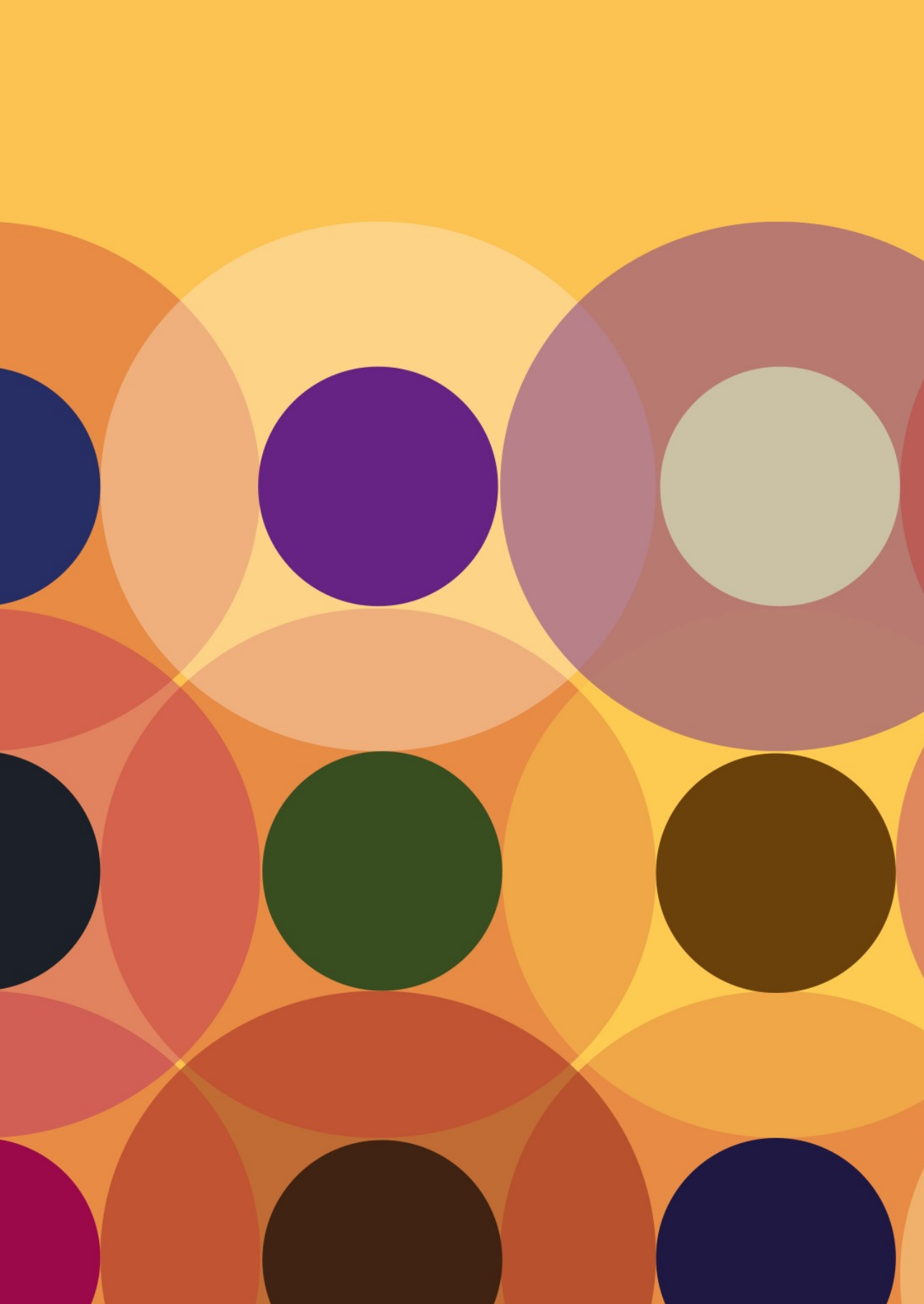
Frailty and outcomes after systemic treatment in older patients with cancer

Baltussen, J.C.



Chapter 11

Summary and general discussion

J. C. Baltussen

SUMMARY

This thesis aimed to study the association between frailty characteristics and treatment- and patient-related outcomes in older adults with cancer who are treated with systemic therapy. The results of the studies conducted in this thesis are discussed below.

