Integrating supportive and palliative care into treatment of immunotherapy-sensitive cancers
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SUMMARY, DISCUSSION, AND FUTURE PERSPECTIVES
Chapter 10

Summary

The introduction of targeted therapies and immune checkpoint inhibitors has greatly improved the prognosis associated with various advanced cancers. For example, in advanced melanoma, the 5-year overall survival improved from 5-19% before 2010 to 26-52% in the current immune checkpoint inhibitor treatment era. Similar trends have been observed in other advanced cancers sensitive to immune checkpoint inhibitors. Nowadays, immune checkpoint inhibitors are standard of care for various recurrent and metastatic cancers and in some cancer types they are also indicated in earlier treatment settings (i.e., adjuvant and neoadjuvant settings). However, not all patients will benefit from these treatments, and it is currently not possible to predict which patients will experience long-term disease control. For these patients, the prognosis is still very uncertain at time of diagnosis of advanced cancer and ranges from long-term survival to (rapid) deterioration and death. Due to the possibility of long-term survival, the main focus of patients and physicians can often be on the anti-tumor treatment, and therefore patients’ and caregivers’ supportive and palliative care needs may be overlooked. Patient-centered care with attention to physical, social, psychological, and existential issues is crucial to improve quality of life of patients and their informal caregivers throughout the disease trajectory. This is best accomplished when supportive and palliative care are integrated with effective anti-tumor treatment. This thesis aimed to describe, analyze, and improve the care of patients with advanced immune checkpoint inhibitor-sensitive cancers across the disease trajectory by improving the integration of supportive and palliative care into effective anti-tumor treatment.

In chapter 1, we briefly introduced the clinical challenges addressed in this thesis regarding the provision of supportive and palliative care and anti-tumor treatment in the current treatment era.

The often impressive and durable responses to immune checkpoint inhibitors in patients with advanced cancers have expanded immune checkpoint inhibitor treatment to earlier disease stages. This is especially attractive in settings where extensive functionally or cosmetically mutilating localized anti-tumor treatments are currently standard of care and for patients with a high risk of disease recurrence after initial localized treatment. In the review included in chapter 2, we described the development of immune checkpoint inhibitors from the metastatic setting to the neoadjuvant setting in patients with melanoma, Merkel cell carcinoma (MCC), cutaneous squamous cell carcinoma (cSCC), and basal cell carcinoma (BCC). In melanoma, neoadjuvant nivolumab plus ipilimumab in the original dosing regimen induced high rates of complete pathological response in patients with stage III melanoma, however, this treatment was associated with high rates of immune-related toxicities. Therefore, the optimal neoadjuvant nivolumab plus ipilimumab dosing regimen with the best balance between efficacy and toxicity was determined. In the large, ongoing phase 3 NADINA study (NCT04949113), neoadjuvant nivolumab plus ipilimumab followed by surgery is currently randomized against surgery followed by adjuvant nivolumab in patients.
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with stage III melanoma with at least one macroscopic lymph node metastasis. This study will provide insight into the optimal treatment approach of stage III melanoma. For MCC, cSCC, and BCC immune checkpoint inhibitors are registered treatments in the advanced setting. The response rates associated with single-agent immune checkpoint inhibitor treatment in the advanced setting range from 31% in BCC to 58-62% in patients with MCC, and are comparable to those in melanoma (34-44%). Considering the similar response rates and efficacy of neoadjuvant treatment in melanoma, there is a rationale to assume neoadjuvant efficacy in non-melanoma skin cancers. This is in line with 2 phase 1/2 trials in MCC and cSCC, which demonstrated that approximately half of the patients experienced a complete pathological response after neoadjuvant immune checkpoint inhibitors. Small (15-76 proposed participants) neoadjuvant immune checkpoint inhibitors studies in patients with MCC, cSCC, and BCC aim to further confirm the efficacy and are currently ongoing.

