Technical Innovations & Patient Support in Radiation Oncology 21 (2022) 36–40

Contents lists available at ScienceDirect

Technical Innovations & Patient Support in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/technical-innovations-and-patient-support-in-radiation-oncology

Neurocognitive functioning following lung cancer treatment: The PRO-Long Study

Lotte van der Weijst [a,*], Yolande Lievens [a], Veerle Surmont [b], Wim Schrauwen [c]

[a] Department of Radiation Oncology, Ghent University Hospital and Ghent University, Ghent, Belgium
[b] Department of Respiratory Medicine, Ghent University Hospital and Ghent University, Ghent, Belgium
[c] Department of Medical Psychology, Ghent University Hospital and Ghent University, Ghent, Belgium

ARTICLE INFO

Keywords:
Lung cancer, health-related quality of life
Patient-reported outcomes
Neurocognitive
Functioning

ABSTRACT

This observational cohort study investigates neurocognitive functioning (NCF) and its associations with overall survival (OS), disease-free survival (DFS) and patient-reported psychological toxicities in locally-advanced and metastatic non-small cell lung (NSCLC) cancer patients receiving loco-regional radiotherapy and/or systemic therapy. Objective NCF data was collected with six psychometrically validated neurocognitive tests. Subjective NCF was assessed with the cognitive domain of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items. Psychological toxicity data was collected with the patient-reported outcomes version of the common terminology criteria for adverse events. Meaningful clinical important differences were determined for changes in NCF. Univariate Cox proportional hazards models and generalized linear models were used to determine statistical significance ($p < 0.01$).

In total, 50 patients were recruited. At baseline, 13 (26%) patients had an impaired objective NCF. Over time, deterioration was seen in 11% (n = 3), 5% (n = 1) and 6% (n = 1) of patients at 2–3, 6 and 12 months post-treatment. The OS of patients with a normal NCF at baseline was longer than those with an impaired baseline NCF (29.5 vs 17.1 months). No statistical significance has been reached between NCF and OS ($p = .353$) nor NCF and DFS ($p = .251$). Objective NCF was not correlated with subjective NCF ($p = .193$), nor anxiety ($p = .504$), depression ($p = .513$), memory problems ($p = .813$) and concentration problems ($p = .813$).

Systemic treatment and loco-regional radiotherapy may have a temporarily negative impact on NCF in a small proportion of locally-advanced and metastatic NSCLC. Baseline NCF could be a predictor for OS.

Introduction

Lung cancer is the deadliest cancer worldwide [1]. The majority of patients is diagnosed with non-small cell lung cancer (NSCLC) (85%) of which the majority has locally-advanced (LA-) and metastatic disease [2].

Treatment for (LA-) advanced NSCLC typically consists of a combination of treatment modalities, of which radiotherapy and/or a combination of systemic oncology treatments (chemo-, targeted and immunotherapy) are among the most important. For medically fit LA-NSCLC patients, the cornerstone of treatment is concurrent chemo-radiotherapy. Immunotherapy has lately been added to the standard of care, further improving survival [3,4]. For metastatic disease, chemotherapy has been the standard treatment for decades. Recently, immunotherapy, either alone or combined with chemotherapy, has emerged to be an important treatment modality for metastatic NSCLC with less toxicity and improved survival [5,6]. Molecular targeted therapy is given to patients with certain onco-drivers [7]. The treatment or combination depends mainly on histology, stage and patient-related factors such as performance status and comorbidities.

Due to the poor prognosis of patients, it is important to take into account the impact of therapy on overall wellbeing. This can be impacted by a broad range of symptoms and toxicities, but of which cognitive impairment has been described to be associated with a decline in health-related quality of life [8]. Therefore, cognitive decline following NSCLC treatment is an important survivor concern [9].