Part I - Outcomes after systemic therapy in real-world populations with cancer
Chapter 2 examined the time trends in treatment patterns and survival in a real-world cohort of all Dutch older patients with synchronous metastatic colorectal cancer diagnosed between 2005 and 2020. Findings showed that treatment patterns rapidly changed over the years, with increasing percentages of patients receiving best supportive care. Unexpectedly, survival of metastatic colon cancer decreased from 2014 onwards, suggesting that only a subset of the older population benefited from novel anticancer therapies. **Chapter 3** provided an overview of predictive biomarkers for response and survival for immune checkpoint inhibitors in patients with metastatic melanoma in order to individualize treatment. Results of the review showed that biomarkers for immune checkpoint inhibitors are widely studied, particularly in real-world cohorts, but heterogeneity between studies was high, average sample sizes were low, and validation was often lacking, limiting their usefulness in daily practice.

Part II – Geriatric deficits and their associations with treatment-related toxicity
Chemotherapy remains the cornerstone treatment for most cancer types in older adults. The aim of **Chapter 4** was to identify predictors of poor treatment tolerability in older patients treated with fluoropyrimidine-based chemotherapy from the prospective Alpe2U study. Poor treatment tolerability during the first two cycles increased with the accumulation of impaired geriatric domains. The findings that deficits in three or four geriatric domains, indicating frailty, were predictors of poor treatment tolerability, highlights the importance of pre-treatment frailty assessment to estimate risk of treatment intolerance. **Chapter 5** investigated the association between severe chemotherapy-related toxicity and QoL and physical functioning after chemotherapy initiation in older patients with cancer. In patients with frailty, 76% reported a decline in QoL and/or physical functioning or had died after one year. Of the patients without frailty, 64-68% reported a decline in QoL and/or physical functioning or had died. Patients with frailty had an increased risk of severe toxicity, and the occurrence of toxicity also contributed to declined QoL/physical functioning or mortality after one year. These findings again highlight the role of pretreatment frailty screening and individualized treatment adaptions based on frailty status to prevent treatment-related decline of remaining health. In **Chapter 6** we quantified the time toxicity, defined as the time spent with healthcare contact during treatment, in the initial six months of palliative systemic treatment (mostly chemotherapy) among older patients with metastatic cancer. Older adults with metastatic cancer spend one in five days with healthcare contact during the first six months after diagnosis, with a higher burden of time toxicity among patients potentially living with frailty. Overall, our findings underscored

the importance of informing patients about their expected healthcare contact days within the context of a limited life expectancy.

In recent years, novel systemic therapies beyond traditional chemotherapy have become available for many cancer types. To explore the potential benefits of these less toxic, more targeted treatments for older adults with average health or frailty, it is essential to study their use in real-world older populations. In **Chapter 7**, we studied treatment tolerability of palbociclib and predictors for toxicity in older women with metastatic breast cancer using real world data. Although grade 3-4 toxicity occurred frequently, especially in those with polypharmacy, most toxicities were expected and managed by dose reductions. These findings showed that palbociclib is generally well tolerated and represents a valuable treatment option in the older population. **Chapter 8** investigated cognitive functioning up until two years after treatment initiation in older women with early breast cancer and identified geriatric predictors for cognitive decline after endocrine therapy. Endocrine therapy did not have detrimental effects on cognitive functioning, and even older women living with geriatric deficits did not experience a cognitive decline. These data suggest that the fear of declining cognition does not justify the de-escalation of breast cancer treatment in older women.

Part III – Developing new approaches to study patient-related outcomes in older adults with cancer

Chapter 9 described the study protocol for the DOSAGE trial: a randomized controlled trial aiming to show that upfront dose-reduced chemotherapy in older patients with metastatic colorectal cancer is non-inferior to full-dose treatment in terms of progression-free survival, with adaption of the treatment plan based on expected risk of treatment toxicity. We hypothesize that upfront dose-reduced chemotherapy will lead to lower toxicity rates, better QoL and physical functioning, less hospital admissions and lower health care costs, without compromising survival. **Chapter 10** provided an overview of different methods that analyze longitudinal patient-reported outcomes (PROs) in populations with high mortality during the study-follow up. The interpretation of longitudinal PROs strongly depends on the chosen methods and how mortality is addressed, and different methods led to different conclusions. Properly defining the research question and choosing the right analysis to address mortality is essential to select the most appropriate method that will lead to meaningful interpretations.