The implementation of immune checkpoint inhibitors also revolutionized the treatment of patients with melanoma brain metastases, resulting in a more important role for brain MRI-scans. The clinical utility of brain MRI-scans, including screening MRI-scans for brain metastases and follow-up MRI-scans to monitor brain metastases, was examined and reported in chapter 3. Screening MRI-scans performed in 116 patients with metastatic melanoma without brain metastases at diagnosis were examined. During the two years after the initial diagnosis of metastatic melanoma without brain metastases, 28 out of 116 patients (24%) developed brain metastases. Screening MRI-scans detected the brain metastases in 11 out of 28 patients (39%), of which 8 patients were asymptomatic. The number of treatment changes after follow-up MRI-scans was evaluated in 96 patients with melanoma brain metastases. In the first year after the diagnosis of brain metastases, changes in treatment were observed after 75 out of 168 follow-up MRI-scans (45%). In patients that had been treated with immune checkpoint inhibitors for over 6 months, fewer treatment changes were observed after follow-up MRI-scans compared to those performed in patients <6 months on treatment. These outcomes support the need for routine MRI-scans in patients with metastatic melanoma to detect brain metastases at an early time point and, in those with brain metastases, to inform treatment decisions. Furthermore, this study can help develop protocols for the timing of brain-imaging in patients with cancers sensitive to immune checkpoint inhibitors and have a high propensity to metastasize to the brain.

The efficacy and durability of responses associated with immune checkpoint inhibitors resulted in a new group of survivors of advanced cancer. These patients may suffer from long-term treatment sequelae and the impact of the initial diagnosis of a life-threatening disease. Limited knowledge was available on quality of life of this new cancer survivor group and their informal caregivers. Therefore, in chapter 4, we described our study on quality of life, neurocognitive functioning, and psychological issues in patients surviving at least two years after immune checkpoint inhibitors. The preliminary report included 120 patients (64 melanoma, 45 NSCLC, and 11 urogenital patients) and 74 paired informal caregivers. Patients
were at median 19 months (range: 0 – 68) after the last cycle of immune checkpoint inhibitor, and at the time of study visit, 56 patients (47%) still had ongoing treatment toxicity (defined as receiving active treatment for or hormonal supplements due to the toxicity). Compared to the general European population, patients reported lower physical, role, and cognitive functioning, while the global health status was maintained. Fifty-two patients (45%) reported neurocognitive concerns, and neurocognitive impairment on neuropsychological tests was present in 27 (23%) patients. Being in a relationship, actively working at the time of study visit, and the severity of depressive/anxiety symptoms were associated with patient’s reported global health status. Items that were part of the positive adaptation subscale of the caregiver quality-of-life questionnaire were scored lowest. Furthermore, a discrepancy between the reported quality of life was observed in 41% of the paired patients and caregivers. This study demonstrated the ongoing impact of being diagnosed with advanced cancer and having received immune checkpoint inhibitors on both the patients and their informal caregivers. Survivorship care interventions need to be tailored to address these issues in this new survivor population.

We further evaluated neurocognitive functioning in cancer patients and reported these outcomes in Chapter 5. Seventy-seven patients with metastatic NSCLC were included in this cross-sectional study. Forty-one patients had brain metastases (53%), and 23 received cranial irradiation (29%). Neurocognitive impairment was present in 31 patients (40%), and 20 patients (26%) reported neurocognitive concerns. This demonstrates the high proportion of patients dealing with neurocognitive issues. Neurocognitive impairment and neurocognitive concerns were unrelated. Neurocognitive impairment was related to cranial irradiation (OR=2.89, p=0.03), and the presence of neurocognitive concerns was related to greater illness intrusiveness (OR=1.04, p=0.04) and lower self-esteem (OR=0.86, p=0.03). These associations suggest that neurocognitive rehabilitation strategies should focus not only on neurocognitive skills and strategy training, but also on life engagement and preservation of self-esteem.