Neurocognitive impairments may be temporarily, but may also be persistent until years after treatment [9]. The incidence and severity of

* Corresponding author at: Department of Radiation Oncology, Ghent University Hospital, Corneel Heymanslaan 10, Ghent 9000, Belgium.
E-mail addresses: Lotte.vanderweijst@ugent.be (L. van der Weijst), Yolande.Lievens@uzgent.be (Y. Lievens), Veerle.surmont@uzgent.be (V. Surmont), Wim.schrauwen@uzgent.be (W. Schrauwen).

https://doi.org/10.1016/j.tipsro.2022.02.004
Received 18 October 2021; Received in revised form 25 January 2022; Accepted 11 February 2022
Available online 16 February 2022

cognitive dysfunction may be influenced by various factors: disease-related symptoms, such as fatigue, dyspnea, pain and physical impairment; treatment-induced toxicity, including neurotoxicity linked to the pro-inflammatory cytokine pathways of treatment; and psychological distress like anxiety, depression and negative mood [8]. Neurocognitive functioning (NCF) can be measured objectively and subjectively. Objective NCF refers to cognitive performance measured with neurocognitive tests. Objective cognitive impairment is mostly minimal and within a range that is considered normal [10]. Subjective NCF refers to self-reported cognitive dysfunction measured with patient-reported outcome measures (PROM)s. Subjective cognitive problems are generally more prevalent than objective dysfunction and are frequently unrelated [10].

Studies on objective NCF in lung cancer predominantly focus on small-cell lung cancer (SCLC) patients receiving prophylactic cranial irradiation (PCI) [9,11–19]. Relatively little research has focused on the impact of various treatment strategies, also those not specifically targeting the brain, on NCF among NSCLC patients. So far, two studies have been conducted on the impact of chemo- and radiotherapy on NCF in this patient population [20,21]. Conversely, more data is available on subjective NCF, showing no clinically meaningful changes over time [9].

This exploratory study aimed to evaluate NCF of LA- and metastatic NSCLC patients receiving different standard treatment modalities enrolled in the real-world study PRO-Long [22]. Furthermore, real-world evidence on the associations between objective NCF and overall survival (OS), disease-free survival (DFS), patient-reported toxicities and subjective NCF were explored. It was hypothesized that objective NCF deteriorated over time in a proportion of patients as well as objective NCF was associated with OS, DFS and patient-reported toxicity.

Methodology

Patient population

Patients with LA- and metastatic NSCLC receiving loco-regional radiotherapy and/or chemotherapy and/or first- or second-line immunotherapy at Ghent University Hospital (GUH) were included. Patients who received anticancer treatment during the five years prior to the study were excluded. The study was approved by the ethical committee of the GUH. All patients provided written informed consent prior to participation in the study. The study was carried out in accordance with the Declaration of Helsinki.

Data collection

Patient and tumour characteristics were collected at baseline. Treatment details were obtained at the end of treatment. Patient-reported subjective NCF and toxicity data was collected with PROMs.

Subjective NCF was collected with the paper version of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30) [23–25]. The QLQ-C30 measures five functional domains (physical, role, emotional, cognitive, and social), nine cancer symptoms and treatment-associated side-effects, global health and quality of life. The domain of cognitive functioning of the EORTC-C30 questionnaire was considered subjective NCF.

Toxicity data was collected with the patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). The PRO-CTCAE captures patients' perspectives regarding toxicities, rather than diagnosing mood disorders. The following psychological toxicities of the PRO-CTCAE were included in this study: Anxiety, depression, memory and concentration problems [26].

Six psychometrically validated neurocognitive tests were used to assess objective NCF. See Table 1 for an overview of the NCF tests and associated domains.

Details concerning data collection time points have been described previously [22]. Shortly, patient-reported subjective cognitive functioning and toxicity data was collected 7 to 8 times, whereas objective NCF data was collected 4 times. Objective NCF data was collected every 2 – 3 months, to gather as much data as possible of this patient population with a poor prognosis, while taking into account the test–retest practice effect. Different versions of the NCF assessment tools were used for most of the tests, to diminish the learning effect. Data collection started pre-treatment and lasted until 12 months post-therapy. Two months after the onset of treatment was considered end of treatment for immunotherapy.

