blasts, no Auer rods	Dysplasia 1 or more lineages, 5-9% blasts, Auer-
RAEB-2: refractory anaemia with excess blasts-2	5-19% circulating blasts, +/- Auer rods	Dysplasia 1 or more lineages, 10-19% blasts, Auer +/-
MDS-U: unclassifiable	Cytopenia < 1% blasts	Dysplasia < 10% cells, 1 or more lineages + MDS-related cytogenetic abnormality, < 5% blasts
5q- related MDS	Anaemia Normal or high platelet count < 1% blasts	Normal or abnormal megakaryocytes with hypo-lobed nuclei, < 5% blasts 5q single anomaly, Auer-

Prognostic factors

The IPSS[2] prognostic score, which was used to distinguish 4 prognostic groups in terms of survival and risk of transformation into acute leukaemia (low risk, intermediate risk 1, intermediate risk 2, high risk), was replaced by the IPSS-R (revised).[3] This scoring system defines 5 prognostic groups: very good, good, intermediate, poor and very poor (Tables 2 and 3).

Geriatric approach to MDS according to Balducci

Balducci proposed a strategy that included independence and number of comorbidities in the treatment decision.[4] This approach has recently been updated to include other geriatric parameters.[5] Classification using the treatment decision tree proposed by Balducci has several limitations. It was never evaluated for MDS. In addition, the only age criterion of 85 years or over considers the patient to be frail and excludes them from specific treatment (Table 4). The recently proposed new score combining geriatric criteria (frailty and comorbidities) with the IPSS-R score seems more relevant as it improves the prognostic impact of the IPSS-R score in terms of overall survival.[6]

Therapeutic

- *Low risks according to IPSS*

Aim: improve quality of life.

- *Treat anaemia first of all*

EPO

EPO must be started **early** and at a **high dose**. The aim is to maintain a haemoglobin level of > 10 g/dL without exceeding 12 g/dL and to delay transfusion.

The response rates observed on EPO are around 50% with an average response duration of 24 months. The predictors of a good response are transfusion independence and an EPO level of less than 200 U/L and a bone marrow blast rate < 10%.[7] In the case of inefficacy, additional responses could be obtained with a low dose of a combination of EPO-GCSF or a combination of EPO-Lenalidomide.[8]

Table 2: *IPSS-R score calculation.*

Points	0	2	4	6	8
Cytogenetic	Very good	Good	Intermediate	Poor	Very poor
% BM blasts	< 5%	5 to 10%	11 to 20%	21 to 30%	
Haemoglobin g/dL	> 10	< 10			
Platelets G/L	> 100	< 100 and > 50	< 50		
PNN G/L	> 0.8	< 0.8			

Table 3: *IPSS-R.*

Prognostic groups	Number of points	Median overall survival (years)	Transformation into AML 25% (years)
Very good	0 to 2	8.8	NA
Good	3 to 5	5.3	10.8
Intermediate	6 to 7	3	3.2
Poor	8 to 9	1.6	1.4
Very poor	> 9	0.8	0.7

Table 4: *Classification according to L. Balducci*

Patient type	Parameters	Treatment
"Fit" patients	ADL and iADL are maintained No significant comorbidities No geriatric syndromes	Best treatment identical to in young patients
"Vulnerable" patients	ADL maintained iADL impaired Comorbidities are controlled Moderate cognitive impairment and/or depression No geriatric syndromes	Individually tailored treatment
"Frail" patients	Aged > 85 years ≥ 3 severe comorbidities Geriatric syndrome(s)	Exclusive supportive care Palliative care

Transfusions

Patients who are failing will need PRBC transfusion at fairly regular intervals and are therefore exposed to the risk of post-transfusion **iron overload**.

Chelation is recommended if the serum ferritin level is over 1,000 or if there is transfusion of more than two red cell units per month for a year.[9]

The risk-benefit ratio for chelation therapy is difficult to define in older patients.[10]

There are three molecules: **deferoxamine** (SC over 8 to 12 hours, 5 to 7 days a week) which has limitations in terms of its use and carries a risk of cochleovestibular and retinal involvement.

Deferasirox, administered orally, is used if renal function is normal. Its adverse events are digestive problems, skin rashes and increased creatininemia.[11]

Oral **deferiprone** only has an MA for the treatment of thalassemia and exposes patients to a risk of agranulocytosis in 1 to 2% of cases.

Luspatercept

This molecule traps TGF-β ligands which inhibit erythropoiesis. Particularly interesting results in patients failing EPO treatment were reported for MDS with ring sideroblasts (ARS) and/or SF3b mutation.[12] It should be covered by the French health insurance system from 2022.

Treating thrombocytopenia

Platelet transfusions with a high risk of alloimmunisation make the patient refractory to platelet transfusions.

Androgens such as danazol improve thrombocytopenia in some patients.[13] Thrombopoietin receptor agonists (TPO) are being developed for MDS.

Specific case of 5q- syndromes with low or int-1 IPSS score

This syndrome is frequently associated with anaemia and a normal or increased platelet count. EPO treatment can be tested. If it fails, **lenalidomide** at a dose of 10 mg/d, 21 days per month, achieves excellent results with 67% transfusion independence.[14] Moderate to severe neutropenia and thrombocytopenia were observed

in 55% and 44% of patients respectively. Renal failure requires a dose adjustment.

- *High risks according to IPSS*

Aim: slow transformation into AML and prolong overall survival.

Allograft

This is the only curative treatment. Allograft is only offered to patients aged over 65 and requires them to be in excellent general condition.

Demethylating agents

Azacitidine has an MA for high-risk patients.

It is administered subcutaneously at a **dosage of 75 mg/m²** for **7 days/months**.

Treatment efficacy is usually assessed after **4** to **6 cycles**.

The question of adapting the dosage in people with renal failure remains.

Azacitidine slows MDS progression to AML with a median transformation time of 13 months versus 7 months for standard treatment, and increases overall survival, with a median of 24.5 months versus 15 months.[15] The study showed improvement in cytopenia in 49% of patients with transfusion independence in 45%.

The treatment shows similar benefits in terms of survival in patients aged over 75 similar and younger patients.

Overall survival is affected by an ECOG PS > 1, an intermediate or unfavourable karyotype, circulating blast and transfusion requirement of more than 4 PRBC units every 8 weeks.

The major (grade III-IV) toxicity of the treatment is haematological: 13% anaemia, 61% neutropenia, 50% thrombocytopenia. Toxicity is not different in patients aged over 80.

Decitabine, another demethylating agent, can also be used in second-line treatment in high-risk patients.

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MYELOMA TREATMENT

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Systemic treatment

Treatment is started when the disease is symptomatic, so when the patient presents with at least one of the following symptoms: hypercalcemia, renal failure, anaemia or bone lesion.[1] New criteria have been drawn up for starting earlier treatment: bone marrow plasmacytosis > 60% or a kappa/lambda serum light chain ratio > 100 or more than one focal lesion (> 10 mm) on the MRI.[2] Myeloma treatment in patients aged over 65, classified as older and not eligible for autograft, was transformed with the introduction of new molecules, and two drug classes in particular: immunomodulatory drugs (IMiDs) and proteasome inhibitors. Melphalan + prednisone (MP) standard treatment, developed by Dr Alexanian in the 1960s, can be combined with thalidomide (MPT) or bortezomib (MPV),[3-6] or a combination of lenalidomide + dexamethasone (Rev/Dex) can be used.[7]

First-line treatment

There are currently 4 combinations with an MA: melphalan + prednisone + thalidomide (MPT), melphalan + prednisone + bortezomib (MPV) and lenalidomide + dexamethasone, and what can now be considered a

new standard treatment, the combination of lenalidomide + dexamethasone + daratumumab.

The MPV combination is preferred in cases of aggressive disease, thromboembolic history or unfavourable cytogenetic profile, whereas MPT is better if fully outpatient treatment is preferred. MP alone is still offered to particularly "frail" patients. The lenalidomide + dexamethasone combination is superior to MPT,[7] and a recent study showed the superiority of bortezomib + lenalidomide + dexamethasone over the lenalidomide + dexamethasone combination.[8]

Both treatments, MPT and MPV, can be offered to patients with renal failure. Lenalidomide can also be prescribed in this situation, but the dose must be adapted to the creatinine clearance. The older the patient is, the more the dose must be reduced. The patient must be monitored very closely at the start of treatment, in order to adapt the doses to the toxicity in particular. A monthly consultation is required for the first six months, followed by a consultation every three months.

