GENERAL DISCUSSION

PATIENT REPORTED OUTCOMES IN LUNG CANCER

To this date lung cancer has the highest incidence of all major cancer types and is the main cause of cancer-related mortality worldwide [1]. Despite recent advancements in the treatment of advanced-stage lung cancer with Endothelial Growth Factor Receptor tyrosine kinase inhibitors [2-6], Anaplastic Lymphoma Kinase inhibitors [7-10], and more recently PD-1 and PD-L1 inhibitors [11-14], the survival benefits of these treatments often apply to relatively few patients. Therefore, to further assess if these treatments are worthwhile, patient reported outcomes (PROs), such as Quality of Life (QoL), are included as an outcome parameter to monitor the impact of side effects on patients' well-being and to facilitate drug approval and legislation.

Unfortunately, different definitions of QoL are often used in studies that report the consequences of new treatments. According to the definition of QoL, as formulated by the World Health Organization, QoL is 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns' [15]. 'It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs, and their relation to salient features of their environment' [15,16]. However, considering the questionnaires (i.e., patient reported outcome measures (PROMs)) that are used in studies that assess novel therapies, QoL is conceptually equated with Health-Related Quality of Life (HRQoL) and Health Status (HS). As a result, differences exist between the concepts these studies aim to measure and those that are actually measured, which hampers comparison of outcomes and may lead to doubtful conclusions. Therefore, prior to the start of a study that investigates patient-reported outcomes (PROs) (i.e., HS, HRQoL, and QoL), it is highly recommended to first define the concept of interest (i.e., PRO), subsequently to search for PROMs that claim to asses this concept and inspect their items and psychometric properties, and, lastly, to choose the PRO and associated PROM that bests reflects the concept of interest and the study requirements [17].

In the introduction of this thesis examples of PROMs that are commonly used in patients with lung cancer (i.e., Distress Thermometer [18], EQ-5D [19], EORTC QLQ-C30 [20], WHO-QOL-BREF [21]) are mentioned. These instruments assess different concepts (i.e., distress, HS, HRQoL, and QoL) and, in general, have satisfactory psychometric properties and can be used in patients with lung cancer. Application of PROs may be worthwhile during daily clinical practice. For instance, PRO outcomes observed in studies or in previously treated patients may be used to compare treatments with similar survival benefits to aid patients and physicians in making personalized treatment decisions. During treatment, results of individual patients may be used to monitor the effects of therapy on a patient's well-being so that additional care can be provided if needed [22]. This is of importance given that few patients with advanced-stage lung cancer benefit from new treatments.

INTERPRETATION OF MAIN FINDINGS AND FUTURE PERSPECTIVES

Distress in patients with lung cancer

A PROM that is frequently applied in lung cancer patients treated with chemotherapy to monitor the effects of disease and treatment on a patient's well-being is the Distress Thermometer (DT). The DT measures the unpleasant psychological (i.e., cognitive, emotional, and behavioral), social, and spiritual experience associated with a diagnosis and treatment of cancer [23,18]. Previously, in patients with breast cancer, moderate to severe distress was related to a decrease in HRQoL [24]. Furthermore, several studies demonstrated that HS and HRQOL are predictive for survival [25-32]. In addition, depressive symptoms have been associated with decreased survival in patients with lung cancer [33,34]. These results could indicate that a relation may exist between distress and survival independent of HRQoL. Therefore, it was hypothesized that the DT would have similar prognostic significance as HS and HRQoL. However, a relationship between the DT and overall survival was not observed in patients with stage III lung cancer [35]. At the first cycle of chemotherapy, the DT-score was not prognostic for overall survival. This may be explained by the inability of the DT to measure the concept of HRQoL. Moreover, the included patients could represent a population in which patients with the best and those with the worst clinical status were not included resulting in selection bias. This could also have contributed to the negative results. Remarkably, the reported distress was less than observed in patients with other types of cancer [36,37]. This seems unexpected given the, in general, limited prognosis and the high burden of disease and side effects in patients with lung cancer. Patients' increased age could be an explanation for the lower observed levels of distress as increased age is previously related with the experience of less distress in cancer [38]. In the described study, a large number of patients (n= 214) was excluded since they did not complete the DT. This may be due to experience of side effects and deterioration of patients' well-being. For future studies, it may be worthwhile to determine whether completion of PROMs (e.g., the DT) is influenced by a reduced HS, HRQoL, and QoL or the experience of side effects. This may provide health care professionals with new insights in patients' willingness to complete PROMs. Knowledge about these insights may help physicians and nurses in aiding patients with the completion of PROMs by providing additional care.

Quality of Life in lung cancer

PROMs need to be reliable and valid given the patient population of interest. Since patients with advanced-stage lung cancer, in general, have a limited prognosis compared to other patients with cancer, and that their disease and treatment comes with a significant burden of adverse events, psychometric analysis of PROMs may be mandatory in these patients. For clinical purposes, it may be interesting to determine which patient-related factors (i.e., both clinical and demographic) are related to these PROs. For instance, some factors (e.g., older age, low performance status) could be used to identify patients prone to decreases in their well-being. In addition, treatment of other factors such as anxiety or depressive symptoms may provide opportunities to enhance a patient's well-being.