Table 1
Overview of neurocognitive tests.

Test	Neurocognitive function tested
Reys-Osterrieth Complex Figure Test (ROCF)[26,27]	Immediate and delayed recall
Hopkins Verbal Learning Test-Revised (HVLT-R)[28]	Immediate and delayed recall
Trail Making Test (TMT) part A[29]	Cognitive processing speed
TMT Part B	Executive functioning
Benton Controlled Oral Word Association Test (COWA)[30]	Verbal fluency
Wechsler Adult Intelligence Scale (WAIS) digit span[31]	Working memory
Stroop Color and Word Test (SCWT)[32]	Executive function

Data analyses

This was an exploratory analysis on the impact of treatment on NCF and the associations between baseline NCF, OS, DFS, patient-reported toxicities and subjective NCF. Summary statistics, including percentages, means and standard deviations (SD) were calculated for both categorical and continuous data.

The domain cognitive functioning assessed with the EORTC QLQ-C30 was calculated based on the scoring manual of the EORTC [24]. A linear transformation was used to calculate a score ranging from 0 to 100. The higher the score, the better the cognitive functioning is perceived. Subjective cognitive functioning data was considered missing if at least half of the items on cognitive functioning were missing. A minimum of 10-points difference was used to determine meaningful clinical important differences (MCID) (improved or worse, versus stable) [27].

Based on the recommendations of the International Cognition and Cancer Task Force, impairment of objective NCF was defined as a minimal −1.5 standard deviation (SD) on at least two tests at baseline as well as a −1.5 SD between baseline and subsequent time points [28]. In case no impairment was found, we considered the neurocognitive performance as normal.

Univariate Cox proportional hazards models and generalized linear model were used to assess the association between neurocognitive failure at baseline and OS and DFS. The same models were used to analyse the associations between subjective and objective NCF, age, OS, DFS and education level. The model used NCF as a dichotomized variable (0, normal NCF vs 1, impaired NCF) and age as a continuous variable. SPSS version 27 was used to analyse the data. To determine statistical significance, the p-value was set at 0.01 to correct for multiple comparisons and to adjust for level I error [29].

Results

Patient characteristics

From January 2016 to December 2018, 50 NSCLC patients were enrolled in the PRO-Long study [22]. Seventeen patients refused participation, mainly due to mental burden. Patient, tumour and treatment have been described previously. Briefly, the majority of patients were male (64%), had a WHO performance status of 1 and had LA-

disease (54%); while the dominant treatment strategies were concurrent chemo-radiotherapy (38%), chemotherapy alone (24%) or first-line immunotherapy (12%). Three (6%) patients had brain metastases at baseline. Table 2 provides an overview of patient characteristics. Data was available for 50, 33, 21 and 17 patients at baseline, 2–3, 6 and 12 months post-treatment.

Neurocognitive functioning

Details concerning subjective functioning have been reported previously [22]. Shortly, subjective NCF did not change over time (p = .494). More meaningful deterioration was reported in patients, 41%, 32% and 27% of patients at respectively 2/3, 6 and 12 months post-treatment compared to improvements. Meaningful improvements were seen in 18%, 13% and 20% of patients respectively at aforementioned time points. At baseline, 13 (26%) of patients had an impaired objective NCF. Most failure was seen in the HVLT-R immediate recall test (18%), COWA (20%) and WAIS backwards (22%). Patient, treatment and tumour characteristics and subjective NCF data of the patients with impaired objective NCF at baseline can be found in Table 2. No major differences in baseline data were found between patients with pre-treatment impaired and normal NCF. Statistical analyses on objective NCF have been shown previously [22]. Briefly, visual memory (p = .000) and cognitive processing speed (p = .000) improve over time.