The treatment duration is 18 months for the MPT combination, nine 6-week cycles for MPV and at least 18 months for Rev/Dex. Maintenance treatment can be considered. The Daratumumab/Rev/Dex combination is given until progression. Prophylactic antithrombotic therapy, at least aspirin-based, is always combined with MPT and Rev/Dex (whenever IMiDs are prescribed), but this prophylaxis is not essential for MPV. On the other hand, an antiviral prophylaxis is systematically combined with MPV to avoid reactivating the herpes zoster virus. Valacyclovir, 500 mg x2 per day, may be used.

Second-line treatment

The lenalidomide + dexamethasone combination has an MA for this indication. It is particularly indicated if the first-line treatment was MPV. On the other hand, if the initial treatment was Rev/Dex, MPV is the preferred regimen. The initial treatment may be restarted if delayed relapse occurred after treatment was stopped (at least 6 months). Another combination particularly suited to older patients is bendamustine + bortezomib + dexamethasone.[9] The decision is based on the comorbidities and the toxicity of previous treatments, neurotoxicity in particular.[10]

Biphosphonate-based bone disease treatment is combined with systemic treatment after a dental assessment.

Recent therapeutic developments

Four major trials showed the benefit of combining a monoclonal antibody, an anti-CD38 and daratumumab with standard treatments.

As first-line treatment, MPV + daratumumab is superior to MPV[11] and adding daratumumab to the lenalidomide-dexamethasone combination produces remarkable results.[12] This trial included patients aged over 65, 45% of whom were aged over 75. Patients were randomised to lenalidomide-dexamethasone or lenalidomide-dexamethasone + daratumumab until progression. The results are impressive. Progression-free survival (PFS) at 30 months is 70.6% in the daratumumab arm compared with 55.6% in the control arm ($p < 0.001$). The percentage of patients achieving a complete or better response is 47.6% compared with 24.9% ($p < 0.001$), and residual disease is undetectable in 24.2% compared with 7.3% ($p < 0.001$) (daratumumab versus control respectively). The latest update,[13] with median follow-up of 56 months, reports median PFS not achieved with the lenalidomide + dexamethasone + daratumumab combination and PFS of 34 months in the daratumumab arm. Median overall survival is not reached in either arm. Slightly more cytopenia and pneumonia is observed with daratumumab. This combination now has an MA for first-line treatment in patients who are not eligible for autograft. This is a new standard treatment for myeloma, and the subcutaneous delivery of daratumumab makes it easier to administer.

As relapse treatment, the addition of daratumumab to bortezomib-dexamethasone[14] and the addition of daratumumab to lenalidomide-dexamethasone[15] have an MA after at least one line of treatment.

Another important therapeutic development is the reduction of corticotherapy, which is a particularly significant modification in older patients. A trial[16] compared the standard treatment (before the introduction of daratumumab) from first-line treatment with lenalidomide plus dexamethasone until progression with an identical arm but without corticosteroids after 9 months.

Improved event-free survival, identical PFS and even a tendency to better overall survival were observed in patients with fixed-term corticotherapy.

The place of radiotherapy in the treatment of multiple myeloma and solitary plasmacytomas in older patients

Radiotherapy is included in the multidisciplinary treatment of bone localisations of haematological origin in older patients such as multiple myelomas, plasmacytomas and lymphomas.[17-20]

Radiotherapy (RT) can be used as radical treatment (for plasmacytomas), but also as consolidation treatment (for diffuse myelomatosis) or analgesic treatment.[20]

The aims of RT are:
- antitumour effect;
- pain relief;
- fracture consolidation and prevention;
- decompression, neurological improvement.

A specific consideration when treating older patients is that radiotherapy must be tailored to the patient, with a radiation schedule and technique tailored to the patient's age, general condition, ability to travel and comorbidities.[20] The volume, duration and number of fractions must be adapted to each patient - hypofractionated radiotherapy (1 x 8 Gy, 2 x 6.5 Gy, 5 x 4 Gy, 10 x 3 Gy).

It is also highly important to be able to treat this population of patients with appropriate low-toxicity techniques. Specific cases such as the patient having a pacemaker must be assessed and the treatment and monitoring adapted.[20]

New radiation techniques such as intensity-modulated radiotherapy (IMRT) seem particularly interesting for older patients.[20] Figure 1 shows the dose distribution for tomotherapy treatment of a plasma cell lesion in an older patient treated with several lines of systemic treatment.

During the Covid pandemic, hypofractionated radiotherapy protocols were recommended by learned societies such as the ILROG (International Lymphoma Radiation Oncology Group) with, for myelomas, a single session

of 8 Gy of radiotherapy, which is acceptable apart from in the case of spinal cord compression, when 5 x 4 Gy can be offered. These protocols are particularly well suited to older patients.[21,22]

Conclusion

Myeloma treatment in older patients using new molecules and new radiation techniques must be delivered in a tailored way according to the patient's profile, history and comorbidities.

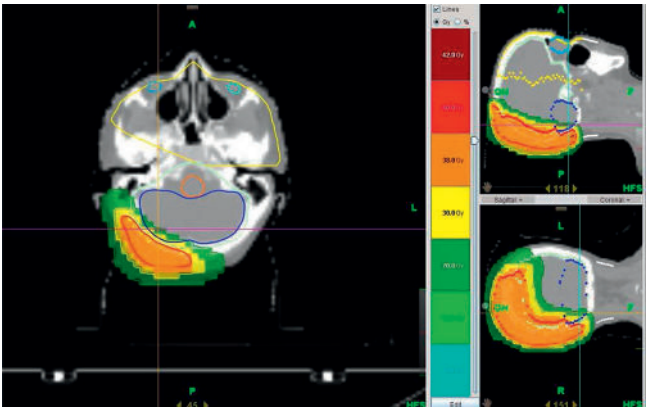

Figure 1: *Dose distribution for tomotherapy treatment of a plasma cell lesion in an older patient treated with several lines of systemic treatment. This highly conformal radiotherapy (IMRT) prevents toxicity that may be related to irradiating organs at risk such as the brain and eyes in the case presented here.*

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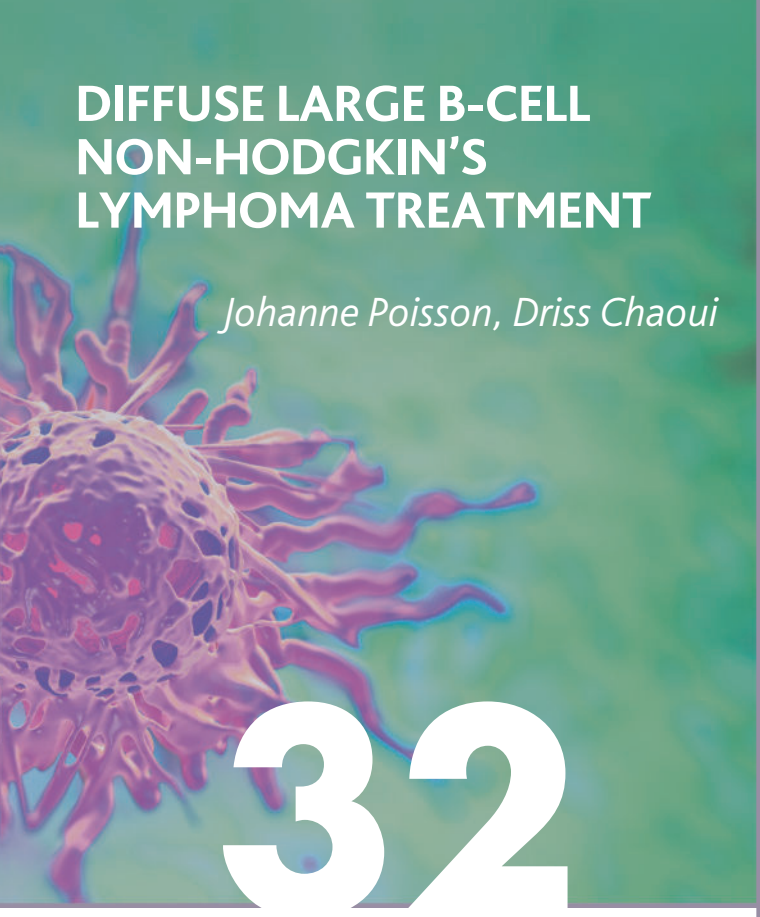
DIFFUSE LARGE B-CELL NON-HODGKIN'S LYMPHOMA TREATMENT

Johanne Poisson, Driss Chaoui



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Diagnosis

Diagnosis requires a good quality histological sample (lymph node or extranodal).