Chapter 11

DISCUSSION AND FUTURE PERSPECTIVES

Because evidence regarding the optimal oncological treatment for older patients with frailty or in average health remains limited, this thesis aimed to study the association between frailty characteristics and treatment- and patient-related outcomes in older adults with cancer receiving systemic therapy. Our objectives were to assess outcomes in real-world populations of older patients with cancer, examine the association between geriatric deficits and poor outcomes in those undergoing systemic treatment, and develop new approaches for studying patient-related outcomes in this population.

The importance of frailty identification in treatment decision-making

This thesis highlights the importance of frailty assessment before initiating chemotherapy. Frailty is consistently associated with a high risk of poor chemotherapy tolerability, decreased quality of life and functional status and increased treatment-related time toxicity. Therefore, physicians and patients should integrate frailty status into the shared decision-making to start chemotherapy. Clinical judgement of frailty by cancer specialists has been shown to be insufficient in several studies.[1,2] Another international survey revealed that only one-third of physicians treating cancer currently use frailty screening tools in clinical practice.[3] Therefore, we need fundamental changes in delivery of care, education, research and policy to implement frailty identification in daily practice.

Models-of-care for frailty identification

In recent years, multiple methods for identifying frailty in routine oncology care have emerged, with evidence supporting their effectiveness in lowering treatment toxicity, reducing hospital visits, and improving quality of life for all types of methods.[4-7] A commonly adopted approach is a two-step strategy: initial frailty screening followed by a (comprehensive) geriatric assessment for those who screen positive. The specific method used may vary depending on the hospital's available resources and what best integrates into existing care pathways.

Within a consultative model (GAP70+ trial), the oncology team refers patients to the geriatrics team for a geriatric assessment and their recommendations on interventions.[6] The geriatric team is not involved in the follow-up. In a shared-care model (GAIN trial), the oncology teams refer patients to a geriatric medicine or a geriatric oncology team, with care shared by both teams.[7] In a comprehensive model (INTEGERATE trial), the geriatric assessments and interventions are performed by a geriatric oncologist who is also responsible for the oncologic treatment (**Figure 1**).[5]

In health care systems with limited resources and time, we propose a practical geriatric assessment where a significant part of the questionnaires is completed digitally by patients

themselves.[8] Mobile apps for the geriatric assessment do not require geriatricians and can reduce the burden on time and support staff.[9,10] Another option is the development of a restricted or simplified geriatric assessment, assessing only the most essential domains. A large observational study identified deficits in cognition, comorbidities, and fall risk as the most common factors leading to treatment modifications, suggesting that these three domains may best define an abnormal geriatric assessment.[11] Further studies are needed to determine the value of eHealth or a restricted assessment in clinical practice.