Another issue that can significantly impede a patient’s quality of life across the disease trajectory is existential distress, such as death anxiety. Early identification of such distress can aid healthcare providers in deciding which patients should be proactively offered tailored interventions. In Chapter 6, we determined which factors were associated with death anxiety in patients with metastatic NSCLC (same study cohort as described in Chapter 5). At least moderate death anxiety was reported by 43% (n=33), including 15 patients with severe death anxiety. Demoralization and depression were reported by 25 (33%) and 19 (25%) patients, respectively. Greater demoralization and illness intrusiveness were associated with higher levels of death anxiety, highlighting the need for interventions that support life engagement while also facing and preparing for death.

Despite the rapid developments in anti-tumor treatment, most patients with melanoma brain metastases will still die of their disease. In Chapter 7, the study in which we retrospectively
evaluated the treatments provided and healthcare consumption in the last three months of life in 100 patients with melanoma brain metastases was reported. This insight was needed because the implementation of immune checkpoint inhibitors and targeted therapies may also result in changes in anti-tumor treatment near death. Systemic anti-tumor treatments were provided to 72% of patients during the last three months, 34% in the last months, and 6% in the last week of life. Significantly more patients harboring a \textit{BRAF}-mutation received systemic anti-tumor treatment during the last three (85% vs. 47%) and last month of life (42% vs. 18%) compared to patients without a \textit{BRAF}-mutation. Furthermore, more patients that received anti-tumor treatment visited the ER more often (75% vs. 36%) and were more frequently hospitalized (75% vs. 36%) than those who did not. The acquired insight into this last phase of life can inform the development of care pathways for patients with melanoma brain metastases. What remains to be determined is the impact of ongoing anti-tumor treatment on the patient’s quality of life in the current treatment era.

In patients that eventually die of their disease, the preferred place to die is most often at home. Hospitalized, terminally ill patients are frequently discharged home to die. These discharges are complex and require adequate collaboration between the hospital, home care organizations, and general practitioners (GPs). However, these complex hospital discharges have hardly been explored. In chapter 8, we described a method to systemically analyze the hospital discharge procedures and the results of the evaluation of the hospital discharges from the UMCG between June and November-2014. The proposed method includes an inventory questionnaire to determine the required care at home prior to the discharge and a subsequent evaluation questionnaire to assess the provided care. Furthermore, within this evaluation method, home care nurses were asked to score the quality and completeness of the hospital discharge handovers. This method was applied to 130 hospital discharges of terminally ill patients. The transfer succeeded on the desired discharge date for the majority of patients (n=112, 86%). In the patients that were not discharged on the desired discharge date, the most common reason for the delay was that the home care organization could not deliver the required care in time (n=6). In 23% of patients, discrepancies between the required and delivered care existed, and 29% of home care nurses had questions regarding medication use. The overall grade for the discharge was 7.4 on a 10-point scale (range: 3 – 9.5). The proposed evaluation method can be used in any hospital to systematically analyze the hospital discharge procedures and identify areas of improvement. In the UMCG, these areas were related to the mismatch in required and provided care and the discharge handover’s clarity.