Initial and pre-treatment assessment

The initial assessment must include, among other things, an FBC to detect cytopenia which may indicate suspected macrophage activation syndrome or bone marrow invasion; LDH as a disease aggressiveness factor; and staging with a thoracic-abdominal-pelvic scan. A PET scan is recommended at the diagnosis stage and at the end of treatment. An osteomedullary biopsy (or myelogram) can be discussed in certain cases (cytopenia with suspected myelodysplastic syndrome). Cardiac ultrasound (LVEF before using anthracyclines) and viral serologies for HIV and hepatitis B and C are part of the initial assessment.[1]

Standard prognostic factors for DLBCL

After an immunohistochemical +/- molecular morphological analysis, the germinal centre (GC) or non-germinal centre phenotype (ABC), as well as the high-grade

double- or triple-hit NHL subtype (C-MYC, BCL2, BCL6 rearrangement) are determined. Patients with a double- or triple-hit NHL have a very poor prognosis and have a higher risk of neuromeningeal involvement.

The age-adjusted International Prognostic Index (aaIPI) (around 60 years) includes 3 factors: the WHO status according to ECOG (0, 1 versus 2, 3, 4), LDH levels (normal versus high) and the stage according to the Ann Arbor staging system (I, II versus III, IV).

It is important to assess the risk of neuromeningeal relapse with the CNS-IPI which includes age, LDH, performance status, stage, extranodal involvement and renal or adrenal gland involvement. Patients with a high CNS-IPI have a post-R-CHOP risk of neuromeningeal relapse of around 10%, requiring appropriate exploratory and preventive measures.[2]

Treatments

• *Therapeutic goal*

In the Coiffier *et al.* cohort, 10-year recurrence-free survival after first-line treatment of 8 courses of R-CHOP chemotherapy (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2, prednisone 1 mg/kg from D1 to D5) in 60- to 80-year-old patients with DLBCL was 64%.[3] According to Pey-rade *et al.,* in patients aged over 80 treated with 6 courses of R-miniCHOP (rituximab 375 mg/m^2, cyclophosphamide 400 mg/m^2, doxorubicin 25 mg/m^2, vincristine 1 mg/m^2, prednisone 40 mg from D1 to D5), 47% showed recurrence-free survival at 2 years.[4] These results support the fact that the therapeutic goal is cure, even in older and much older patients.

• *Standard treatments*

For patients aged 60 to 80, like for younger patients, the number of courses is determined by the aaIPI score. A total of 4 courses must be administered to patients with an aaIPI score = 0, and a total of 6 courses to other patients. The standard chemotherapy is R-CHOP with a 21-day cycle. Polatuzumab (anti-CD79 antibody conjugated to MMAE spindle poison) combined with R-CHP improves progression-free survival compared with R-CHOP. This treatment does not have an MA.[5]

For patients aged over 80, the standard treatment is 6 courses of R-miniCHOP with a 21-day cycle regardless of the aaIPI score.[4] Pre-phase treatment on D7 of R-miniCHOP is recommended, combining prednisone (60 mg/m^2) with vincristine 1 mg total dose. This reduces serious complications occurring in the first cycle.[1] Neuromeningeal prevention is still debated. It is guided by the CNS-IPI score.

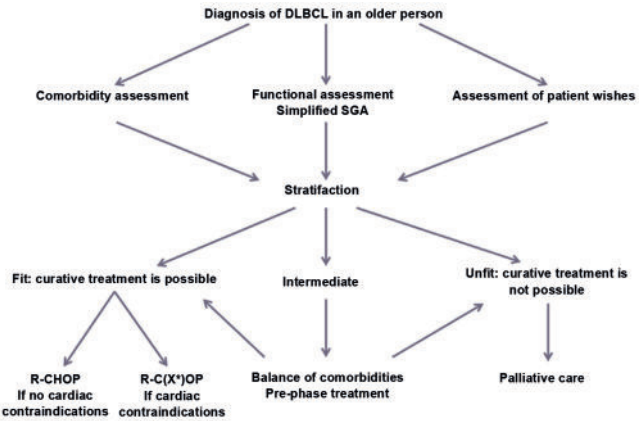
• *Specific characteristics of older patients*

Take comorbidities into accountOlder patients have more comorbidities than younger patients. These comorbidities may require the standard regimen to be adapted:[6]

- a left ventricular ejection fraction < 50% contraindicates the use of anthracyclines. They can be eliminated (R-COP)[7] or replaced by etoposide (R-CEOP). Fields *et al.*[8] suggested replacing doxorubicin with gemcitabine (R-COP at D1 + gemcitabine at D1 and D8) with a 21-day interval between cycles. The median age was 75 years. The patients included in the study had an LVEF < 50%. 2-year overall survival was 55% and the median progression-free survival (PFS) was 16 months with 49% showing PFS at 2 years. Grade 3/5 haematological toxicity was found in 34% of patients. Three patients died of cardiac complications and 5 grade 3/4 and 15 grade 1/2 cardiac events were observed, reflecting the frailty of this population;
- neuropathy contraindicates the use of vincristine;
- anti-diabetic measures must be put in place in diabetic patients in the first 5 days of each cycle due to the use of corticosteroids;
- at diagnosis, frail patients and patients with a significant impairment of general condition can benefit from pre-phase chemotherapy with corticotherapy alone, corticotherapy combined with vincristine or COP or R-COP chemotherapy. Standard R-CHOP or R-miniCHOP chemotherapy can be used from the second course onwards.[9]***Take the standardised geriatric assessment (SGA) into account***

It was shown that adapting the chemotherapy protocol and dosage according to comorbidities and SGA criteria (ADL-IADL) achieved a high level of efficacy while limiting toxicity.[10]

A recent retrospective study including patients aged over 70 with DLBCL confirmed this data. A frailty score was assigned to 5522 patients then confirmed in 5262 others. Three groups were identified: Fit, unfit and frail. 2-year survival was 82%, 47% and 14% respectively. R-CHOP is preferable to R-miniCHOP for fit patients. However, for unfit and frail patients, R-CHOP is not superior to R-miniCHOP and an anthracycline-free regimen was associated with a shorter survival time. [11] An easy-to-use application was introduced: https://wide.shinyapps.io/app-frailty/. An Italian prospective study also classified patients into 3 groups: fit, intermediate and frail. No significant improvement in survival was observed with curative treatment versus tailored treatment in intermediate and frail groups.[12]



- *Supportive care*

Preventing febrile neutropenia using granulocyte colony-stimulating factors (G-CSF) is crucial and must be systematic in patients over 60 with DLBCL and undergoing R-CHOP chemotherapy, but also in patients over 80 treated with R-miniCHOP (40% grade 3 or higher neutropenia).[4,13] It reduces serious infectious complications and avoids reducing the dose intensity by maintaining the interval between chemotherapy courses and doses.[14]

PCP and herpes virus and VZV reactivation prevention must be prescribed for the duration of the treatment and for at least 6 months after the last course of chemotherapy. In the case of recurrent infections, the patient must be tested for hypogammaglobulinemia and treated with intravenous polyvalent immunoglobulins.

For hepatitis B, before introducing rituximab, any positivity in unvaccinated patients (isolated positivity of anti-HBs Abs) must be accompanied by a hepatitis B viral load. Treatment is recommended for patients with positive antigens (Ag) and patients with isolated positive anti-HBc Abs. Reactivations also occur in patients considered to be cured (positive anti-HBs Ac and anti-HBc). They must be closely monitored along with viral load if preventive treatment is not prescribed, but the current trend is to treat them as well. Hepatitis C does not contraindicate the use of rituximab. For all cases of hepatitis with positive viral load, a complete assessment must be carried out by hepatologists before commencing treatment (FibroTest, etc.).[15]

- *Relapse treatment*

Patients aged over 60 are not eligible for autograft. Standard salvage treatments such as R-ESHAP in older patients and R-GemOx have a very low cure rate. Tafasitamab until progression (anti-CD19 antibody) combined with lenalidomide for 12 months, which is currently available with a temporary authorisation for use (ATU) in France for second-line treatment for patients who are ineligible for CAR T-cell therapy, shows very promising results. The median age of included patients was 71 years (41-86). After over 35 months of monitoring, the median PFS was 23.5 months and the median OS was 45.7 months versus 7.6 months and 15.5 months respectively for third-line treatment.[16]

Two types of CAR T-cells (chimeric antigen receptor T-cells) have had an MA (tisagenlecleucel and axicabtagene-ciloleucel) for third-line treatment since 2019. This procedure, which was initially reserved for patients aged under 70 due to the risk of serious complications relating to neurotoxicity and cytokine release syndrome, is currently accessible to patients in good general condition. Ram *et al.* recently reported a retrospective study comparing patients aged under and over 70 after matching. No significant difference was observed in terms of toxicity and IS and PFS.[17]

- *Palliative care*

This concerns patients who are very frail due to comorbidities, have a complete loss of independence and

whose quality of life does not make a curative treatment "reasonable". Radiotherapy can be offered in cases of localised DLBCL in frail patients or in certain palliative situations. Corticotherapy +/- etoposide and chlorambucil or cyclophosphamide (CEP) may relieve symptoms (particularly painful ones) relating to the lymphoma.

