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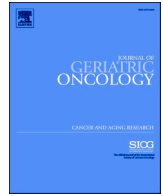
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Research Paper

Challenges of caring for older patients with multimorbidity including cancer



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ABSTRACT

Introduction: As the population is ageing, the number of older patients with multimorbidity including cancer continues to increase. To improve care for these patients, the European Union-funded project “Streamlined Geriatric and Oncological evaluation based on IC Technology” (GERONTE) was initiated to develop a new, patient-centred, holistic care pathway. The aim of this paper is to analyse what challenges are encountered in everyday clinical practice according to patients, their informal caregivers, and healthcare professionals as a starting point for the development of the care pathway.

Materials and Methods: An expert panel of cancer and geriatrics specialists participated in an online survey to answer what challenges they experience in caring for older patients with multimorbidity including cancer and what treatment outcomes could be improved. Furthermore, in-depth interviews with older patients and their informal caregivers were organised to assess what challenges they experience.

Results: Healthcare professionals ($n = 36$) most frequently mentioned the challenge of choosing the best treatment in light of the lack of evidence in this population and how to handle interactions between the (cancer) treatment and multimorbidities. Twelve patients and caregivers participated, and they most frequently mentioned challenges related to treatment outcomes, such as how to deal with symptoms of disease or treatment and how to maintain quality of life. From the challenges, five main themes emerged that should be taken into account when developing a new care pathway for older patients with multimorbidity including cancer. Two themes focus on decision making aspects such as personalized treatment recommendations and inclusion of non-oncologic information, two focus on patient support and monitoring to maintain quality of life and functioning, and one overarching theme addresses care coordination to prevent fragmentation of care.

Discussion: In conclusion, the management of older patients with multimorbidity including cancer is complex and although progress has been made on improving aspects of their care, challenges remain and patients are at risk of receiving inappropriate, unnecessary, and potentially harmful treatment. A patient-centred care pathway that integrates solutions to the five main themes and that moves away from a single-disease centred approach is needed.

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1. Introduction

As life expectancy has extended over the past decades, older persons form an increasing proportion of the population. It is expected that by 2030, one in six people will be aged over 60 years [1]. Living longer does not mean that these extra years will be spent in good health [2]. An increased population living with disability and disease will have a major impact on the organisation of care and treatment of diseases, which is why the World Health Organisation has shifted their focus towards chronic, non-communicable health conditions [3].

Of patients aged >64 years, 65% have multiple diseases at the same time and this percentage increases with age [4]. Patients with multimorbidity often have additional impairments such as reduced mobility and care dependence [5]. Such impairments result from an age-related decline in multiple physiological systems, which collectively contribute to patient frailty. This results in vulnerability to sudden health status changes in response to even small stressors and, consequently, to new care needs in addition to the needs caused by cancer and its treatment [6,7].

Despite the high prevalence of multimorbidity and frailty in older patients, current healthcare is primarily single-disease oriented [4,8]. While this offers benefits in terms of specialist knowledge, in the absence of integrated care it can result in inefficient, ineffective, and potentially harmful management of patients with multimorbidity [4,9], as treatment for one disease may destabilize other diseases. This is particularly evident when multimorbidity includes cancer. Due to the wide variety of potentially intensive and burdensome treatments and involvement of many disciplines, cancer care pathways are already complex even without patients having other diseases. The high disease and treatment burdens demand specialist care for individual diseases as well as coordination and integration of all aspects of care to deal with possible interactions in patients with cancer and multimorbidity [4].

Geriatric oncology has advocated for many years now to integrate the patient's general fitness into the treatment decision making process in addition to considering the cancer alone. Little attention has been given to patients with multimorbidity including cancer, in which cancer is one of the multiple diseases, but a disease with possibly high risk and high impact medication. To improve care for older patients with multimorbidity including cancer, the European Union-funded project "Streamlined Geriatric and Oncological evaluation based on IC Technology" (GERONTE) was initiated to develop and test a new, patient-centred, holistic care pathway [10]. The aim of this paper is to analyse what problems are encountered in everyday clinical practice according to patients, their informal caregivers, and healthcare professionals. During a scoping search about challenges in management of older patients with multimorbidity including cancer and challenges that patients experience themselves, no articles describing this combination were found. In this paper, we therefore asked both health care providers as well as patients and their informal caregivers which challenges they have experienced during the management of older patients with multimorbidity including cancer or during their trajectories as a starting point to further develop the GERONTE pathway.