To support the integration of supportive and palliative care into anti-tumor treatment, from cancer diagnosis to long-term survival or death, care pathways can be used. We, therefore, aimed to develop and implement a care pathway for patients with melanoma and NSCLC brain metastases (chapter 9). Patients with brain metastases are vulnerable, and limited intracranial progression can cause rapid deterioration and death. Their vulnerability makes integrated supportive and palliative care of great importance. To
inform the development of the care pathway, we evaluated the care of patients with brain metastases from the perspectives of patients, informal caregivers, GPs, and UMCG-based healthcare professionals. These evaluations showed that patients and informal caregivers experienced high levels of distress, were interested in additional supportive/palliative care, and experienced unmet informational needs. The GPs expressed the wish to receive additional guidance on the management of brain metastases symptoms. The hospital-based healthcare professionals requested a more structured approach to information-, supportive care-, and palliative care provision. The outcomes of this evaluation and the available literature on supportive and palliative care in neuro-oncological patients (e.g., potential interventions strategies regarding the expressed issues) informed the development of the care pathway. The developed care pathway begins at diagnosis of brain metastases and ends when patients enter the survivorship program or die. The care pathway included patient pamphlets with information on potential treatments, symptoms, and palliative care availability. Guidelines for the GPs on managing brain metastases symptoms in a home setting were also constructed. These guidelines are now sent to the GP at time of brain metastases diagnosis and when the care is transferred from the oncologist to the GP. Furthermore, the care pathway included healthcare evaluation conversations to improve the early identification of supportive and palliative care needs and initiate advance care planning. The subsequent implementation phase showed some initial problems with patient accrual and inclusion. These issues were tackled by providing additional information on the care pathway to the medical and pulmonary oncologists involved and providing help by identifying eligible patients. Additionally, the care pathway was individualized according to patient’s needs. The upcoming evaluation will inform the impact of the care pathway on perceived provision of adequate supportive and palliative care and information by patients and their informal caregivers.

**Discussion and future perspectives**

As described in this thesis, we can effectively manage various advanced cancers with targeted therapies and immune checkpoint inhibitors. However, this success has also created challenges in optimizing anti-tumor treatment while still meeting patients’ and informal caregivers’ supportive and palliative care needs. Some of these challenges were assessed in this thesis, and the findings can guide future research.

**Neoadjuvant immune checkpoint inhibitory treatment approaches**

The implementation of neoadjuvant immune checkpoint inhibitors in patients with melanoma, MCC, cSCC, and BCC is an important development to improve patient outcomes ([chapter 2](#)). However, the current neoadjuvant approaches still consist of neoadjuvant immune checkpoint inhibitors followed by surgical resection of the lesion and (sometimes) adjuvant treatment. By resecting the lesion, the aim is to remove any residual (microscopic) tumor. The subsequent pathological evaluation of the lesion provides additional insight into
the anti-cancer response, potentially informing further treatment strategies, and providing valuable research data. Still, the surgical resection can lead to functionally debilitating or cosmetically mutilating effects, especially when lesions are in functional or visible areas or when the resection is associated with a high risk of complications. In melanoma patients with macroscopic lymph node metastases, complete lymph node dissection is standard of care. However, the additive value of the complete lymph node dissection can be questioned in patients with a complete response to immune checkpoint inhibitors. Similar questions regarding de-escalation of treatment are arising in other immune checkpoint inhibitor-sensitive cancers, such as in patients with (colorectal) cancers that are deficient in mismatch repair proteins. These types of cancers are highly responsive to immune checkpoint inhibitors. Future research needs to focus on identifying surrogates for pathological response evaluation and evaluating the safety of omitting surgical resections after neoadjuvant treatment in patients with immune checkpoint inhibitors-sensitive cancers.