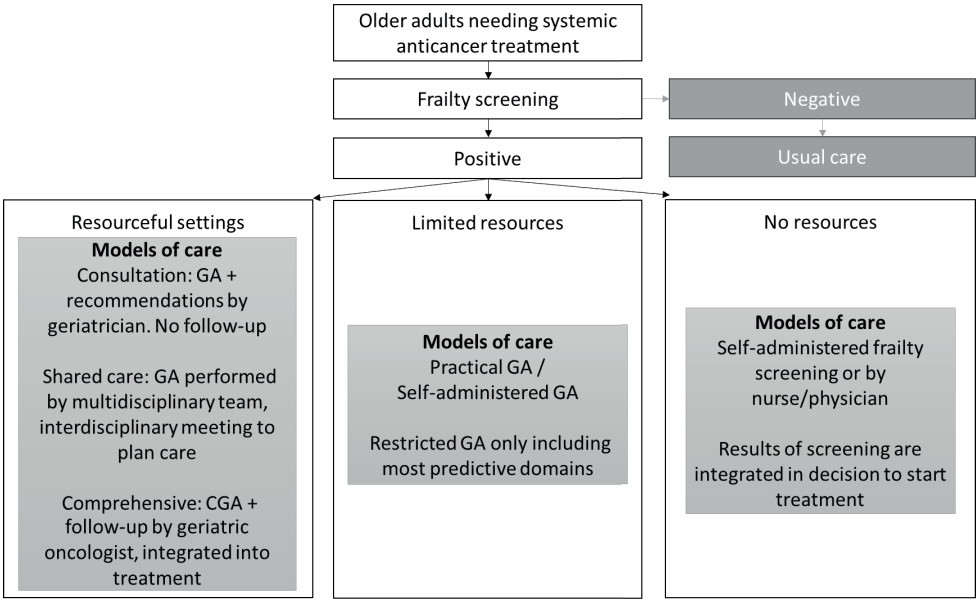


Figure 1. Abbreviations: CGA; comprehensive geriatric assessment, GA; geriatric assessment.

Even in health care systems and hospitals where a geriatric assessment is not feasible, we recommend integrating a brief screening tool into routine care that helps predict which older adults are at increased risk of functional decline, toxicity or mortality.[12,13] Options such as the G8, VES-13, or Clinical Frailty Scale are all reasonable choices, as these tools are all associated with poor outcomes after systemic therapy and can be used in the shared decision to de-escalate treatment.[14-18] Several studies have shown that a self-reported G8 is feasible in older adults with cancer.[19,20] In some oncological care pathways in the Netherlands, the G8 is already implemented as standard screening. For example, 97% of Dutch hospitals offering colorectal cancer surgery use the G8 in hospitalized patients, as it was mandated by a national safety program focused on older patients with frailty in 2008.[21] While Dutch oncological guidelines do not provide recommendations regarding frailty screening, initiatives like these could facilitate its implementation in oncology care.

Education about frailty

More than half of older adults with cancer nowadays are pre-frail or frail and therefore at risk of poor outcomes[22]. Simultaneously, we are facing a global shortage of healthcare staff and healthcare expenses are rising rapidly. Projections of the National Institute for Public Health and the Environment (RIVM) indicate that, by 2060, the Netherlands will be spending 60 billion euros on cancer care alone.[23] Frailty identification can help alleviate these challenges by lowering toxicity-related emergency visits and hospitalizations, consequently reducing pressure on healthcare systems and making oncology care more financially sustainable. Despite these benefits, only 42% of physicians treating cancer worldwide are aware of frailty screening tools beyond performance status scores.[3] This highlights a need for better education on frailty and its role in treatment planning. While palliative care is part of the Dutch curriculum of clinicians in training who will treat patients with cancer, geriatric oncology is not formally incorporated into the training. Organizations such as ESMO and SIOG offer courses, e-learning modules and seminars on geriatric oncology, which could be made mandatory for healthcare professionals treating cancer. In the Netherlands, individual cancer treatment plans are routinely discussed in multidisciplinary teams (MDT), typically consisting of a medical oncologist, surgical oncologist, radiotherapist, pathologist and radiologist. A key opportunity to strengthen knowledge and awareness about caring for older adults would be to include a geriatric expert as part of these MDTs discussing new treatment plans.

The balance between hope and reality

One barrier to treatment de-escalation based on frailty status lies in finding the balance between hope with reality when discussing prognosis and treatment options. Oncologists may find it difficult to reduce or withhold oncological treatment, especially in the metastatic setting. Both patients and clinicians may feel compelled to pursue active treatment, even when its benefits are minimal and side effects are substantial. Active treatment can provide a sense of control over the disease for both patients and oncologists. Moreover, industry marketing campaigns and media reports often hype novel oncological treatments based on trials conducted in younger, fitter populations, which could contribute to their overuse in older patients.[24] Last, oncologists tend to overestimate remaining survival time.[25] However, this thesis emphasizes that the harms of systemic therapy like chemotherapy often outweigh their benefits in older adults with frailty. Clear communication about the true benefits and risks of systemic therapy in patients with frailty is necessary to ensure that they make informed treatment choices, supported with evidence-based guidance, that align with their individual goals. Robust evidence demonstrating the limited benefit and high toxicity of systemic therapy in older patients with frailty can empower clinicians and patients in making the shared decision to opt for de-escalation or supportive palliative care with greater confidence.