2. Methods

Our primary goal was to identify challenges when caring for older patients with multimorbidity including cancer, both from the perspective of health care professionals and patients/caregivers. Study protocols for both the patient/caregiver interviews and the expert surveys were separately reviewed by the ethics committee (Medical Research Ethics Committees United) and received a waiver for full ethics review; the protocol was subsequently approved by the local research committee of the Diaconessenhuis, the Netherlands.

2.1. Healthcare Professional Surveys

The healthcare professional perspective was acquired from an international group of European healthcare professionals who participated in an expert panel set up to assist in the development of the new GERONTE care pathway for older patients with multimorbidity including cancer (geronteproject.eu). It included medical specialists, nurses, and other health care professionals with expertise in geriatric medicine or oncology who were approached based on purposive sampling. Cancer specialists with a special interest in older patients were mainly approached. The aim was to represent a mixture of backgrounds and specialities involved in the care of older patients with cancer. For the healthcare professionals, the following data were collected: age, sex, profession, years in clinical practice, and the treatment types and cancer types they were involved in.

The expert panel was asked to respond to open-ended questions in online surveys on a range of topics, such as what they thought were the biggest challenges in caring for older patients with multimorbidity including cancer, what health outcomes could be improved in this population and what were the most important outcomes lacking evidence, because they are not routinely measured in clinical trials (for more details see Appendix A).

2.2. Patient and Caregiver Interviews

To obtain the patient and caregiver perspective, potential participants were recruited at the Diaconessenhuis, Utrecht, the Netherlands, and Dublin City University, Ireland. Patients were eligible if they currently had breast, colorectal, prostate, or lung cancer and were in a stable situation (as judged by their treating oncologist or nurse practitioner), or if they had recently completed their treatment and if they had a least one other disease. A purposive sampling method was used to identify patients with multimorbidity including cancer. They were excluded if they had cognitive impairment, depressed mood, or anxiety issues impacting their participation. During regular consultations in outpatient clinics, medical oncologists, surgical oncologists, and advanced practice nurses handed out >50 flyers to eligible patients with information on how to contact the research team if they were willing to participate. All patients that replied between September 2021 and January 2022 and that met the inclusion criteria were interviewed.

After acquiring informed consent, patients and caregivers were interviewed at their home (NS) or by phone or video call (BOS). The first author (NS), a resident in geriatric medicine and PhD candidate in geriatric oncology, who is experienced in patient interviews, or by a clinical nurse specialist and research nurse (BOS). Before the visit the interviewer had contacted the participants for a brief explanation and goal of the study, but they had not met each other in person. Interviews were semi-structured. Conversations were recorded and a written edited transcript was made. Patients and caregivers were asked what they felt had been their biggest challenge during their cancer trajectory, what issues they had encountered and what could be improved in the care for patients with cancer above 70 years who had other disease as well (see Appendix A for interview guide). Sex, age, and cancer type were recorded. Some patients and caregivers also mentioned their cancer stage, anti-cancer treatments received, or other diseases.

2.3. Data Analysis

From the open-ended questions, answers from the healthcare professionals were categorized into challenges using inductive coding by the first author (NS). The initial round consisted of open coding, in the consecutive two rounds focused coding was used. For patients' and caregivers' transcripts inductive coding was used as well. After some initial rounds of coding of the patient and caregiver interviews, the list from the healthcare professional answers was used as a starting point to add new codes or to recode to match the patient and caregiver codes.

Every time a new challenge was mentioned, it was added as a new code; if similar challenges were mentioned they received an existing code. At the end of this process, all written answers of the healthcare professionals and all transcripts of the patients and caregivers were read again to verify that they received appropriate codes. Some participants mentioned multiple challenges in their answers. Afterwards, challenges were combined into five main themes that should be taken into account when developing a new care pathway for older patients with multimorbidity including cancer. The emerging themes were then checked, refined, and changed as needed by a second author (MH) to validate the results.

Results were reported using descriptive data only. For normally distributed data, means with standard deviations were used; for non-normal distributions, medians with range were used.