In conclusion, significant progress has been made, particularly in terms of relapse and the transition to an IPI including geriatric parameters.

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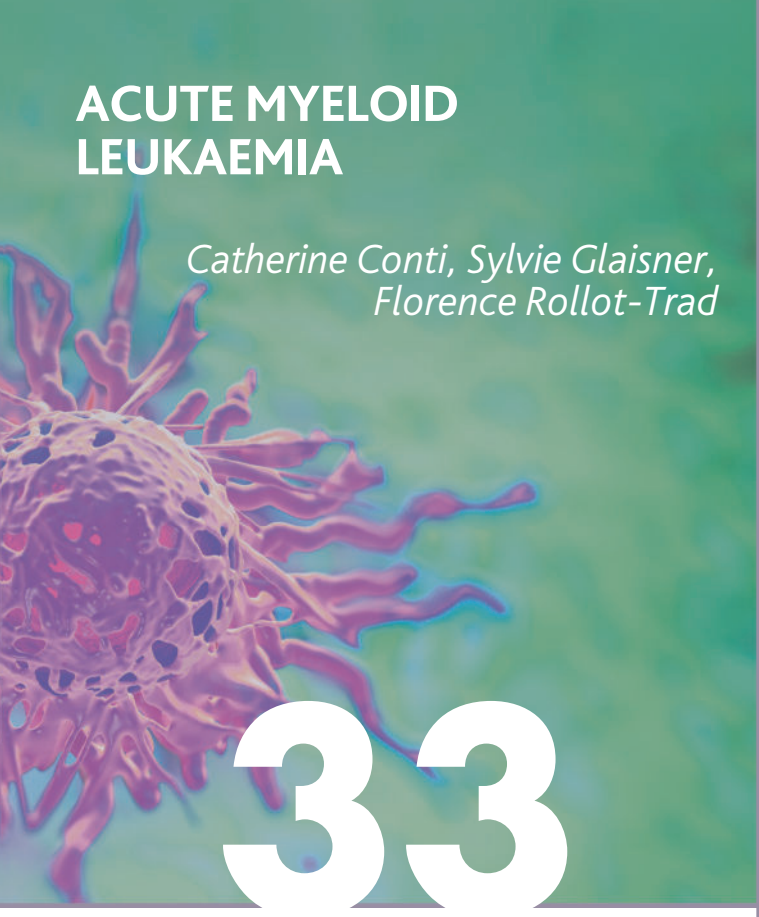
ACUTE MYELOID LEUKAEMIA

Catherine Conti, Sylvie Glaisner, Florence Rollot-Trad



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Acute myeloid leukaemia is an older person's disease, with a median age at diagnosis of 68 years and incidence gradually increasing beyond 70 years. More than 30% of patients with AML are aged over 75.

Overall survival (OS) has increased in recent years but varies according to age with 5-year OS of 60% in patients aged under 50 compared with less than 20% in patients aged 65 to 74, and under 5% after the age of 75.

Like with numerous other diseases, age remains a determining factor in the therapeutic approach but must not be the only decision-making criterion. Other prognostic variables directly related to the disease must be taken into account.

Definition, diagnosis and prognosis

Acute myeloid leukaemia (AML) = clonal diseases characterised by the proliferation of blasts, precursors to the myeloid lineage which completely or partially lose their ability to differentiate.

Diagnosis is based on a bone marrow sample which is also used to evaluate the disease prognosis: WHO 2016

classification including cytology, immunophenotyping and genetic study based on the karyotype, in situ hybridisation (FISH) exploring some genes of interest and molecular biology exploring the expression of a gene panel (myeloid panel) with a diagnostic, prognostic or therapeutic benefit (targeted therapy).

Diagnosis:
- bone marrow smear (myelogram) describing > 20% of myeloid-like blasts.

Prognosis:
- cytogenetic study;
- blast immunophenotyping;
- molecular study, which can also guide some therapeutic choices (targeted therapies).

Diagnosis and prognosis:

1. Karyotype

Cytogenetic risk			5-year survival
FAVOURABLE	t(8;21)(q22;q22) inv(16)/ t(16; 16)(p13q22) t(15;17)(q22;q 12-21)	CBF LAP	60-80%
INTERMEDIATE	Normal karyotype +8, +21 Other abnormalities		≈ 40-50%
UNFAVOURABLE	-7/del7q, -5/del5q, add5q 3q26, 17p abnormalities 11 q23 except t(9;11) t(6;9), t(9;22) Complex karyotypes (>3)		< 20%

Grimwade, Blood 1998

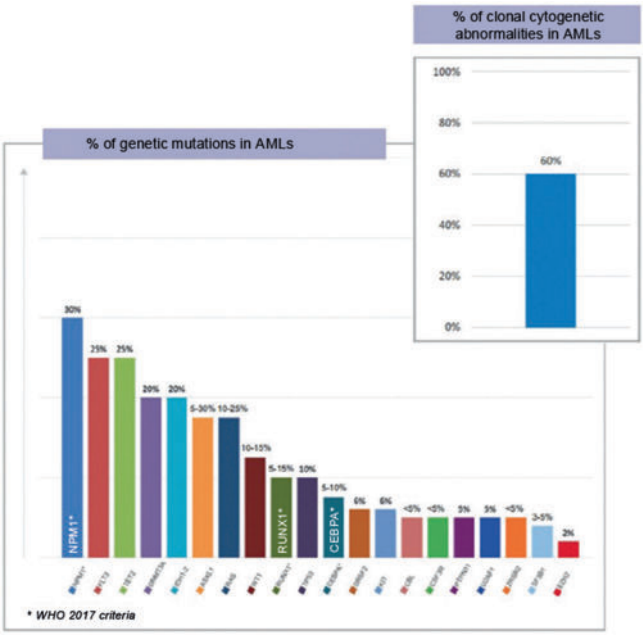
2. Myeloid NGS (Next Generation Sequencing) panel

- According to the WHO 2017, the NPM1, CEBPA and RUNX1 mutation status is included in the diagnostic criteria of the WHO classification of acute myeloblastic leukaemia with somatic mutation ("AML with genetic mutation").

- Prognostic value (2017 ELN recommendations[1]) for defining molecular factors for unfavourable prognosis (non-mutated NPM1 and high FLT3-ITD, RUNX1 mutation, ASXL1 mutation, TP53 mutation) or favourable prognosis (NPM1 mutation without FLT3-ITD or with low FLT3-ITD, biallelic CEBPA mutation). This molecular prognosis stratification is in addition to cytogenetic prognosis stratification. The WHO 2017 also places the

prognostic value of molecular abnormalities in the same cytogenetic groups: unfavourable prognostic value of CKIT mutation in AMLs with t(8;21)(q22; q22.1) or inv(16)(p13.1q22)/t(16;16)(p13.1;q22), a WT1, TET2, ASXL1, DNMT3A or IDH1/2 mutation in AMLs with normal karyotype, a TP53 mutation in AMLs with complex karyotype.

- Theranostic contributions guiding the choice of targeted therapy: looking for FLT3, cKIT, IDH1, IDH2 or NPM1 mutation.



In older patients

Survival has changed very little over the last 4 years in patients aged over 65: median survival of 4 to 6 months from 65 to 75 years and 2 to 3 months from 75 to 90 years.[2] Many older patients do not benefit from the specific treatment of the disease, which accounts for the poor results.[3,4]

Prognostic factors involved in poor control of the disease in older patients

- Resistance to treatment relating to cytogenetic or genetic abnormalities, leukaemia secondary to chemo-radiotherapy-based treatment or other blood disease.

- The patient's general condition is rarely taken into account in studies so extrapolation is difficult.