Imaging modalities may aid in identifying patients with or without residual disease. Radiological response using conventional CT- or MRI-scans correlated with pathological response in 112 melanoma patients treated with immune checkpoint inhibitors. All patients with a complete radiological response had a (near) pathological complete response, as did most patients with a partial radiological response (83%). However, there are also limitations to the use of conventional radiological imaging. Non-melanoma skin cancers are often poorly defined, have an infiltrative appearance on scans, and potential scarring of tumors may impede interpretation of the response after neoadjuvant treatment. PET-imaging (e.g., FDG-PET-scans) can also detect skin cancer lesions. More importantly, metabolic (complete) responses on FDG-PET-scans have been associated with prolonged progression-free survival and overall survival in, for example, advanced melanoma and MCC. Evidence is also emerging that immuno-PET imaging can predict response to immune checkpoint inhibitors in the advanced setting. Future studies need to establish the potential role of PET-imaging in the neoadjuvant setting. Another technique to visualize cancer is fluorescent molecular imaging, which has been used to identify cancerous lesions and guide surgery. The location of skin cancers on the body's surface facilitates the use of fluorescent molecular imaging. As such, cancer lesions as small as 0.3 mm³ can be detected. However, the clinical utility of such techniques, especially in the evaluation after neoadjuvant immune checkpoint inhibitors are yet to be determined. Next to these imaging modalities, the role of circulating tumor DNA (ctDNA) in cancer management has also been receiving increasing attention. ctDNA is the fraction of cell-free DNA (i.e., DNA present in the plasma or serum) that originates from the tumor cells. The potential application of ctDNA varies widely from detecting oncogenic mutations to early detection of disease progression or residual disease. The latter may be of interest in the neoadjuvant setting and may aid in selecting patients that require additional treatment after neoadjuvant treatment. To date, results of studies that evaluated the potential of differentiating patients with a complete pathologic response and those with residual disease prior to surgery by ctDNA are conflicting and warrant future studies. A Dutch initiative (FORCE) to establish an infrastructure to collect big-data,
including clinical data, tumor tissue, and ctDNA, of patients with rare cancers, such as MCC, is ongoing. Analyses of data from such initiatives will help understand the potential use of ctDNA.

Next to the identification of patients in which de-escalation of treatment is safe, it remains important to determine the optimal treatment strategies in those (eventually) progressing. Future studies may, therefore, also focus on the efficacy of retreatment with immune checkpoint inhibitors in those that received neoadjuvant treatment.

**MR-imaging for brain metastases in the era of effective treatment options**

We demonstrated that brain MRI-scans aid in the early diagnosis of melanoma brain metastases and inform treatment strategies in patients with melanoma brain metastases (*chapter 3*). These outcomes are also relevant to patients with other cancers with a high propensity to metastasize to the brain and for which effective treatment approaches are available (e.g., NSCLC, renal cell carcinoma, and breast cancer). To optimize scanning protocols, studies may focus on identifying patients at high risk of brain metastases development. Several risk factors for brain metastases have already been identified, including mutations (e.g., ALK-, HER2-, BRAF-mutation), extracranial metastases burden, and high LDH-levels. However, differences in the mutational profiles between primary tumors and paired brain metastases have been described. Evidence is emerging that brain metastasis-initiating cells have a distinct genetic profile, which may already be detected in the primary tumor and such profiles may help identify patients in which active screening for brain metastases is beneficial.23,24

Future research also needs to determine the optimal treatment approach for brain metastases and how MRI-scans can inform these treatment decisions. In the case of asymptomatic brain metastases, stereotactic radiosurgery can be provided to minimize the chance of developing symptoms. However, after stereotactic radiosurgery 10-25% of patients develop radionecrosis.25,26 Symptomatic radionecrosis can, in turn, impede a patient’s quality of life. Considering the intracranially effective systemic treatments, the need for stereotactic radiosurgery at the different time points in the disease trajectory (e.g., at diagnosis or progression on systemic treatment) need to be investigated.