Over time, deterioration in NCF was found only in small percentages. At 2–3 months, 6 months and 1-year post-treatment, 11% (3 out of 28), 5% (1 out of 20) and 6% (1 out of 17) respectively of patients had a deterioration in NCF from baseline. The failures in the NCF assessments at the different time points were observed in different patients, meaning that 5 patients deteriorated in NCF at one specific time point.

Neurocognitive functioning and survival

At the time of submission (21/12/2021), 15 patients were still alive of which 4 had no progressive disease. More patients with a normal NCF (n = 13; 35%) than with an impaired NCF (n = 2; 15%) were still alive. Education was not correlated with baseline NCF failure (p = .466). The OS of patients with a normal NCF is about 12 months longer compared to those with an impaired baseline NCF (29.5 vs 17.1 months). However, no statistical significance has been reached between NCF and OS (p = .353) nor NCF and DFS (p = .251).

The difference in survival did not yet show at one year (similar survival rates, normal NCF (67.6%) and impaired NCF (61.5%)), while the two-year survival rate was substantially better in those with normal NCF compared to those with an impaired NCF (51.4% vs 30.8%).

In terms of statistical analyses, no significant differences in 1-year (p = .353and 2-year survival (p = .254; d = 0.38) were seen between those with impaired and normal NCF. However, the effect sizes at one year (d = 1.28) and two year (d = 0.38) show a large and moderate effect respectively.

Associations between objective and patient-reported outcomes

Subjective and objective NCF were not correlated (p = .193). Furthermore, none of the toxicities, including anxiety (p = .504), depression (p = .513), memory problems (p = .813) and concentration problems (p = .813) were correlated with objective NCF. However, certain toxicities were correlated with subjective NCF. Particularly, fatigue, depression and anxiety were associated with concentration problems. Memory problems are significantly associated with subjective cognitive functioning. See Table 3 for an overview between pain, fatigue, dyspnoea, depression, anxiety, and memory and concentration problems and subjective cognitive functioning.

Table 2
Patient, treatment and HRQoL characteristics.

Baseline characteristics, n (%)	Overall population (n = 50)	Patients with neurocognitive impairment (n = 13)
Male	32 (64)	7 (54)
Mean age ± SD (y)	63.4 (8.86)	67.2 (7.52)
WHO Performance Status		
0	15 (30)	1 (8)
1	33 (66)	11 (84)
2	2 (4)	1 (8)
Stage		
III	26 (54)	7 (54)
IV	24 (46)	6 (46)
Histology		
Adenocarcinoma	34 (68)	9 (69)
Squamous-cell carcinoma	13 (26)	2 (15)
Neuroendocrine carcinoma	2 (4)	1 (81
Undifferentiated	1 (2)	
Treatment		
Concurrent chemo-radiotherapy	19 (18)	6 (46)
Chemotherapy	12 (24)	1 (8)
Radiotherapy	4 (8)	1 (8)
Sequential chemo-radiotherapy	5 (10)	2 (15)
Chemo-immunotherapy	1 (2)	1 (8)
Immunotherapy (1st line)	6 (12)	2 (15)
Immunotherapy (2nd line)	3 (6)	
Comorbidities		
COPD	30 (60)	7 (54)
Myocardial disease		
Hypertension	19 (38)	3 (23)
Arrhythmias	3 (6)	2 (15)
Other heart myocardial disease	3 (6)	1 (8)
Depression	8 (16)	1 (8)
BMI		
Underweight (<18.5)	3 (6)	
Normal (18.5 – 24.9)	24 (48)	6 (46)
Overweight (25 – 29.9)	16 (32)	6 (46)
Obese (>30)	7 (14)	1 (8)
Smoking status		
Never smoker	5 (10)	4 (31)
Ex-smoker before cancer diagnosis	23 (46)	2 (15)
Ex-smoker, since cancer diagnosis	7 (14)	6 (46)
Current	15 (30)	1 (8)
Education		
Primary school	6 (12)	3 (23)
Secondary school	31 (62)	9 (69)
Higher education	10 (20)	
University	5 (10)	1 (8)
Relationship status		
In relationship	42 (84)	11 (85)
Single	8 (16)	2 (15)
Children		
Yes	44 (88)	13 (100)
Currently employed		
Currently employed	6 (12)	
Unemployed	21 (42)	4 (31)
Retired	23 (46)	9 (69)
Subjective cognitive functiong, average score	82.31	83.33
Neuro-psychological toxicity		
Anxiety	1.80	1.54
Depression	1.73	1.62
Memory problems	1.59	1.69
Concentration problems	1.47	1.38