To further increase the confidence among oncologists in recommending de-escalated treatment or supportive care, guidelines could incorporate specific treatment recommendations for patients with frailty. For instance, the ESMO guideline for metastatic colorectal cancer acknowledges that patients with frailty do not tolerate combination chemotherapy and recommends focusing on maintaining quality of life and symptom management instead.[26] Unfortunately, most guidelines currently lack such tailored recommendations for patients with frailty[27], as trials investigating treatment outcomes in older adults with cancer are still scarce. A future priority should therefore be to include such treatment recommendations based on robust data to help oncologists and patients in selecting personalized treatment.

The gap between oncology trials and real-world practice

The findings from this thesis also highlight the gap between outcomes observed in oncology trials and the actual outcomes in older patients with cancer treated in daily practice. Oncology trials are typically conducted in highly selected trial populations and pharmaceuticals are approved by regulatory bodies like the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) based on these observations in highly controlled environments. The generalizability of positive survival outcomes observed in trials often appears to be limited when prescribed to more diverse, real-world populations. Based on the poor outcomes found in such observational studies, de-escalation trials like the DOSAGE trial have to be initiated, aiming to reduce toxicity and preserve quality of life. To close the gap between trials and daily practice, older patients should be included more frequently in early trials investigating oncological treatments when they are among the future target population of these treatments.

Why are older patients not included in clinical trials?

In recent years, the FDA and EMA have emphasized the importance of enrolling older patients in industry-sponsored trials.[28,29] Despite their strong recommendations for more inclusive trials designs and the assessment of physical frailty status[29], older patients remain significantly underrepresented in clinical studies. One contributing factor is that older patients are less likely to be offered trial participation due to multimorbidity and frailty.[30] Oncologists may be hesitant to expose older or more frail patients to new compounds that may have unforeseen side effects. Additionally, poor participation may result from the complex protocols and overly restrictive inclusion criteria set by pharmaceutical companies. In the past few decades, there has been a shift from predominantly publicly funded clinical trials, designed to answer questions important to patients, to industry-funded trials focused on achieving regulatory approval or commercial advantage.[31] Sponsors may prefer not to include older patients with frailty due to competing causes of death and a higher risk of poor tolerability and treatment discontinuation, which could diminish the treatment effect and asks for a larger sample size. However, this diminished effect is an accurate estimation of the true clinical benefit in the older population.

Improving trial participation of older patients

Several strategies can be implemented to increase the trial participation of older patients. First, when the primary target population for a new drug comprises older patients with average health status and these have not been included in the original trial, regulatory agencies could mandate pharmaceutical companies to conduct phase IV trials specifically assessing the tolerability in older and less fit patients before approving the drug for this population. Second, sponsors should be encouraged to perform a geriatric assessment in all older participants to assess frailty and provide subgroup analyses of outcomes in frail groups. While the EMA currently recommends the relatively time-consuming Short Physical Performance Battery (SPPB) to assess physical frailty[29], more feasible screening tools, such as the Clinical Frailty Scale (CFS), may serve as practical alternatives.[32,33] A geriatric assessment would offer an even more comprehensive approach to identifying frailty within trial populations. The feasibility of incorporating such assessments has been demonstrated by the CALGB 361006 phase II trial, which successfully embedded a self-reported geriatric assessment among participants aged ≥60 years receiving intensive therapy for acute myeloid leukemia.[34] Similarly, in the Dutch Alpe2U trial investigating toxicity after fluoropyrimidine-based chemotherapy, all participants aged ≥70 years underwent a geriatric assessment by telephone, as described in this thesis. Another approach is to add an extended cohort of older patients to the superior treatment arm. This extended cohort can start with lower dosages, with dose-escalation allowed in case of good tolerability. Last, a separate registration arm for ineligible patients could provide insight into selection bias and the generalizability.