**Prevention of brain metastases formation**

Despite intracranially effective treatments, patients with brain metastases still have a poorer prognosis compared to patients without brain metastases. Moreover, symptoms due to brain metastases can decrease quality of life. Healthcare costs are also higher for patients with brain metastases compared to patients without brain metastases (ranging from $6,029 to 6,366 per patient per month in NSCLC patients with a driver mutation27,28). Therefore, future studies may focus on preventing brain metastases development.
Four essential steps have been proposed for the development of brain metastases: the arrest of cancer cells at blood vessel branches, early extravasation, maintaining a strict perivascular position, and angiogenesis or vessel cooption. Hence, prevention strategies targeting those steps might inhibit brain metastases formation. The arrest of cancer cells in brain microvessels is influenced by blood clot formation and von Willebrand factor deposition in mice. In mice, clot formation, cancer cell arrest, and brain metastases formation were prevented by treatment with low molecular weight heparin, dabigatran, or an anti-von Willebrand factor antibody. However, the impact of such an approach may be limited to the first phase of brain metastases development in which cancer cells colonize the brain. The last step of the development of NSCLC brain metastases was found to be dependent on vascular changes followed by angiogenesis. Therefore, angiogenesis inhibitors, like bevacizumab and nintedanib, have been tested as a means to prevent the development of brain metastases in patients with NSCLC, and these agents resulted in lower rates of brain metastases development. Immune checkpoint inhibitors, which are effective against developed brain metastases, can also reduce brain metastases development. The latter has been demonstrated in a retrospective study of 293 patients with advanced melanoma. To confirm these outcomes, data on brain metastases occurrence needs to be collected from the adjuvant and metastatic immune checkpoint inhibitor trials. To eventually determine the clinical implication of prevention strategies, the balance between the cost of therapy (e.g., toxicity and healthcare costs) versus the benefits of reducing brain metastases incidence warrants further investigation. For example, for prophylactic cranial radiotherapy, the cost-benefit ratio might be questioned considering the established impact on neurocognitive functioning and the possibility of long-term survival. Though newer techniques to minimize the neurocognitive sequelae, including prophylactic cranial irradiation with hippocampal-sparing, may change this cost-benefit ratio and warrants further study.

Ongoing BRAF/MEK-inhibition in patients with melanoma brain metastases near death

If melanoma patients with a BRAF-mutation develop brain metastases, BRAF/MEK-inhibitors are an effective treatment option. These agents may be provided as initial treatment to induce rapid tumor responses to alleviate symptoms. Furthermore, as we demonstrated in chapter 4, BRAF/MEK-inhibitors are also provided as re-challenge and postprogression treatment near death, in our study in a quarter of patients in the last three months of life. However, there is limited evidence on the effectiveness of these approaches in melanoma brain metastases.

In three small studies, the efficacy of re-challenge BRAF/MEK-inhibition was determined. A phase 2 study including 24 patients (including 17 with brain metastases) reported a re-challenge response rate of 32%, and two retrospective studies reported re-challenge response rates of 27% and 43% in 51 patients (31 with brain metastases) and 116 patients (51 with brain metastases), respectively. When BRAF-inhibitors are ceased due to progressive disease, outgrowth of tumor cells that are sensitive to BRAF-inhibition can
occurs.\(^{41,42}\) Hence, explaining treatment response at time of re-challenge. An important side note of these studies, which demonstrated efficacy of re-challenge BRAF/MEK-inhibition, is that many of these patients were initially treated with BRAF-inhibitor monotherapy. Nowadays, the combination of BRAF- and MEK-inhibitors is the standard. Therefore, future studies should determine the response rates associated with re-challenge BRAF/MEK-inhibition in a sufficiently large cohort of patients with melanoma brain metastases initially treated with combinational BRAF/MEK-inhibition treatment.

Postprogression BRAF/MEK-inhibition aims to avoid rapid tumor progression and clinical deterioration.\(^{43}\) Patterns of disease progression in patients with melanoma treated with BRAF/MEK-inhibitors were evaluated in 180 patients, and 47 of these patients (26\%) continued BRAF/MEK-inhibition beyond disease progression.\(^{44}\) The impact on symptom control and quality of life, considered to be more important in the last phase of life, was not evaluated in this study. Some of the quality indicators of end-of-life care include the degree of symptom control and the number of patients dying at the preferred place of death, receiving palliative care, or receiving aggressive care near death.\(^{45-47}\) Ongoing anti-tumor treatment may impede adequate preparation for death, as anti-tumor treatments may provide hope for the patients and caregivers. Therefore, it is crucial to determine the impact of ongoing targeted therapies near death on symptom burden and patients’ and informal caregivers’ preparation for death. Furthermore, despite most of the care being often transferred to the GPs in this phase of life, the oncologists will provide the postprogression treatment. This requires intensive collaboration and can complicate the care transition. Therefore, the GPs’ perception on the care transitions including the collaboration with the hospital-based healthcare professionals should also be assessed.