Note: Whether a patient is scored having a co-morbidity is based on the prescribed medication for the condition in the electronic patient records

Table 3
Overview of associations between toxicities and subjective NCF.

	Memory problems	Concentration problems	Subjective cognitive functioning
Pain	0.306	0.069	0.781
Fatigue	0.047	0.002	0.014
Dyspnoea	0.056	0.037	0.044
Depression	0.211	0.004	0.131
Anxiety	0.067	0.002	0.301
Memory problems	–	0.012	<0.001
Concentration problems	0.012	–	0.023

P-value ≤ 0.01

Discussion

This study analysed NCF of LA- and metastatic NSCLC patients undergoing systemic and/or loco-regional radiotherapy. This is one of the first studies on long-term objective NCF in this patient population. The results show that only a small percentage of patients had a meaningful clinically important deterioration in objective NCF at each time point. The pilot study (n = 14) of Whitney et al. on NCF in LA-NSCLC undergoing concurrent chemo-radiotherapy showed different results. The results showed that the majority of patients (62%) had a cognitive decline at one-month post-treatment. Most decline was observed in executive functioning and immediate verbal memory. Nonetheless, at 7 months post-treatment, NCF returned to baseline. No data was collected between 1 and 7 months. In accordance with our data, this could implicate that NCF deterioration is temporary and limited to the first month(s) post-treatment and may rather be a result of acute toxicities such as fatigue, pain and distress. On the other hand, attention, visual memory and visuospatial abilities improved significantly over time as was seen in our study, potentially due to the practice effect. This refers to the improvement in cognitive test performance due to re-evaluation of performance and may confound the interpretation of the results [30].

The short-term decline in NCF following chemotherapy has also been found in a Norwegian RCT on NCF in inoperable NSCLC patients receiving either radiotherapy alone or combined with chemotherapy [20]. The results showed that patients undergoing chemotherapy deteriorated in NCF performance compared to the radiotherapy group. However, the interval between last treatment and the follow-up NCF test was substantially shorter in patients receiving chemotherapy than radiotherapy (5 vs 11 weeks). Therefore, acute toxicities such as fatigue linked to chemotherapy may still be present, potentially influencing the results. Unfortunately, no long-term follow-up was done.

Our results show that baseline NCF may potentially be a prognostic factor for OS. Although, no statistical significance levels were found, a particular large effect size at one-year post-treatment survival was found, indicating that baseline NCF predicts one-year survival.

This has been previously found in patients with malignant glioblastoma [31] and cancer patients with brain metastases [32]. Johnson and colleagues found that early cognitive impairment is an indication for a poor prognosis in newly diagnosed malignant glioblastoma [31]. Executive functioning and attention were the strongest predictors for survival. In patients with brain metastases, objective NCF, particularly memory, fine motor speed, executive functioning and overall neurocognitive dysfunction were associated with brain tumour volume and prognostic factors of overall survival [32].