3. Results

3.1. Healthcare Professionals' Surveys

Between May 2021 and October 2021, four online survey rounds with the expert panel were completed on various topics, of which the question about the challenges was included in round two (June 2021). In this round, 36 healthcare professionals responded out of 87 that were invited. The expert panel had a range of different backgrounds, either geriatric or with expertise in oncology. The oncologists were involved in various cancer types and treatments (Table 1). Respondents had a mean age of 47 years, with a mean of 17 years of experience in clinical practice (Table 1).

3.2. Challenges Experienced by Healthcare Professionals

The challenges experienced most frequently by healthcare

Table 1
Demographics of the healthcare professionals.

Healthcare professionals	
Mean age	47 years
Mean Years in clinical practice	17.1 years
Profession	
Nurse	10%
Physician	85%
Other (research)	8%
Specialty	
Surgery	21%
Medical oncology	30%
Primary care	8%
Geriatrics	23%
Other hospital- based specialist / organ based specialist	10%
Other specialty...	23%
Cancer type involved with *	
Breast cancer	23%
Colorectal cancer	33%
Lung cancer	18%
Prostate cancer	21%
All cancer types	31%
Which treatments do you provide to patients yourself? *	
Surgery	31%
Radiation therapy	13%
Chemotherapy	36%
Targeted and/or immune therapy	36%
Hormone therapy	36%
None	23%
Other, namely	18%

* multiple answers per participant possible.

professionals when treating older patients with multimorbidity including cancer are listed in Table 3. The most frequently reported challenges were, "to balance harms and benefits of cancer treatment after carefully weighing all information," (44%), followed by, "to deal with the lack of evidence and uncertain prognosis in this population," (19%; see Table 3). When healthcare professionals were asked for the most important outcomes lacking evidence, 25 participants replied and data on quality of life was commonly mentioned (56% of the participants), followed by functioning/ independence by 40% (see Table 4).

The question about which health outcome could change the most when applying a new care pathway specifically for older patients with multimorbidity including cancer was answered by 26 participants. Improved quality of life was most frequently mentioned, namely by 69% of the experts (n = 18), followed by better functional outcomes (27%, n = 7), decreased toxicity (15%, n = 4), fewer emergency visits and unplanned hospitalisations, and increased survival (both 12%, n = 3; see Table 5).

3.3. Patient and Caregiver Interviews

Between September 2021 and January 2022, nine patients and three caregivers were included. Inclusion was difficult due to COVID-19. Three patients had prostate cancer, four had colorectal cancer, one had breast cancer, and one lung cancer. The median age of the patients was 79 years (range 77–90), and there were five males and four females (Table 2). Patients received various types of treatment, had various stages of disease and had at least one other somatic disease. Other diseases that the participants had were melanoma, cerebrovascular disease, obstructive sleep apnoea syndrome, hypertension, and pulmonary embolism. The three caregivers were female and spouses to a patient with cancer and other diseases such as a recent myocardial infarction, atrial fibrillation, multiple myeloma, or peripheral vascular disease (Table 2).

3.4. Challenges Experienced by Patients and Caregivers

Interviews lasted between 24 and 65 min (median 37 min). The most frequently reported challenges by patients and caregivers were, "to monitor and deal with symptoms, side effects, and destabilisation of multimorbidities," and, "to improve coordination of care and interdisciplinary communication" (both mentioned by 92%; Table 3). Other reported challenges included, "to increase patient involvement and personalize treatment and care based on patient preferences with shared decision making," and, "to maintain quality of life and functional status and prevent dependence" (both reported by 75%; Table 3).

Based on the challenges for both patients and their caregivers, as well as healthcare providers, five main themes were identified: (1) To choose the most suitable treatment for an older individual with shared decision making, (2) To increase awareness of the importance and enhance the inclusion of non-oncologic information, (3) To maintain and optimize

Table 2
Demographics of patients and caregivers.

	Country	Age	Sex	Cancer type
Patient 1	NL	85	Male	Colorectal cancer, stage IV
Patient 2	NL	78	Male	Prostate cancer, stage IV
Patient 3	NL	76	Male	Prostate cancer, stage I
Patient 4	NL	79	Female	Breast cancer, stage IV
Patient 5	NL	90	Female	Lung cancer, stage IV
Patient 6	IRE	76	Female	Colorectal cancer, stage IV
Patient 7	IRE	70	Male	Colorectal cancer, early stage
Patient 8	IRE	87	Male	Prostate cancer, stage unknown
Patient 9	IRE	85	Female	Colorectal cancer, stage IV
Caregiver 1	NL	70 +	Spouse	Prostate cancer, early stage
Caregiver 2	NL	70 +	Spouse	Prostate cancer, stage IV
Caregiver 3	NL	70 +	Spouse	Prostate cancer, stage unknown

NL; The Netherlands, IRE; Ireland.