**Neurocognitive issues in advanced cancer patients and survivors require more attention**

Luckily, more patients with advanced cancers are experiencing long-term disease control. In those patients, long-term functional abilities and independence are of great importance. We demonstrated that neurocognitive issues (neurocognitive impairment and neurocognitive concerns) are frequent in advanced cancer patients and survivors (chapter 5 and chapter 6). Worryingly, these neurocognitive issues are not regularly assessed in oncology clinics. In line with other research, we observed that neurocognitive impairment on neuropsychological tests was unrelated to patient-reported neurocognitive concerns.\(^{48-50}\) Therefore, patients may exhibit neurocognitive impairment without complaining about these symptoms. Vice versa, patients can experience neurocognitive concerns without showing impairment on neuropsychological tests.\(^{51}\) Both neurocognitive issues can pose significant patient and caregiver burden and, therefore, merit clinical and research attention. Most studies that have evaluated neurocognitive issues are cross-sectional or small longitudinal studies. Therefore, there is a high need for large longitudinal studies evaluating neurocognitive impairment and concerns. These studies may provide better insight into neurocognitive issues in this advanced cancer population. Those findings can help tailor neurocognitive rehabilitation strategies for cancer patients and their caregivers.
Illness intrusiveness as a target to improve quality of life of cancer patients and survivors

Another common issue in cancer patients is illness intrusiveness. Illness intrusiveness derives from illness- and treatment-related lifestyle disruptions that interfere with continued involvement in activities and interests that the patient values. Earlier research has suggested that illness intrusiveness links the circumstances of cancer and treatment with patient well-being and distress. The impact of illness intrusiveness has been proposed to result from less engagement in valued activities and experiencing decreased personal control due to the limitations caused by the disease burden. We observed that neurocognitive concerns (chapter 6) and death anxiety (chapter 7) were linked to illness intrusiveness, assessed by a validated measure, in patients with metastatic NSCLC. Furthermore, the global health status of advanced cancer survivors was associated with being employed at the time of study visit, which may also indicate the positive association between life engagement and quality of life (chapter 5). Various studies demonstrated that cancer survivors experience limitations in engaging in activities and experience lifestyle disruptions. Those findings make illness intrusiveness an interesting target for interventions that aim to improve the overall quality of life. In patients actively receiving treatment with a still uncertain outcome, life engagement should be enhanced in parallel with facing and preparing for the possible death. Such a capacity is referred to as double awareness. Managing Cancer and Living Meaningfully (CALM) is a brief, psychotherapeutic intervention that provides reflective space for patients and their caregivers to recover the capacity to mentalize and reimagine possibilities for living in the face of their disease. This may result in enhanced engagement in meaningful activities while acknowledging the life-threatening nature of their disease. For cancer survivors, interventions may focus on skills-building, support in maintaining active involvement, or finding substitute activities that are less vulnerable to illness- or treatment-related disruptions.