Despite recommendations from the FDA and EMA advocating for participation of older adults, they are not mandatory. Regulatory agencies could set specific demands for the number of older adults with frailty that have to be included in trials.[32] Major journals and reporting guidelines can also mandate the reporting of frailty status or a geriatric assessment in trial publications. Clinicians are other important gatekeepers for the inclusion of older patients, as they decide which patients are offered trial participation. Finally, involving patient advocates in all trial phases can contribute to meet the needs of older patients.

Tailored trials for older adults measuring relevant endpoints

To further promote trial participation for older adults, we have to design trials specifically tailored for this group. One example of such a trial is the DOSAGE trial, described in this thesis. The DOSAGE trial features a unique study design with minimal participation burden, aiming to closely resemble daily oncology practice. While the current guidelines do not provide concrete advise on how to decide between mono- or doublet chemotherapy in older adults, the DOSAGE individualizes the choice between doublet or monochemotherapy based on geriatric variables. By selecting endpoints that matter to older patients, such as quality of life and physical functioning, the results of the DOSAGE will be relevant for the

older population. The GO2 trial is another example of a trial specifically designed for and with older patients with frailty.[35] In this non-inferiority trial, investigating upfront lower-dose chemotherapy in older patients with advanced gastroesophageal tumors, a new composite endpoint was designed by physicians and patients, combining clinical progression, toxicity and quality of life.

Patient-reported outcome (PROs) such as quality of life, cognitive functioning, and time spent on treatment are essential for guiding treatment decisions. For example, Soto-Perez-de-Celis and colleagues recently showed that 83% of older adults with cancer prioritized maintained cognition above prolonged survival[36]. Given the high prevalence of cognitive impairments among older adults, studies assessing cognitive functioning are crucial to understand the impact of treatments on cognition.[37] Another emerging outcome that measures the patient experience of a treatment is time toxicity, or "time spent at home", which refers to the time lost due to treatment-related effects.[38] This is especially relevant in metastatic settings, where patients often trade limited remaining time for marginal treatment benefits. Understanding where and how time is spent—at home, in hospitals, or clinics—can inform more patient-centered decisions. Finally, the concept of resilience (the ability to completely recover from stressors like chemotherapy) has gained increasing attention in geriatric oncology research.[39]. Unlike frailty, which emphasizes vulnerability, resilience focuses on an individual's strengths, resources, and ability to adapt, offering a more positive perspective on older adults' health status. Studying novel outcomes such as cognitive functioning, time toxicity and resilience lead to a better estimation of the true benefits and harms of oncologic treatment in older adults. The growing use of eHealth tools and digital questionnaires will further support the routine assessment of these patient-reported outcomes in clinical studies.

Methodological challenges in measuring patient-reported outcomes

Despite growing interest in PROs in oncology, analyzing longitudinal PROs remains methodologically challenging, especially in geriatric oncology, where many participants die during follow-up, resulting in missing data. Many PRO studies fail to adequately address this mortality in their methodology[40], leading to biased estimates of PRO changes over time with limited clinical relevance. To optimize the validity and relevance of PRO analyses in older adults with cancer, researchers should clearly define the study's research question and choose methods that also address patients who died during follow-up.[40] Involving both patients and clinicians in shaping these questions can further enhance clinical relevance. The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL-IMI) initiative was established recently to develop standardized methodologies for analyzing PRO data in clinical trials.[40,41] By promoting consistent and rigorous approaches, this initiative aims to improve the methodological robustness and interpretability of PRO findings, ultimately supporting more informed clinical decision-making.

Chapter 11

CONCLUSION

In geriatric oncology, tailor-made cancer care remains a challenge. This thesis consistently demonstrates that older adults with frailty have an increased risk of poor clinical and patient-reported outcomes after chemotherapy. A key message of this research is the importance of tailoring treatment plans based on an individuals' frailty status. Furthermore, we must continue to assess the impact of cancer treatments on PROs using methodologically robust studies to build evidence that informs everyday oncology practice. By systematically integrating frailty screening into routine oncology care and generating high-quality data through trials and real-world studies that include PROs, we can move closer to delivering personalized care to the growing population of older adults with cancer.