In older patients, the main cause of death is directly linked to disease complications and progression rather than treatment complications (TRM), implying that insufficiently effective treatment plays a major role in survival and quality of life in older patients with AML.[5]

European and American registries confirm the use of intensive treatments in most patients aged up to 80 years, who have better survival than patients treated non-invasively, including in patients at risk of complications and treatment failures including age, comorbidities and cytogenetic abnormalities. However, these studies have selection bias (fit patients).[6]

This improved survival in patients treated intensively does not guarantee quality of life, an essential criterion in the geriatric population. New protocols tend to take into account quality of life assessment. A study in the recruitment phase in Nebraska compares standard intensive regimens with lower intensity treatments. There are geriatric variables in secondary outcomes, particularly quality of life (measured by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire).[7]

Treatment decision prerequisites

- Assess TRM: multifactorial and taking into account a combination of factors such as age, performance status, albumin, creatinine, leukocyte and platelet count, percentage of circulating blasts, de novo or secondary leukaemia.[8]

- Chances of remission in induction and survival: many studies have evaluated the likelihood of complete remission (CR or CRi) based on different cytogenetic and molecular markers in addition to age and performance status defining low-, intermediate- and high-risk groups influencing overall survival.[9,10]

- Geriatric assessment: to assess the patient's level of vulnerability (fit versus unfit patient) and therefore the feasibility of intensive treatment.

- The ASCO (American Society of Clinical Oncology) recently published geriatric oncology guidelines.[11]

- Abel and Klepin propose a literature review on the assessment of frailty in older people with haematological cancers.[12]
- In a series of 1424 patients aged 75 and over with haematological malignancies, Liu and colleagues show that walking speed is a valuable outcome measure, independently of age, performance[A31] status, comorbidities, the aggressiveness of the cancer and the type of treatment. Although easy to measure, walking speed is governed by a complex process involving size physiological systems: the central nervous system, peripheral nervous system, perception, muscles, bones and joints and energy production (reflecting nutritional status, cardiopulmonary comorbidities, anaemia, etc.).[13]
- SOROR *et al.* published a composite score taking into account the Hematopoietic [A32]Cell Transplantation-Specific Comorbidity Index (HCT-CI), which was initially developed to assess allograft eligibility, hypoalbuminemia, thrombocytopenia, LDH level, age and cytogenetic and molecular risk criteria. This score is used to assess mortality one year after initial treatment and, in particular, highlighted that patients with a low or intermediate score benefited significantly in terms of survival with intensive treatment compared with non-intensive treatment. The difference was not significant for patients with a high score.[14]
- Ferrara describes three at-risk groups: FIT patients who seem to benefit from intensive treatment whereas UNFIT patients have similar results with non-intensive treatments. FRAIL patients do not seem to benefit from any treatment other than supportive care.[15]

Available AML treatments

• Fit patients, first-line

- Intensive (induction) chemotherapy with daunorubicin and aracytine (type 3 + 7 regimen).[16]
- Intensive (consolidation) chemotherapy with high-dose aracytine.[17]
- RYDAPT (midostaurin) tyrosine kinase inhibitor in addition to induction chemotherapy in patients with FLT3-mutated AML.[18]

MA: Rydapt is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with FLT3 gene mutation, combined with standard induction chemotherapy with daunorubicin plus cytarabine, and consolidation chemotherapy with high-dose cytarabine followed by, for patients in complete remission, maintenance treatment with Rydapt monotherapy.

- Gemtuzumab ozogamicin, humanised anti-CD33 antibody, in addition to induction chemotherapy (Mylotarg).[19]

MA: Mylotarg is indicated in combination with daunorubicin and cytarabine for the treatment of adult patients with previously untreated de novo acute myeloid leukaemia, with favourable or intermediate cytogenetics or FLT3-ITD mutation.

- Stem cell allograft, mainly in the highly controlled setting of therapeutic trials (French Alpha 1200 protocol, closed and currently being assessed). It must, however, be discussed for fit patients[20] according to the allograft-related independent prognostic scores, apart from those with a good cytogenetic prognosis.

• Fit or intermediate-fit patients with secondary leukaemia or poor cytogenetic prognosis, first line

- Selective BCL2 inhibitor venetoclax is indicated in combination with demethylating agent azacitidine: compared with the standard treatment (azacitidine), it improves survival (OS 14.7 versus 9.6 months), the complete cytological remission rate (66.4 versus 28.3%) and the CR duration (17.8 versus 13.9 months). The combination benefits all at-risk groups but more specifically patients with an intermediate risk and mutated *IDH*. It is, however, associated with a significant risk of prolonged haematological toxicity and infectious complications.[21-23]

- CPX-351, intensive cytarabine and daunorubicin-based liposomal chemotherapy.

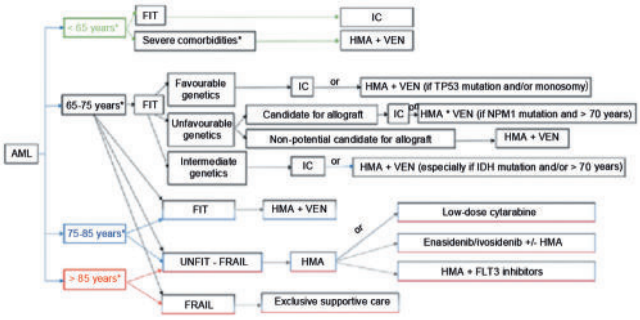
MA (not covered by the French health insurance system): in the treatment of adult patients presenting with newly diagnosed acute myeloid leukaemia secondary to treatment (t-AML) or AML with myelodysplasia-related

changes (AML-MRC), only in patients aged 60 to 75 years.[24]

- *Unfit patients, first-line*

- Demethylating agents: decitabine (no MA in France), azacitidine.[25] The azacitidine-venetoclax combination is under discussion but haematological tolerance can be an obstacle to this combination and some people propose several cycles of azacitidine alone beforehand.[19]
- Low-dose aracytine[26].
- Hydroxycarbamide and supportive care.

Proposed decision-making algorithms for first-line treatment according to initial assessment criteria (Urbino *et al.*[29] translation).



Abbreviations: Allograft: allograft of haematopoietic stem cells; IC: intensive chemotherapy; HMA: hypomethylating agent; VEN: venetoclax.

- *Fit or unfit patients, refractory or in relapse: place for targeted therapies if indicated*

- IDH (isocitrate dehydrogenase) inhibitors: IDH1 ivosidenib and IDH2 enasidenib (IDHIFA) for patients with a mutation of one of these genes. ATU (temporary authorisation for use) for monotherapy for relapses (second- or third-line).[27,28]
- Demethylating agents alone: azacitidine or combined with venetoclax.
- New drugs as part of therapeutic trials and precision medicine taking into account molecular markers of the disease to guide therapeutic choices (p53 activator, azacitidine/venetoclax/IDH inhibitors triplet, etc.).

Conclusion

There are currently numerous drug approaches to treat AML. The choice of proposed molecules depends on the AML characteristics but also, and in particular in the older population, the patient's ability to cope with them. The older person's comorbidities, geriatric frailty and wishes need to be considered to tailor the care plan. Let us stress the importance in geriatric oncology of early integration of palliative care and the regular reassessment of needs, which change more rapidly than in younger patients.

Supportive care is systematically combined with curative treatment throughout the haematological oncology journey.

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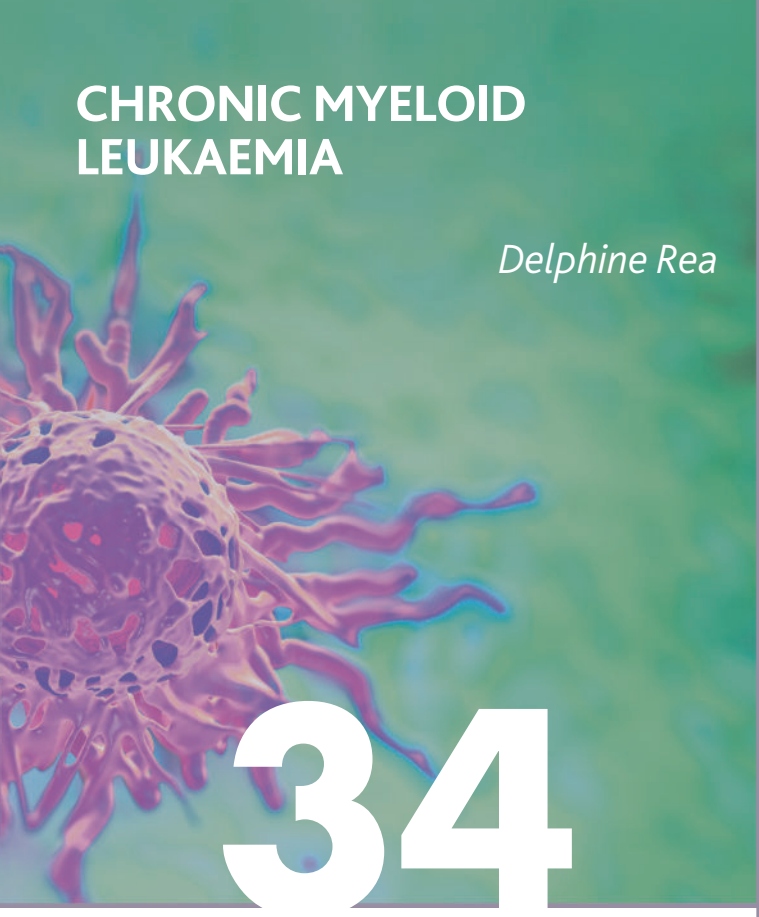
CHRONIC MYELOID LEUKAEMIA

Delphine Rea



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Summary

Since 2001, treatment, vital prognosis and quality of life for patients with chronic myeloid leukaemia (CML) have been radically transformed by the use of oral therapies targeting the BCR-ABL1 oncogene.