Table 3
Challenges identified by healthcare professionals, patients and their informal caregivers.

Challenges identified	by healthcare professionals (n = 36)*	by patients and caregivers (n = 12)*	Main themes for a new care pathway
To balance harms and benefits of cancer treatment after carefully weighing all information	44%	67%	
To increase patient involvement and personalize treatment and care based on patient preferences with shared decision making	14%	75%	To choose the most suitable treatment for an older individual with shared decision making
To deal with the lack of evidence and uncertain prognosis in this population	19%	33%	
To increase awareness of the importance of relevant non-oncologic parameters in decision making	17%	8%	To increase awareness of the importance and enhance the inclusion of non-oncologic information
To deal with cognitive impairment and compliance	8%	0%	
To also look at non-oncologic aspects such as general health problems that an older individual may have	11%	17%	
To adequately implement non-oncological interventions to optimize the patient's general health status	11%	0%	
To maintain quality of life and functional status and prevent dependence	11%	75%	To maintain and optimize quality of life, functioning and care independence during and after treatment
To take into account the caregiver role and social network such as caregiver burden, caregiver abilities and absence of social network	3%	58%	
To cope with worries and uncertainty	6%	58%	
To monitor and deal with symptoms, side effects and destabilisation of other diseases	11%	92%	To monitor and deal with symptoms, side effects and interaction between multimorbidity and cancer(treatment)
To handle interactions between (cancer) treatment and other diseases	17%	50%	
To improve coordination of care and interdisciplinary communication	14%	92%	To improve coordination of care and communication between healthcare professionals (and overcome other organizational challenges) to prevent fragmentation of care
To find adequate support and deal with a lack of resources (service	11%	8%	

Table 3 (continued)

Challenges identified	by healthcare professionals (n = 36)*	by patients and caregivers (n = 12)*	Main themes for a new care pathway
capacities and financing)			
To better organise the frequent hospital visits that are often planned separately	0%	25%	

* Multiple answers per respondent were possible. The three most frequently mentioned challenges per respondent group are in bold and underlined.

Table 4
Most important outcomes with lacking evidence.

Health Outcome	%
Quality of life outcomes	56%
Functioning/independence	40%
Satisfaction/ spiritual status	12%
Cognitive function	8%
Number of happy / good days	8%
Overall survival	8%
Continuing social activities	4%
Quality of dying	4%
Symptom controlled survival	4%
Patient preferences	4%
Toxicity	4%
Progression free survival	4%

The question was answered by 25 participants. Multiple answers per participant possible. They were asked: "One of the challenges mentioned in caring for this patient group, is the lack of information on outcomes that matter in this specific patient group. Which outcomes would you especially be interested in?"

Table 5
Outcomes that could be improved by a holistic care pathway.

Health outcome	%
Improved quality of life	69%
Better functional outcomes	27%
Decreased toxicity	15%
Fewer emergency admissions/ unplanned hospitalisations	12%
Increased survival	12%
Increased treatment feasibility	8%
Better disease specific outcomes	8%
Improved shared decision making	4%
Improved patient satisfaction	4%
Greater ability for taking part in social activities	4%
More time without treatment	4%
Less burden of disease	4%

Answered by 26 healthcare professionals, multiple answers per participant possible. They were asked "Which outcomes do you think could be most improved using an holistic care pathway for older patients with cancer and multimorbidity?"

quality of life, functioning, and care independence during and after treatment, (4) To monitor and deal with symptoms, side effects, and interactions between multimorbidity and cancer (treatment) and (5) To improve coordination of care and communication between healthcare professionals to prevent fragmentation of care. These five themes are listed in [Table 3](#). Examples of quotes from patients and caregivers related to these themes are listed in [Table 6](#).

4. Discussion

In this study, challenges experienced in clinical practice of managing older patients with multimorbidity including cancer were analysed and

Table 6
Examples of patient and informal caregiver quotes relating to the challenges they experience.