Improving implementation of routine symptom assessment tools

Identifying symptoms that patients suffer from is critical to ensure those in need are offered access to adequate interventions. Routine symptom assessment can help to identify symptoms. As such, routine symptom assessments, including their review and interpretation by healthcare professionals, has been shown to enhance communication between patients and healthcare professionals, reduce hospital readmissions, and improve patients’ quality of life. Nevertheless, symptom assessment is still rarely performed systematically and is not always included in the decision-making processes. Barriers to the adequate implementation of routine symptom assessments include time constraints, difficulties related to the interpretation, and lack of resources, including the inability to promptly refer patients for appropriate support. The challenges related to the interpretation may be caused by the many symptom assessment tools available and difficulties in presenting the outcomes of the previous assessments. The first may be tackled by determining which validated symptom assessment tool captures (differences in) symptoms important to the patient and can predict who needs to be referred to additional supportive or palliative...
care services. The difficulties with tracking symptoms can be resolved by using electronic assessment tools that are embedded in the patient records. Electronic assessments and presentation of results have been shown to facilitate communication and might result in more efficient and focused use of time. Most trials on routine symptom assessment have been performed within the large academic cancer centers. Therefore, generalizability to the larger field of community hospitals might be questioned. The ongoing multicenter, cluster-randomized study examining electronic patient-reported outcome tools in routine care at community oncology practices based in the United States of America (PRO-TECT trial, NCT03249090) is therefore of great interest. A Dutch initiative to improve routine symptom assessments is the Multidimensional Strategy to Improve Quality of Life in patients with Multiple Symptoms and Palliative Care Needs (MuSt-PC, NCT03665168). This nationwide study aims to develop a tool that captures the presence of simultaneously occurring, multidimensional symptoms. Identification of these multiple symptoms allows a combined treatment approach.

**Improving provision and healthcare provider and public knowledge of palliative care**

Multiple palliative care trials have demonstrated that early palliative care improves symptom control, quality of life of patients and caregivers, decreases time spent in hospitals, and enhances communication about end-of-life care preferences and prognosis. 63–67 Considering this large body of evidence on palliative care, 30 experts in oncology, palliative care, public health, and psycho-oncology concluded that the question is no longer whether and why the integration of palliative care is worthwhile, but how this can best be accomplished to optimize the patient-centered care. 59 This “Lancet Commission” also presented two clusters of barriers to integration of palliative care: (1) traditional and current attitudes to palliative care and (2) lack of commitment from decision-makers.

To overcome the first cluster, public and healthcare provider knowledge on palliative care should be increased. A recent survey among over 1500 Canadian citizens revealed that over half of the participants agreed that palliative care was a last resort when other treatment had failed and was the same as end-of-life care. 68 Furthermore, only 54% of participants knew that palliative care could be provided concurrently with other treatments that aim to prolong life, and only 40% understood it could be provided early in the disease course. Encouragingly, 90% of participants agreed that Canadians should be made aware that palliative care can be included early in the disease course. These findings highlight the need for awareness initiatives and education programs to ensure that palliative care is optimally utilized. Next to the knowledge of the public, healthcare provider knowledge on palliative care also needs to be increased. For example, a study examining patient’s perceptions of palliative care revealed that their healthcare providers had equated palliative care with end-of-life care. 69 Considering the broad application of palliative care across different diseases, palliative care education should start as early as medical school. A European Association of Palliative Care (EAPC) study from 2015 demonstrated that palliative medicine was only taught in 30% in the
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medical schools of the participating countries, revealing a high need to improve palliative care education among medical students. To further improve the quality and provision of palliative care, healthcare culture palliative care education programs need to be developed, and basic palliative care education should be mandatory in all curricula from medical student education to specialization training. Looking at our home country, the Netherlands, the nationwide bachelor and master medical curriculum (Raamplan Artsopleiding) started to include specific palliative care education sections from 2020. This implementation provides medical faculties with opportunities to further embed palliative care education in the education of medical students.

The second cluster of the proposed barriers regarding the lack of commitment from decision-makers is visible in the large focus, including financial incentives, on promising new cancer therapies in contrast to palliative care. For example, only a minor proportion of research spending on cancer research is allocated to palliative or end-of-life care (e.g., 0.3% in the UK in 2019-2020 and 1% in the USA in 2010). To improve the much-needed integration of palliative care with oncological care, politicians and healthcare bureaucrats need to combine the integration plans with economic incentives and basic funding. Happily, the Netherlands National Program of Palliative Care, which aims to implement and improve the quality of palliative care and includes research funding, has been extended from 2021 to 2026. Furthermore, one of the Dutch Cancer Society main goals is to ensure that high quality palliative care is available for all patients.

Overall, future studies need to focus on concurrently improving palliative care and anti-cancer treatments and finally bringing it together into oncological care.
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