These treatments, including pioneering imatinib, are kinase inhibitors (TKIs). This drug class has gradually grown. Five ATP-competitive TKIs (3 generations) have an MA in France and an allosteric inhibitor of BCR-ABL1 has been developed, which is the most selective of them all due to its mode of action.

This article summarizes questions specific to older patients in terms of therapeutic choices, which must meet the dual objective of optimal efficacy and minimal iatrogenic damage.

Introduction

Chronic myeloid leukaemia (CML) has low incidence and is characterised by an acquired cytogenetic abnormality in haematopoietic stem cells, the Philadelphia chromosome (Ph1). Ph1 is the result of reciprocal translocation t(9;22)(q34;q11), which causes the *BCR* gene of

chromosome 22 to fuse with *ABL1* on chromosome 9.[1] The BCR-ABL oncoprotein deregulates numerous intracellular signalling pathways and establishes a state of genetic instability responsible for the progression of CML to acute leukaemia if not treated appropriately.

The development of inhibitors of BCR- ABL1 tyrosine kinase, the driver of the disease, has revolutionised patients' futures. CML can occur at any age, but older populations are particularly affected as the median age at diagnosis is around 60-65 years in "high-revenue" countries.[1] Before the introduction of TKIs, advanced age was a detrimental prognostic factor due to the poor tolerance of existing treatments such as interferon alpha and the fact that older patients are ineligible for extensive procedures like haematopoietic stem cell allograft.[1] This explains the significant weight of age in the factors taken into account when calculating Sokal and Euro prognostic scores developed before TKIs were introduced.[2] With TKIs, advanced age does, nonetheless, seem to be one of the risk factors for death linked to blood disease progression, at least with imatinib, and the ELTS score would seem to assess this risk better than the Sokal or Euro score.[3-7] Provided there is an optimal anti-leukaemic response, overall survival and progression-free survival are excellent, life expectancy for patients diagnosed in the chronic phase (CP) is similar to that in the general population, and therapeutic benefits are observed in all age brackets.[8] With well-conducted treatment, the impact of comorbidities on survival becomes even more significant than the impact of the blood disease.[9]

Five ATP-competitive TKIs have a marketing authorisation to treat adult CML in France. Imatinib (first-generation) has been used as first-line treatment since the 2000s. Dasatinib, nilotinib and bosutinib (second-generation) are more powerful than imatinib and can be used as first-line treatment or in the case of poor tolerance or resistance to imatinib. Ponatinib (third-generation) is used if other TKIs fail or if there is resistance relating to the emergence of BCR-ABL1 T315I point mutation. In 2022, allosteric inhibitor asciminib was added to the range. It has an MA for third-line treatment after demonstrating its benefit in phase 1 then its superiority in terms of efficacy and tolerance compared with bosutinib.[10-12] In a high dose, it can be used against T315I mutation-related resistance. It is currently being evaluated

as first- and second-line treatment and combined with ATP-competitive TKIs.

Although the patient's age does not affect the efficacy of the 5 ATP-competitive TKIs, it affects their tolerance significantly. Imatinib is frequently responsible for anaemia and fluid retention in older patients. Although more effective than imatinib, second- or third-generation TKIs may be responsible for concerning side effects, particularly cardiovascular, cardiac, pulmonary, metabolic or hepatic ones. These side effects are more frequent the older the patient is, or if they have comorbidities. In addition, all TKIs interact with drugs metabolised by the CYP3A4 fraction of cytochrome P450. Polymedication is very frequent in older patients with CML.[13] As a result, if older patients with CML are to be treated with TKIs like younger patients, the therapeutic choices must be tailored and given careful consideration. In addition, molecular response targets may have to be adapted to life expectancy and expected quality of life, and drug risks must be avoided as far as possible.

There is currently no international consensus on the treatment of CML in older patients. It is important to note that these patients are under-represented in clinical trials and that most of the studies available are primarily based on patients belonging to a specific age bracket and rarely on a broader geriatric oncology approach. International recommendations like those of the European LeukemiaNet (ELN) simply advise, without any further details, adapting therapeutic choices to the intrinsic characteristics of CML and the comorbidities specific to each patient, probably due to the significant variation in state of health of older people.[14] The aim of this article is to summarize current knowledge and issues relating to TKIs in older patients with CML, not including advanced phases of the disease.

TKI tolerance in older individuals

- *Imatinib*

Prospective clinical trials specifically investigating imatinib tolerance in older individuals are practically non-existent, but the limited data available indicates a risk of lower tolerance of the drug at the standard dose of 400 mg/d. French prospective trial AFR04 involving 30 patients aged 70 and over with newly diagnosed

CP-CML evaluated imatinib at 400 mg/d taken orally.[15] Grade 2 or 3 anaemia was particularly common, affecting around 30% of patients. Due to their symptomatic nature, these anaemias had to be corrected with the administration of recombinant erythropoietin. Fluid retention occurred in around 50% of patients, requiring the administration of diuretics due to the risk of left heart failure, particularly in patients with pre-existing myocardial function impairment. Finally, 30% of patients developed diarrhoea. All these adverse events resulted in numerous treatment interruptions and imatinib dosage reductions, most commonly to a dose of 300 mg/d. Spanish observational prospective study ELDERGLI, involving 36 patients aged 65 to 87, confirmed this tolerance data, with the most common side effects being fluid retention, digestive problems (diarrhoea, nausea, vomiting), cytopenia and musculoskeletal pain.[16] Treatment had to be interrupted in 30% of cases and the dose of imatinib frequently had to be reduced to 300 mg/d. Finally, imatinib was suspected of impairing long-term renal function, however it is worth noting that chronic renal failure risk factors such as high blood pressure and diabetes, and the reduction in renal function with age, could be confounding factors.[17]

The British DESTINY trial involving adult patients in all age categories showed that reducing the imatinib dose after achieving an optimal response enabled this response to be maintained in the majority of cases and improved tolerance of the drug.[18] A Spanish study confirmed these results.[19] The possibility of starting imatinib at a reduced dose from the outset in older individuals has never been formally evaluated despite the strategy sometimes being adopted in clinical practice. Therefore, dosage optimisation in older patients could be a way forward in improving tolerance of the drug.