REFERENCES

1. van Walree IC, Scheepers ERM, van den Bos F, van Huis-Tanja LH, Emmelot-Vonk MH, Hamaker ME. Clinical judgment versus geriatric assessment for frailty in older patients with cancer. *J Geriatr Oncol*. Sep 2020;11(7):1138–1144.
2. Kirkhus L, Saltyte Benth J, Rostoft S, et al. Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. *Br J Cancer*. Aug 8 2017;117(4):470–477.
3. Banna GL, Cantale O, Haydock MM, et al. International Survey on Frailty Assessment in Patients with Cancer. *Oncologist*. Oct 1 2022;27(10):e796–e803.
4. Seghers PAL, Alibhai SMH, Battisti NML, et al. Geriatric assessment for older people with cancer: policy recommendations. *Glob Health Res Policy*. Sep 1 2023;8(1):37.
5. Soo WK, King MT, Pope A, Parente P, Darzins P, Davis ID. Integrated Geriatric Assessment and Treatment Effectiveness (INTEGERATE) in older people with cancer starting systemic anticancer treatment in Australia: a multicentre, open-label, randomised controlled trial. *Lancet Healthy Longev*. Sep 2022;3(9):e617–e627.
6. Mohile SG, Mohamed MR, Xu H, et al. Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. *Lancet*. Nov 20 2021;398(10314):1894–1904.
7. Li D, Sun CL, Kim H, et al. Geriatric Assessment-Driven Intervention (GAIN) on Chemotherapy-Related Toxic Effects in Older Adults With Cancer: A Randomized Clinical Trial. *JAMA Oncol*. Nov 1 2021;7(11):e214158.
8. Dale W, Klepin HD, Williams GR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy: ASCO Guideline Update. *J Clin Oncol*. Sep 10 2023;41(26):4293–4312.
9. Berkowitz CM, Zullig LL, Koontz BF, Smith SK. Prescribing an App? Oncology Providers' Views on Mobile Health Apps for Cancer Care. *JCO Clin Cancer Inform*. Nov 2017;1:1–7.
10. Tan LF, Chan YH, Tay A, Jayasundram J, Low NA, Merchant RA. Practicality and Reliability of Self Vs Administered Rapid Geriatric Assessment Mobile App. *J Nutr Health Aging*. 2021;25(9):1064–1069.
11. Carrozzi A, Jin R, Monginot S, Puts M, Alibhai SMH. Defining an Abnormal Geriatric Assessment: Which Deficits Matter Most? *Cancers (Basel)*. Dec 9
12. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol*. Oct 2012;13(10):e437–44.
13. Rier HN, Meinardi MC, van Rosmalen J, et al. Association Between Geriatric Assessment and Post-Chemotherapy Functional Status in Older Patients with Cancer. *Oncologist*. Nov 3 2022;27(11):e878–e888.
14. Pearce J, Swinson D, Cairns D, et al. Frailty and treatment outcome in advanced gastro-oesophageal cancer: An exploratory analysis of the GO2 trial. *J Geriatr Oncol*. Apr 2022;13(3):287–293.
15. Stokoe J, Pearce J, Sinha R, Ring A. G8 and VES-13 scores predict chemotherapy toxicity in older patients with cancer. *Journal of Geriatric Oncology*. 2012;3
16. Cavdar E, Iriagac Y, Karaboyun K, Avci O, Seber ES. Prospective comparison of the value of CARG, G8, and VES-13 toxicity tools in predicting chemotherapy-related toxicity in older Turkish patients with cancer. *J Geriatr Oncol*. Jul 2022;13(6):821–827.
17. van Walree IC, Scheepers E, van Huis-Tanja L, et al. A systematic review on the association of the G8 with geriatric assessment, prognosis and course of treatment in older patients with cancer. *J Geriatr Oncol*. Nov 2019;10(6):847–858.
18. Gomes F, Lorigan P, Woolley S, et al. A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients - the ELDERS study. *ESMO Open*. Feb 2021;6(1):100042.