Our results show that objective and subjective NCF are not correlated. This has been demonstrated previously [10]. Patient-reported neurocognitive problems are more prevalent than objective neurocognitive impairment. Naturally, patients may focus on the worst neurocognitive problems they experienced during the last week, whereas objective tests assess the best performances of patients in an ideal environment without distractions seen in everyday situations. These tests may therefore not detect mild cognitive problems relevant in daily life. Alternatively, subjective cognitive dysfunction may rather suggest psychological distress related to cancer and its treatment, such as anxiety and depression. Notwithstanding the discrepancy between objective and perceived cognitive functioning, both provide relevant data to the functioning of cancer patients [33].

It is important to look into individual changes over time. Patients may perform within the normal range of NCF, however it could be that prior to treatment, performance was high and therefore a patient may experience a meaningful decline. This study used a decline of 1.5 SD as a meaningful clinical important decline in NCF as recommended by the International Cognition and Cancer Task Force [28]. However, research on standards of meaningful clinical important cognitive impairment, developed cooperatively with patients, is currently lacking.[10] Whereas statistical significance refers to the reliability of the data, MCID indicates the smallest change in outcome that is meaningful to the patient [34]. MCIDs facilitate the interpretation of clinical relevance of score changes over time.

Limitations of this study include the relatively small sample size. However, this is the largest recent study on NCF in systemic treatment and loco-regional radiotherapy in NSCLC patients. Furthermore, this study has missing data mainly due to death and worsening of health, a known phenomenon in longitudinal observational lung cancer studies [35,36]. Moreover, follow-up was discontinued by the patients or due to change in treatment. Particularly, data was missing from metastatic patients. This is expected, since these patients have a shorter life-expectancy and disease-free survival. The small sample size and the decreasing compliance over time may limit generalizability and reduces statistical power. Accordingly, the study aim was rather explorative. In the interpretation of the long-term NCF results it should be considered that patients with a better survival and response to treatment usually over-represent these data.

At baseline, three patients were diagnosed with brain metastases. None received cerebral irradiation, they only underwent systemic therapy. In addition, no progression occurred over the time of evaluation, clinically nor at imaging. Moreover, as each patient was evaluated compared to his/her baseline results, the fact of having cerebral metastases was not considered a confounding factor in the statistical analysis. It can, however, not be excluded that the presence of brain metastases may have impacted the study results.

Psychological toxicities (anxiety, depression, memory and concentration problems) were assessed with the PRO-CTCAE [26]. The PRO-CTCAE is a validated and reliable tool to capture patients perspectives' on symptomatic toxicities, rather than a diagnostic tool. Therefore, conclusions regarding particularly anxiety disorder and depression diagnosis cannot be made. Although, the aim of this paper was to provide the patients' perspectives on psychological symptoms rather than to diagnose them.

Finally, as our study demonstrated how difficult it is to perform data collection in this often-frail population, every attempt should be made to alleviate participation burden for the patients. More research is therefore needed to understand the potential of electronic PRO data collection and NCF testing at patients' homes outside of clinical trials to help detect early relapse and deterioration of patients' wellbeing, while limiting the burden of unnecessary travel to and from the hospital [37].

In conclusion, systemic treatment and loco-regional radiotherapy may have a temporarily negative impact on NCF in a small proportion of LA- and metastatic NSCLC. Baseline NCF in this patient population could be a predictor for overall survival. Although, due to the explorative nature of this study and the small sample size, no firm conclusions can be drawn. More research is needed to understand the impact of treatment on cognitive wellbeing in this vulnerable patient population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Acknowledgement

None

Bibliography

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2021;71(3):209–49. https://doi.org/10.3322/caac.21660.

[2] Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28(13):2181–90. https://doi.org/10.1200/JCO.2009.26.2543.

[3] Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC—Update from PACIFIC. Journal of Thoracic Oncology 2020;15(2):288–93. https://doi.org/10.1016/j.jtho.2019.10.002.

[4] Senan S, Brade A, Wang L-H, Vansteenkiste J, Dakhil S, Biesma B, et al. PROCLAIM: Randomized Phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2016;34(9):953–62. https://doi.org/10.1200/JCO.2015.64.8824.