- *Dasatinib*

The recommended dosage of dasatinib is 100 mg/d taken orally for CP-CML, whether it is used as first-line or subsequent treatment. Tolerance of the drug in older patients has been evaluated in retrospective academic studies or analyses of subgroups of patients included in these clinical trials. Dasatinib is frequently responsible for pleuropericardial effusion.[20] Lymphocyte-predominant exudative unilateral or bilateral pleural effusions

are usually not severe if there is no underlying cardiopulmonary comorbidity, and regress after interrupting and/or reducing the dose of dasatinib. Exploratory punctures and/or paracenteses are only carried out in cases of severe clinical impact or uncertainty regarding drug causality. The dose of dasatinib and the patient's age significantly influence the risk of pleural effusion and the recurrent nature of these effusions may be problematic.[21,22] In the DASISION first-line dasatinib registration study, the frequency of pleural effusions after a total observation period of 60 months was 16% in patients aged under 46, 37% in patients aged 46 to 65 and 60% in patients over 65.[22] In an Italian multicentre retrospective study of 65 patients aged over 65 and treated with first-line dasatinib, pleural effusions occurred in 18.5% of cases after a median treatment duration of 3 months and the effusion recurrence rate was around 58%.[23] Half of the patients who developed a pleural effusion had to stop taking dasatinib permanently. In another Italian multicentre retrospective study of 172 patients aged over 60 and treated with dasatinib after imatinib failure or intolerance, pleural effusions were observed in 30.2% of patients after a median treatment duration of 11 months, there was recurrence in 48% of them and 21.1% of these patients had to stop taking dasatinib.[24] Although the efficacy of dasatinib is not in doubt in older patients, most of whom have one or more comorbidities, the pulmonary tolerance of the drug at 100 mg/day raises questions. Studies evaluating the tolerance and efficacy of dasatinib at doses lower than 100 mg/day were carried out in addition to studies based on adapting the dasatinib dosage to the residual drug concentration plasma test results.[25,26]

- *Nilotinib*

The recommended dosage of nilotinib is 300 mg x 2/d for de novo CP-CML and 400 mg x 2/d following imatinib intolerance or resistance. Again, nilotinib tolerance in older patients has only been evaluated in retrospective academic studies or analyses of subgroups of patients included in these clinical trials. Nilotinib is associated with a risk of ischemic arterial events as well as dyslipidaemia and type 2 diabetes.[27] Several independent studies have shown a link between the patient's intrinsic cardiovascular risk and the occurrence of cardiovascular events, and age is one of the major risk

factors for cardiovascular disease in the general population. In a French single-centre prospective study in 57 patients with CP-CML and treated with first-line or later nilotinib, arterial event-free survival at 48 months was 33% in patients with high or very high arterial risk and 97% in patients with low or moderate risk according to the ESC 2012 European classification.[27] In the *ENEST1st* European trial, it was observed that the frequency of arterial events on first-line nilotinib at 300 mg x 2/d increased with the patient's age.[28] In the *ENESTnd* European registration trial of first-line nilotinib, the frequency of ischemic arterial events was significantly higher with nilotinib than with imatinib, and increased all the more with nilotinib the higher the Framingham score and the higher the nilotinib dose were.[29] These results prompted the French chronic myeloid leukaemia intergroup (FiLMC) to issue recommendations for minimising the risk of arterial events with nilotinib in patients with CML.[30] In addition to the standard primary cardiovascular preventive measures, it is essential to ask patients, particularly older patients, about previous cardiovascular disease and assess their arterial status before considering treatment with nilotinib. There are currently no studies evaluating the benefit of nilotinib at initial doses lower than 300 mg x 2/d in older patients but early dose reduction strategies based on molecular response are starting to be used.

- *Bosutinib*

Bosutinib has an MA for an initial dose of 500 mg/d following other TKI failure or intolerance, and 400 mg/d as first-line treatment (BFORE trial). The main tolerance problems caused by bosutinib are extremely frequent dose-dependent diarrhoea at the beginning of treatment and hepatic cytolysis which is less sensitive to the reduced dose of bosutinib.[17] An analysis of age-related adverse events was conducted in the 1/2 phase trial of the drug development. It found that patients aged over 65 suffered more frequently from fatigue (38% of cases), loss of appetite (27%) and pleural effusions (22%).[31] In fact, pleural effusions more specifically concern patients having previously developed a pleural effusion while taking dasatinib. A phase 2 academic study is currently being conducted in Italy to test bosutinib doses of 200 mg/d beyond first-line treatment in patients aged over 60, increased to 300 mg/d after 2 weeks then in 100 mg

increments according to molecular response. The aim is to determine the minimum effective dose for each participant.

• *Ponatinib*

The initial recommended dose of ponatinib is 45 mg/d and the drug is reserved for TKI failure situations and patients with T315I mutation following the results of the PACE trial.[32,33] Reducing the dose once the optimal response has been achieved is recommended due to the high risk of ischemic arterial event and de novo or drug-aggravated arterial hypertension. Although ponatinib has not been evaluated specifically in older individuals, it is clear that age and previous ischemic events are associated with a higher risk of cardiovascular events when taking ponatinib.[32,33] A clinical trial called OPTIC compared ponatinib 45 mg/d with ponatinib 30 mg/d, followed by a systematic dosage reduction to 15 mg/d in patients with optimal response.[34] The trial enabled the use of ponatinib to be optimised as although the initial dose of 45 mg/d is most effective, a rapid reduction to 15 mg/d reduces the toxicity of the drug while maintaining its efficacy in the majority of cases. But this study excluded patients with a very high cardiovascular risk so the median age of patients was relatively young, between 46 and 51 years.

It would therefore seem wise to discuss the indications and dosage of ponatinib in older patients on a case-by-case basis and, if there is a formal indication or no satisfactory alternative, to explain the potential risks and benefits to the patient and consult cardiovascular specialists to offer multidisciplinary treatment. French group FiLMC issued recommendations for minimising the risk of arterial events during ponatinib treatment in patients with CML.[35]

• *Asciminib*

Asciminib was the first allosteric inhibitor in the world to be evaluated in humans and to receive an MA.[12] It inhibits the TK activity of BCR-ABL1 in a highly selective way.[10] Human research data indicates significant anti-T315I activity. If we consider that most TKI side effects, particularly cardiovascular or pulmonary ones, are linked to "off-target" effects, the tolerance profile of asciminib

may turn out to be very interesting, including in frail populations. Asciminib could represent an important opportunity, particularly for frail patients, due to its selectivity, but this requires dedicated studies to prove it.

Therapeutic goals in CML: problems in older patients

Obtaining an optimal response is crucial in CML as this delivers maximum clinical benefit, namely a drastically reduced risk of secondary resistance and acute transformation, as well as the hope of life expectancy similar to that in a population of the same age without CML. Optimal response is defined by the gradual reduction of the leukaemic mass until MMR is achieved between the 12th and 18th month of treatment, then by maintaining this response during treatment.[12] In the case of failure, it is very important to change strategy to take into account the presence and type of point mutation in the ABL1 kinase domain.[14] Although continuing TKIs for life was recommended, the discovery that, provided there is a long-term deep molecular response (DMR), some patients could have an optimal response without treatment, is currently changing treatment concepts. Although DMR does not provide any substantial additional benefit in terms of survival compared with MMR, it has become a new goal to achieve in order to stop treatment.[14,36] Randomised registration trials of first-line second-generation TKIs formally demonstrated a higher probability of DMR with these drugs compared with imatinib. Therefore, three types of strategies are theoretically possible for first-line treatment: second-generation TKIs for everyone, which is not without risk, second-generation TKIs if there are no major comorbidities or in intermediate- or high-risk CML, or finally, imatinib for everyone with change of treatment if required. In the oldest patients, the third option would seem the most balanced in terms of efficacy and severe drug risks, however, this dogmatic view may be challenged for independent older individuals in good health, as long as the use of new generation TKIs is optimised.[37] The question of changing treatment in the event of insufficient first-line TKI efficacy is also an important one in older patients, and case-by-case adaptation is required. Therefore, maintaining the same treatment despite a suboptimal response is not unreasonable.[37] Finally, the question of palliative care with hydroxyurea is sometimes raised for much older individuals with multiple

comorbidities or a loss of independence, possibly with impaired cognitive function. It is important to remember that such a choice potentially results in damaging quality of life mainly due to the need for very frequent blood tests to adapt the dosage, and the non-selective cytotoxic effect of hydroxyurea on all the haematopoietic lineages. In fact, obtaining a stable complete haematological response without cytopenia with TKIs in these individuals improves quality of life.

Conclusions and perspectives

The efficacy of TKIs in treating CML in older patients is remarkable and older patients should benefit from the fantastic progress provided by this drug class in the same way as other people. However, age is a risk factor for potentially higher toxicity with ATP-competitive TKIs[A33], particularly in the case of specific comorbidities such as arteriopathies, diabetes and chronic pulmonary disease, or in the case of polymedication. It remains to be determined whether this is the case with asciminib, which is more selective. These therapeutic choices must be adapted on a case-by-case basis to older patients as they represent a heterogeneous category of patients. Studies aiming to optimise TKI tolerance in these individuals are essential in order to maintain maximum efficacy but also to improve their quality of life and limit serious drug risks. Although haematologists in charge of CML are increasingly cooperating with colleagues in other specialisms (particularly cardiologists, pulmonologists, diabetologists and hepatologists) to prevent and manage TKI risks, the relationship with geriatric oncologists remains tentative.