Main themes	Examples of answers given by either patients or their caregivers
To choose the most suitable treatment for an older individual with shared decision making	Regarding the balance between harms and benefits: It was a challenge to receive all relevant information, retrospectively I would have preferred to receive more information about the possible side effects. (patient 3)
	Regarding the patient involvement and shared decision making: In general it is a challenge as patient to stand up for yourself and participate in discussions on treatment decisions etc. (caregiver 1)
	It is always a challenge to remember all information provided during consults, the conversation progresses quickly and a lot of information is given. Therefore, I forget to ask questions. Maybe it would be better to prepare questions in advance. (caregiver 3)
To increase awareness of the importance and enhance the inclusion of non-oncologic information	Regarding the general health problems that an older individual may have: It was hard to get access to a geriatric medicine specialist and to have other (non-oncologic) healthcare needs recognised early and managed optimally. (patient 9)
	Regarding quality of life and functioning: For me it was a challenge to have diarrhoea 24/7, I lost my freedom, therefore it was clear for me that my best option considering quality of life was to go for ostomy, to give me back control over my stools. (patient 1)
To maintain and optimize quality of life, functioning and care independence during and after treatment	Regarding the importance of the caregiver involvement: My husband often does not remember much information due to general weakness and concentration problems, for us it is always a challenge to make sure I am present when treatment decisions and test results are discussed. (caregiver 1)
	Regarding worries and uncertainty: The biggest challenge that I have is that no-one can answer whether or not my husband will ever be better again, if he will have more energy and if he will be able to participate in normal activities such as going to a grocery store. (caregiver 1)
	Regarding tolerating side effects, symptoms and decline: Due to surgery my mobility has declined, for me it is a challenge to move around, I had rehabilitation, which was very helpful, especially since I live alone. (patient 4)
To monitor and deal with symptoms, side effects and interaction between other diseases and cancer(treatment)	The biggest challenge was how to deal with pain and declining mobility and to get useful recommendations from a specialized physiotherapist. (patient 2)
	Regarding interaction of multiple diseases: Currently it is a challenge to deal with multiple problems. My husband has had a myocardial infarct during chemotherapy. Therefore, chemotherapy is no longer possible. This worries me as the cancer needs to be treated as well. (caregiver 3)
	Regarding monitoring: It was a challenge to get good follow-up

Table 6 (continued)

Main themes	Examples of answers given by either patients or their caregivers
To improve coordination of care and communication between healthcare professionals (and overcome other organizational challenges) to prevent fragmentation of care	for a non-cancer related problem, not dealing with it, resulted in decline and a lower quality of life. (patient 7)
	Regarding communication issues Two times it was a challenge to transfer care between two centres. At that time no one was coordinating my care. (patient 2)
	Regarding frequent hospital visits: For me it was not a challenge, but since I drove over 3000 km back and forth to the hospital, I can imagine that this can be challenging for others. (patient 1)

five themes were formulated to take into account when developing a new care pathway for these patients. Two themes focus on the nature and content of decision making and advocated for personalized treatment recommendations and inclusion of non-oncologic information. Two focus on patient support and monitoring to maintain quality of life and functioning, and one overarching theme identifies a need for care coordination to prevent fragmentation of care.

Our study has some limitations. The most important limitation is that we interviewed a relatively small number of patients and caregivers. Nevertheless, was their input valuable. Selection bias may be present, as mainly the relatively fit and stable patients wanted to participate in an interview, whereas the unstable patients with multiple complex diseases declined to participate, because they felt that this was too burdensome and because they were afraid of contamination with COVID-19. As mostly caregivers of patients living with frailty were included, we believe that overall the answers are representative of this heterogenous older population ranging from very fit to very frail. An additional limitation is that there may have been a recall bias in patients, as they were not interviewed while they were undergoing a burdensome cancer treatment, but afterwards. Again, this is balanced by the informal caregivers, who were caring for patients treated for cancer at the time of the interview. Additionally, most participating healthcare professionals had an interest in geriatric oncology or had a geriatric background. The results may have been different if the challenges would have been identified by general cancer specialists, who tend to have less affinity with older patients.

Furthermore, the study was designed to identify challenges, not to look at percentages or differences between stakeholders. Two different methods were used and participants were not asked to check if challenges mentioned by others were also important to them. Caution is thus needed by interpreting the reported frequencies of the challenges and differences between the stakeholders.