[5] Anagnostou VK, Brahmer JR. Cancer immunotherapy: A future paradigm shift in the treatment of non-small cell lung cancer. Clin Cancer Res 2015;21(5):976–84. https://doi.org/10.1158/1078-0432.CCR-14-1187.

[6] Ferrara R, Imbimbo M, Malouf R, Paget-Bailly S, Calais F, Marchal C, et al. Single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer. Cochrane Database of Systematic Reviews 2020. https://doi.org/10.1002/14651858.CD013257.pub2.

[7] Chan BA, Hughes BGM. Targeted therapy for non-small cell lung cancer: Current standards and the promise of the future. Translational Lung Cancer Research 2015;4:36–54. https://doi.org/10.3978/j.issn.2218-6751.2014.05.01.

[8] Lange M, Joly F, Vardy J, Ahles T, Dubois M, Tron L, et al. Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. Ann Oncol 2019;30(12):1925–40. https://doi.org/10.1093/annonc/mdz410.

[9] van de Kamp HJ, te Molder M, Schulkes KJG, Stellingwerf M, van Elden LJR, van Lindert ASR, et al. Impact of Lung Cancer Treatment on Cognitive Functioning. Clinical Lung Cancer 2020;21:114-126.e3. doi: 10.1016/j.cllc.2019.06.006.

[10] Hutchinson AD, Hosking JR, Kichenadasse G, Mattiske JK, Wilson C. Objective and subjective cognitive impairment following chemotherapy for cancer: A systematic review. Cancer Treat Rev 2012;38(7):926–34. https://doi.org/10.1016/j.ctrv.2012.05.002.

[11] Meyers CA. Cognitive deficits in patients with small cell lung cancer before and after chemotherapy n.d.:5.

[12] Wolfson AH, Bae K, Komaki R, Meyers C, Movsas B, Le Pechoux C, et al. Primary analysis of a phase II randomized trial radiation therapy Oncology Group (RTOG) 0212: Impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease. Int J Radiat Oncol Biol Phys 2011;81:77–84. https://doi.org/10.1016/j.ijrobp.2010.05.013.

[13] Bromis K, Gkiatis K, Karanasiou I, Matsopoulos G, Karavasilis E, Papathanasiou M, et al. Altered Brain Functional Connectivity in Small-Cell Lung Cancer Patients after Chemotherapy Treatment: A Resting-State fMRI Study. Computational and Mathematical Methods in Medicine 2017;2017:1–12. doi: 10.1155/2017/1403940.

[14] Belderbos JSA, De Ruysscher DKM, De Jaeger K, Koppe F, Lambrecht MLF, Lievens YN, et al. Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC (NCT01780675). Journal of Thoracic Oncology 2021;16(5):840–9. https://doi.org/10.1016/j.jtho.2020.12.024.

[15] Vees H, Caparrotti F, Eboulet EI, Xyrafas A, Fuhrer A, Meier U, et al. Impact of Early Prophylactic Cranial Irradiation With Hippocampal Avoidance on Neurocognitive Function in Patients With Limited Disease Small Cell Lung Cancer. A Multicenter Phase 2 Trial (SAKK 15/12). International Journal of Radiation Oncology*Biology*Physics 2020;107(2):279–87. https://doi.org/10.1016/j.ijrobp.2020.02.029.

[16] Zeng H, Hendriks LEL, van Geffen WH, Witlox WJA, Eekers DBP, De Ruysscher DKM. Risk factors for neurocognitive decline in lung cancer patients treated with prophylactic cranial irradiation: A systematic review. Cancer Treat Rev 2020;88:102025. https://doi.org/10.1016/j.ctrv.2020.102025.

[17] Nakahara YOSHIRO, Takagi YUSUKE, Okuma YUSUKE, Hosomi YUKIO, Okamura TATSURU, Shibuya MASAHIKO, et al. Neurotoxicity due to prophylactic cranial irradiation for small-cell lung cancer: A retrospective analysis. Molecular and Clinical Oncology 2015;3(5):1048–52. https://doi.org/10.3892/mco.2015.581.