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HODGKIN'S DISEASE

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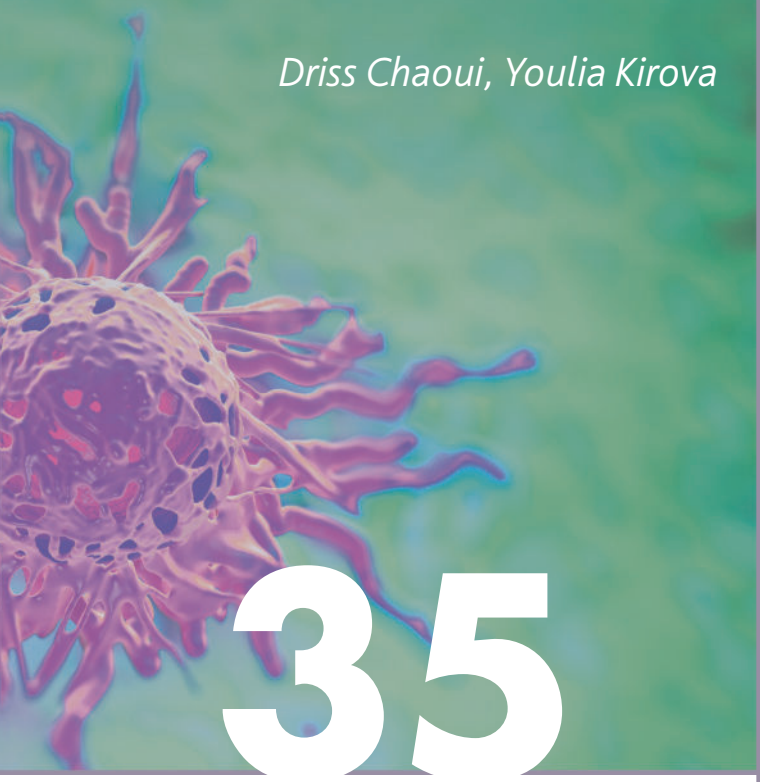

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General information

Hodgkin's disease (HD) has a bimodal distribution with two peaks: one in younger people and one after the age of 50. Age has a clear prognostic impact. Older patients have a more advanced stage at diagnosis and more impaired general condition. Diagnosis requires a good quality histological sample (lymph node or extra-nodal) with an immunohistochemical and morphological analysis. Mixed cellularity and EBV-related types are more frequent in older patients.

Initial and pre-treatment assessment

The initial assessment includes HD prognostic criteria: FBC, sedimentation rate, serum LDH level and albumin test, frontal and profile chest radiograph with mediastinal thoracic ratio measurement (prognostic impact for localised forms: transverse diameter of the mediastinal mass in relation to the thoracic diameter measured in the T5-T6 space on a frontal chest radiograph). A thoracic-abdominal-pelvic scan and PET scan are carried out for staging, a cardiac ultrasound is performed before using anthracyclines, and respiratory functional explorations are carried out before bleomycin. The

pre-treatment assessment must include a geriatric assessment covering comorbidities, independence, general condition and nutritional status among other things. This assessment identifies frailty and has a prognostic impact.

First-line treatments in fit patients

- *Standard ABVD +/- radiotherapy protocol*

Localised forms (stage I, II) are treated with a combination of chemotherapy (3 to 4 cycles of ABVD) and radiotherapy. Localised forms (III, IV) are treated with chemotherapy alone (6 cycles of ABVD). The standard first-line chemotherapy is ABVD. A cycle of ABVD has two courses 15 days apart (D1 & 15): doxorubicin, bleomycin, vinblastine, dacarbazine. The toxicity of the protocol increases with age: more infections, more pulmonary fibrosis related to bleomycin.[1] The result is 20% to 30% mortality according to studies in patients over 65.[2] The RATHL trial showed that bleomycin can be eliminated after 2 cycles of ABVD if the PET scan is negative after the first 2 cycles of ABVD.[3] The AVD-brentuximab protocol also has an advantage in terms of reducing the pulmonary toxicity of bleomycin. The ECHELON 1 trial comparing ABVD with AVD-brentuximab did not, however, show a benefit in patients over 60.[4] The same combination used sequentially (brentuximab then AVD then brentuximab) showed excellent results with 2-year PFS of 84% and lower, particularly neurological, toxicity.[5]

The German group developed the PVAG regimen (prednisone, vinblastine, doxorubicine, gemcitabine). There is reduced pulmonary toxicity but the infection incidence remains high.[6]

French group LYSA's PVAB regimen (prednisone, vinblastine, doxorubicin, bendamustine) also has a certain level of toxicity. After median follow-up of 23 months, 4% toxic deaths and 31.5% serious adverse events were observed.[7]

First-line treatments in frail patients

Brentuximab combined with dacarbazine is a similar option to the standard ABVD-type regimen. This combination was assessed in patients aged over 60. The

overall response rate is 100%, including a complete response of 62%. The median PFS is 17.9 months. The brentuximab bendamustine regimen assessed in the same study was complicated by a level of toxicity considered to be unacceptable.[8]

Relapse treatments

Brentuximab is an excellent option in older patients in relapse. However, neurological toxicity appears to be more frequent.[9] Nivolumab has an MA for relapse treatment after brentuximab treatment.[10] Median PFS is 15 months. Pembrolizumab also has an MA for relapse treatment after 2 lines of treatment. Better efficacy is observed with pembrolizumab (median PFS 13.2 months) compared with brentuximab (median PFS 8.2 months). In all these studies, it is difficult to draw conclusions for older people as they were under-represented.[11]

Radiotherapy: mainly for localised relapses in addition to chemotherapy.[12]

Changes in radiotherapy techniques

Over the last fifteen years, enormous progress has been made in radiotherapy with the development of techniques such as conformal intensity-modulated radiotherapy (IMRT) and image-guided radiation (like MRI and PET). These techniques have become the standard in the treatment of numerous diseases such as prostate cancer and ENT tumours with improved locoregional control and lower toxicity due to reducing doses to organs at risk.[12,13]

Unfortunately, there is no consensus for the use of IMRT in the treatment of Hodgkin's disease. Recently, following the publication of an editorial by Professor R. Hoppe,[13] IMRT has been approved in the USA and is now covered by their health system. In France, IMRT is developing rapidly and is used for numerous locations.[14,15] It has already been shown that the use of VMAT or TomoTherapy IMRT, as well as the use of protons in selected cases, can reduce doses to organs at risk (OAR) such as the heart and lungs, resulting in radical changes in practice in some institutions.[14-17]

For patients with mediastinal presentation, the standard treatment must be "involved site" (IS) according to the

recommendations of the International Lymphoma Radiation Oncology Group (IL-ROG)[12] with an adapted IMRT technique to avoid long-term complications. Organs at risk must be contoured for improved dosimetric optimisation (Figure 1).

All these developments mean that new, much safer and better tolerated radiation techniques should be offered to older patients who will benefit from them.

Changes in fractionation

International recommendations introduced during the Covid-19 pandemic allow hypofractionated radiotherapy to be performed, which appears to be highly suited to older patients.[19,20] For Hodgkin's disease:

- Hodgkin's disease (favourable forms): 5 x 3 Gy can be used as an alternative to 10 x 2 Gy radiotherapy. 6 x 3 Gy must be used for mediastinal forms (due to organs at risk).

- Hodgkin's disease (unfavourable forms or non-Hodgkin's lymphoma [NHL] in complete remission): 5 x 5 Gy as an alternative to the standard 30 Gy/15 fractions. For mediastinal forms due to organs at risk (OAR): 9 x 3 Gy.

- Hodgkin's disease (aggressive forms) or in partial remission: 6 x 5 Gy to replace the standard 36 Gy/18 fractions. For mediastinal forms due to organs at risk (OAR): 11 x 3 Gy.

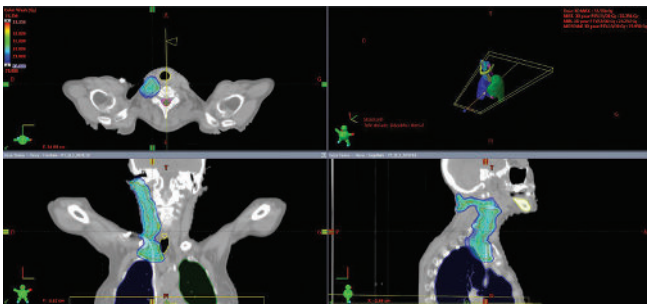

Figure 1: *Example of a patient aged 73 years treated with TomoTherapy on a supraclavicular cervical IS volume for HD at a dose of 30 Gy/15 fractions. The treatment reduced the doses to OAR (salivary glands, mandibular region, lungs).*

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