To stimulate the evaluation of QoL in studies next to HS and HRQoL we tested the psychometric properties of the WHOQOL-BREF in patients with advanced-stage lung cancer and mesothelioma [39]. A Taiwanese study by Lin et al. also reported results of a psychometric analysis of the WHOQOL-BREF. This study included patients with stage I to IV lung cancer [40]. Validation of a QoL instrument in patients with advanced-stage lung cancer was important since patients with stage I or II cancer patients differ from advanced-stage cancer patients. In general, patients with advanced-stage disease have a limited prognosis and experience a substantial burden of disease and treatment-related adverse events. Also an adapted version of the WHOQOL-BREF was used in the study by Lin et al. whereas the study reported in this thesis used the Dutch translation of the original WHOQOL-BREF [40]. Based on our results, the WHOQOL-BREF demonstrated satisfactory psychometric characteristics. These results are comparable to those observed by Lin et al. [40] and the WHOQOL group [41]. Compared to the WHOQOL-BREF field trial, patients in our study scored lower on general health [41]. This finding illustrates the large impact of lung cancer on patients compared with the general population and patients with other diseases and cancer types. In addition to the field trial [41] and the Taiwanese study [40], we reported the minimal clinically important differences (MCIDs) for the WHOQOL-BREF domain scores using two distribution-based methods [39]. These MCIDs further enable the application of the WHOQOL-BREF in research and clinical practice. Future studies should elaborate on these findings by calculating MCIDs with the use of other methods (e.g., anchor-based method).

Several sociodemographic and clinical factors have been associated with (HR)QoL in lung cancer. Increased age, higher performance status, and higher education were positively related to (HR)QoL, while female gender and having a spouse were negatively related [42-44]. Furthermore, in patients with cancer, depressive symptoms are negatively associated with HRQoL [45,46]. Contemplating on these findings, a study describing the relationships between sociodemographic and clinical variables and personality traits with (HR)QoL is reported in this thesis. It was observed that especially depressive symptoms were negatively related to (HR)QoL besides the Eastern Cooperative Oncology Group performance score [47]. This observation provides opportunities to enhance (HR)QoL in patients with advanced-stage cancer. It may be worthwhile to screen patients for the presence of depressive symptoms. Adequate management of these symptoms (e.g., referral to a psychologist) could possibly increase patients' QoL. In a recent meta-analysis, supportive care interventions (i.e., psychotherapy, exercise program) reduced depressive symptoms [48]. In addition, it would be interesting to explore if depressive symptoms also have a role in shared decision making. In patients with diffuse large B-cell non-Hodgkin lymphoma it was observed that depression reduced the chance of being treated with curative intent with chemotherapy by hematologists [49]. Given that patients with advanced-stage lung cancer may also experience depressive symptoms and are treated with chemotherapy, depressive symptoms could also play a part in decision making in these patients.

The role of patients' perspectives about treatment in shared decision making and clinical practice

Although analysis of patients' (HR)QoL in studies and clinical practice may be beneficial , it does not evaluate how patients value their treatment. Given that chemotherapy may have a negative impact on a patients' HRQoL due to its side effects [50], in potential, this could affect patients' satisfaction with care. Several studies have reported about patients' satisfaction with care [51-53], but none of these studies reported on patients' opinions related to side effects. This is unfortunate as in a study by Rha et al. it was observed that clinicians did not correctly estimate the impact of side effects (i.e., nausea and vomiting) on patients [54]. Patients' feelings about treatment can be assessed with the Cancer Therapy Satisfaction Questionnaire (CTSQ) [55]. Completion of this questionnaire by patients may facilitate clinical decision making and in the end patients' (HR)QoL. In this thesis, results of a validation study of the CTSQ in patients with advanced-stage lung cancer was described. The CTSQ is a reliable and valid instrument to assess satisfaction, feelings about side effects, and expectations of treatment in patients with lung cancer [56]. Validation of the CTSQ in these patients seemed legitimate as the questionnaire has not extensively been evaluated in patients treated with chemotherapy [57,58]. In the same study, MCIDs were proposed with the use of two distribution-based methods and one anchor-based approach. These results stimulate the application of the CTSQ not only in studies but also in clinical practice.

In another study in this thesis, the relationship between patients' treatment satisfaction and feelings about side effects with their well-being was analyzed by relating CTSQ domain scores with (HR)QoL. Patients' feelings about side effects and not satisfaction with treatment were associated with (HR)QoL. Especially low-grade side effects (e.g., nausea, constipation, fatigue, anorexia) were related with feelings about side effects [59]. According to these results, it is recommended to have high awareness for the occurrence of low-grade side effects since patients are clearly bothered by them. Given the observed associations, adequate management of low-grade side effects may offer opportunities to improve, maintain or prevent deterioration of (HR)QoL.