Not all identified themes are new in geriatric oncology. Literature based on earlier studies in patients with cancer or geriatrics may provide potential solutions for some of challenges we identified for patients with multimorbidity including cancer [16–23]. Geriatric assessment (GA), for example, is known to aid in the challenges relating to decision-making and enhance the inclusion of non-oncologic information for older patients with cancer [16–23]. However, as these themes were still mentioned as main challenges, GA may not yet be used in all clinics or not used in an effective way for older patients with multimorbidity including cancer. In order to be effective, it is important to incorporate GA results into treatment decision making and to assure that impairments receive an intervention [16]. In the care of older patients with multimorbidity including cancer this could be embedded by involving a geriatric expert as part of the medical team alongside cancer specialists.

Whereas healthcare professionals mostly focussed on difficulties in treatment decision making (first two themes), patients and their caregivers placed more emphasis on the after-effects of treatment, such as dealing with side-effects and maintaining quality of life and functioning (theme 3). The importance of these outcomes has been stressed for many

years now [14], and our expert panel also identified it as most important outcome in need of more evidence. Nevertheless, most oncologic studies still do not include these outcomes or do not provide sufficient details to translate the outcomes to individual patients [15]. In a care pathway for older patients with multimorbidity including cancer, emphasis on the maintenance and optimisation of quality of life, functioning, and care dependence during and after treatment is needed.

Follow-up and re-evaluation of ongoing treatment is important (theme 4) in older patients with multimorbidity including cancer. This follow-up is not yet fully developed in geriatric oncology and, again, those with multimorbidity may require different follow-up than older patients with cancer alone. Remote symptom monitoring was found to be a solution in oncology to better monitor and deal with symptoms and side effects of cancer and cancer treatment. Studies have shown improved quality of life, longer survival, and lower healthcare consumption with remote symptom monitoring [27–31]. However, for our population simultaneous monitoring of other diseases or functioning may be equally important as monitoring the cancer treatment side effects to help in the early detection and management of interaction between treatments, destabilisation of other chronic diseases, and functional decline.

Caregiver involvement and caregiver burden were identified as important only by patients and their caregivers, not by healthcare professionals. Other literature also found an important role for caregivers and stressed the importance of the impact of treatment on family [11–13]. The importance of caregiver involvement may be underestimated in the current way of organising healthcare, since it is mainly designed by healthcare professionals, but needs to be considered as part of the care pathway for older patients with multimorbidity including cancer.

In oncology, multidisciplinary team meetings and the involvement of a nurse navigator have been shown to improve the care coordination and communication among the multidisciplinary team and to improve patient experience [18,24–26]. In older patients with multimorbidity including cancer, a nurse navigator could take this role to coordinate all clinicians, including the non-oncological ones, in addition to being the primary contact point for the patient. Additionally, other specialists need to be involved in multidisciplinary meetings, such as a geriatrician and an organ-based specialist, to assure a holistic approach taking into account destabilisation and interaction of cancer, other diseases, and its treatments.

Although all previously mentioned solutions have evidence-based benefits in oncology or geriatrics and could be used if adapted to older patients with multimorbidity including cancer, research in multimorbidity has emphasized the importance of shifting away from a single-disease care pathway to an integrated patient-centred approach. This also means integrating the above-mentioned solutions, instead of adding them to an already existing single disease centred care pathway [4,9,20,21]. As no single multimorbidity care pathway will exist that fits all patients, customizing each pathway based on thorough assessment of all problems (related to multimorbidity, cancer, and general health) and patient values will be necessary for patients with multimorbidity [4,9].

In conclusion, the management of older patients with multimorbidity including cancer is complex, and although progress has been made on improving aspects of their care, many challenges still remain. Our study provides an overview of those challenges with possible solutions from oncology and geriatrics adapted to the complexity of patients with multimorbidity including cancer. This information may be used to further develop a patient centred care pathway for older patients with multimorbidity including cancer.

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Author Contribution

Conception and Design: MH.
Data Collection: NS, BOS.
Analysis and Interpretation of Data: NS, MH, SR, SH.
Manuscript Writing: NS, MH.
Approval of Final Article: all authors.

Declaration of Competing Interest

Pierre Soubeyran: Board member with TEVA, Sandoz, BMS and EISAI.

All other authors: No competing interests to declare.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jgo.2023.101588>.

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