19. Chon J, Timilshina N, AlMugbel F, et al. Validity of a self-administered G8 screening test for older patients with cancer. *J Geriatr Oncol*. Sep 2023;14(7):101553.
20. van Walree IC, Vondeling AM, Vink GR, et al. Development of a self-reported version of the G8 screening tool. *J Geriatr Oncol*. Nov 2019;10(6):926–930.
21. Molenaar CJL, Reudink M, Sabajo CR, et al. Prehabilitation for patients with colorectal cancer: a snapshot of current daily practice in Dutch hospitals. *Perioper Med (Lond)*. May 8 2023;12(1):15.
22. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol*. Jun 2015;26(6):1091–1101.
23. RIVM. *Toekomstverkenning zorguitgaven 2015-2060*. 2020.
24. Rubagumya F, Galica J, Rugengamanzi E, et al. Media coverage of cancer therapeutics: A review of literature. *J Cancer Policy*. Jun 2023;36:100418.
25. Gripp S, Moeller S, Bolke E, et al. Survival prediction in terminally ill cancer patients by clinical estimates, laboratory tests, and self-rated anxiety and depression. *J Clin Oncol*. Aug 1 2007;25(22):3313–20.
26. Cervantes A, Adam R, Rosello S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. Jan 2023;34(1):10–32.
27. Pinker I, Lafont C, Liposits G, et al. Representation of geriatric oncology in cancer care guidelines in Europe: a scoping review by the International Society of Geriatric Oncology (SIOG). *ESMO Open*. Apr 11 2025;10(5):105052.
28. Kim ES, Bruinooge SS, Roberts S, et al. Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. *J Clin Oncol*. Nov 20 2017;35(33):3737–3744.
29. EMA. *Reflection paper on physical frailty: instruments for baseline characterisation of older populations in clinical trials - First version*. 2018. 09–01–2018.
30. Unger JM, Hershman DL, Fleury ME, Vaidya R. Association of Patient Comorbid Conditions With Cancer Clinical Trial Participation. *JAMA Oncol*. Mar 1 2019;5(3):326–333.
31. Del Paggio JC, Berry JS, Hopman WM, et al. Evolution of the Randomized Clinical Trial in the Era of Precision Oncology. *JAMA Oncol*. May 1 2021;7(5):728–734.
32. Wildiers H, de Glas NA. Anticancer drugs are not well tolerated in all older patients with cancer. *Lancet Healthy Longev*. Oct 2020;1(1):e43–e47.
33. Church S, Rogers E, Rockwood K, Theou O. A scoping review of the Clinical Frailty Scale. *BMC Geriatr*. Oct 7 2020;20(1):393.
34. Klepin HD, Ritchie E, Major-Elechi B, et al. Geriatric assessment among older adults receiving intensive therapy for acute myeloid leukemia: Report of CALGB 361006 (Alliance). *J Geriatr Oncol*. Jan 2020;11(1):107–113.
35. Hall PS, Swinson D, Cairns DA, et al. Efficacy of Reduced-Intensity Chemotherapy With Oxaliplatin and Capecitabine on Quality of Life and Cancer Control Among Older and Frail Patients With Advanced Gastroesophageal Cancer: The GO2 Phase 3 Randomized Clinical Trial. *JAMA Oncol*. Jun 1 2021;7(6):869–877.
36. Soto-Perez-de-Celis E, Dale W, Katheria V, et al. Outcome prioritization and preferences among older adults with cancer starting chemotherapy in a randomized clinical trial. *Cancer*. Apr 17 2024;
37. Galvin A, Soubeyran P, Brain E, et al. Assessing patient-reported outcomes (PROs) and patient-related outcomes in randomized cancer clinical trials for older adults: Results of DATECAN-ELDERLY initiative. *J Geriatr Oncol*. Jan 2024;15(1):101611.
38. Gupta A, Eisenhauer EA, Booth CM. The Time Toxicity of Cancer Treatment. *J Clin Oncol*. May 20 2022;40(15):1611–1615.
39. George T, Shah F, Tiwari A, et al. Resilience in older adults with cancer: A scoping literature review. *J Geriatr Oncol*. Jan 2023;14(1):101349.
40. Liu L, Choi J, Musoro JZ, et al. Single-arm studies involving patient-reported outcome data in oncology: a literature review on current practice. *Lancet Oncol*. May 2023;24(5):e197–e206.

41. Pe M, Alanya A, Falk RS, et al. Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative (SISAQOL-IMI): stakeholder views, objectives, and procedures. *Lancet Oncol*. Jun 2023;24(6):e270–e283.