Earlier, it was found in a prospective, randomized cross-over trial that HRQoL-related issues (i.e., social functioning, dyspnea, and fatigue) were more often discussed between doctors and patients when the EORTC QLQ-C30 was completed by patients [60]. These observations demonstrate the value of such questionnaires in oncological practice. In addition, their application may also be worthwhile due to other reasons. The CTSQ is used as an example to illustrate these advantages, although other items, domains/scales or questionnaires (e.g., general facet of WHOQOL-BREF, global Health Status/QoL scale of the EORTC QLQ C30) may also be suitable. For instance, by asking patients to complete the feelings about side effects domain of the CTSQ, this identifies if they are bothered by side effects or not. If the results indicate that they are bothered, additional care can then be provided to treat these side effects. Also patients' CTSQ responses could facilitate the process of making shared treatment decisions. This is of importance, since it is known that shared decisions are related to better patient-reported quality of care [61]. Given that, according to our results, patients with negative feelings about side effects could have low (HR)QoL (i.e., WHOQOL-BREF domains: $\beta = 0.36$ to 0.58, $P < 0.005$; EORTC QLQ-C30 scales: $\beta = 0.33$ to 0.61, $P < 0.013$) and that prognosis is limited in advanced-stage lung cancer, it is proposed that the CTSQ results of previously treated patients can be used to help newly diagnosed patients at risk for adverse events in making treatment decisions. For instance, if a considerable proportion of patients who received chemotherapy were often hampered by adverse events according to their CTSQ results, newly diagnosed patients with a limited prognosis could take knowledge of these results and make a more considered treatment decision. In such a way, CTSQ results are handled in a similar manor during decision making as response and survival rates. This role of the CTSQ should be further explored in future studies that aim to analyze treatment decision making.

In addition to the feelings about side effects domain of the CTSQ, it is recommended to use also the results of the satisfaction with therapy domain upon making treatment decisions. Knowledge about patients' treatment satisfaction may provide important supplementary information besides patients' QoL and treatment toxicities'. Moreover, many patients receiving chemotherapy for metastatic (lung) cancer overestimate their life expectancy [62-65], which might explain the discordance between the treatment decisions they make and their actual preferences. Given these considerations, information about treatment satisfaction may help patients to formulate their actual treatment preferences (e.g., the continuation or stop of treatment with chemotherapy). This thesis describes a study on the CTSQ in patients with advanced-stage lung cancer treated with palliative chemotherapy [66]. Eighty-six percent of the included patients reported that they probably or definitely would like to receive the same treatment again despite side effects or deterioration of their well-being. Satisfaction with therapy explained less than 10% of the observed variance of the functional scales and domains of the EORTC QLQ-C30 and the WHOQOL-BREF, except for the global Health Status/QoL scale of the EORTC QLQ-C30 and the psychological health domain of the WHOQOL-BREF. Furthermore, it was observed that patients who experienced increases in global Health Status/QoL during treatment were more satisfied than those that did not or experienced a decrease in that scale. These results contribute to previous findings [56] and demonstrate that the assessment of satisfaction with therapy offers supplementary information about the impact of therapy on patients next to (HR)QoL. In addition, patients' feelings about side effects were associated with their satisfaction with therapy. This may imply that adequate management of side effects could result in higher patients' satisfaction with care. Future studies should evaluate satisfaction with therapy at an earlier stage during treatment (e.g., after the first or second cycle of therapy), which could increase our understanding about satisfaction in patients who experience significant side effects, poor response to treatment, and decreases in (HR) QoL.

As mentioned earlier, implementation of PROs in clinical practice may facilitate shared treatment decision making. To determine if this may be worthwhile in patients with lung cancer, their role in clinical decision making was assessed [67]. Most patients felt themselves to be sufficiently involved in treatment decision making, although 26% of the patients experienced no involvement or felt insufficiently involved. About 80% of the included patients thought that treatment decisions were ideally taken together with physicians. In addition, about 40% of patients experienced decisional conflict (i.e., 40% of the surgically treated patients and 48% of the patients treated with stereotactic body radiotherapy). Uncertainty about chosen treatment and the feeling to be insufficiently informed explained decisional conflict mostly. The results demonstrated that improvements have to be made if shared treatment decision making in clinical practice truly wants to play a role of significance. Better patient information and patient involvement in treatment decision making is warranted in order to improve patient knowledge and reduce decisional conflict. This can be facilitated by inviting patients to complete PROMs before making treatment decisions as this gives patients more insight about which factors are of influence on their disease and treatment-related opinions.

CONCLUSION

The acquirement and implementation of PRO data holds much promise for the management of a cancer patient's well-being. According to the results in this thesis, it is recommended that all patients with advanced-stage lung cancer complete the CTSQ. Given that it directly evaluates patients' feelings about side effects and that it is associated with HRQoL and QoL, its role may be of more importance than that of the DT. In addition, new approaches are recommended with an increasing role of PROs (e.g., (HR)QoL, feelings about side effects, satisfaction with therapy) in the process of shared decision making and as an equal outcome parameter next to response rates and survival. This work aimed to contribute to these developments. However, as is demonstrated, there are multiple controversies regarding the definition and the interpretation of these PROs, which impedes their use in research and clinical practice. To enable an optimal use of PROs in these settings, standardized procedures for PRO management and use have to be followed.

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