[18] Robin TP, Rusthoven CG. Strategies to Preserve Cognition in Patients With Brain Metastases: A Review. Front Oncol 2018;8:1–10. https://doi.org/10.3389/fonc.2018.00415.

[19] Grosshans DR, Meyers CA, Allen PK, Davenport SD, Komaki R. Neurocognitive function in patients with small cell lung cancer: Effect of prophylactic cranial irradiation. Cancer 2008;112(3):589–95. https://doi.org/10.1002/cncr.23222.

[20] Kaasa S, Olsnes BT, Mastekaasa A. Neuropsychological evaluation of patients with inoperable non-small cell lung cancer treated with combination chemotherapy or radiotherapy. Acta Oncol 1988;27(3):241–6. https://doi.org/10.3109/02841868809093532.

[21] Whitney KA, Lysaker PH, Steiner AR, Hook JN, Estes DD, Hanna NH. Is"chemobrain" a transient state? A prospective pilot study among persons with non-small cell lung cancer. The Journal of Supportive Oncology 2008;6:313–21.

[22] Van Der Weijst L, Surmont V, Schrauwen W, Lievens Y. Real Life Data on Patient-Reported Outcomes and Neuro-Cognitive Functioning of Lung Cancer Patients: The PRO-Long Study. Front Oncol 2021;11:685605. https://doi.org/10.3389/fonc.2021.685605.

[23] Groenvold M, Klee MC, Sprangers M a. G, Aaronson NK. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. Journal of Clinical Epidemiology 1997;50:441–50. doi: 10.1016/S0895-4356(96)00428-3.

[24] Aaronson N, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organistaion for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of National Cancer Institute 1993;85:365–76.

[25] Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 1994;30A:635–42. https://doi.org/10.1016/j.ejca.2010.08.021.

[26] Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the national cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). Journal of the National Cancer Institute 2014;106. doi: 10.1093/jnci/dju244.

[27] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of- life scores. J Clin Oncol 1998;16(1):139–44. https://doi.org/10.1200/JCO.1998.16.1.139.

[28] Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol 2011;12(7):703–8. https://doi.org/10.1016/S1470-2045(10)70294-1.

[29] Palesch YY. Some Common Misperceptions About P Values. Stroke 2014;45(12). https://doi.org/10.1161/STROKEAHA.114.006138.

[30] Duff K, Beglinger L, Schultz S, Moser D, Mccaffrey R, Haase R, et al. Practice effects in the prediction of long-term cognitive outcome in three patient samples: A novel prognostic index. Archives of Clinical Neuropsychology 2007;22(1):15–24.

[31] Johnson DR, Sawyer AM, Meyers CA, O'Neill BP, Wefel JS. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. Neuro-Oncology 2012;14(6):808–16. https://doi.org/10.1093/neuonc/nos082.

[32] Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: Results of a randomized phase III trial. J Clin Oncol 2004;22(1):157–65. https://doi.org/10.1200/JCO.2004.05.128.

[33] Hardy SJ, Krull KR, Wefel JS, Janelsins M. Cogni ve Changes in Cancer Survivors. ASCO EDUCATIONAL BOOK 2018:795–806.

[34] Fleischmann M, Vaughan B. Commentary: Statistical significance and clinical significance - A call to consider patient reported outcome measures, effect size, confidence interval and minimal clinically important difference (MCID). Journal of Bodywork and Movement Therapies 2019;23(4):690–4. https://doi.org/10.1016/j.jbmt.2019.02.009.

[35] Karahalios A, Baglietto L, Carlin JB, English DR, Simpson JA. A review of the reporting and handling of missing data in cohort studies with repeated assessment of exposure measures. BMC Med Res Method 2012;12:1–10. https://doi.org/10.1186/1471-2288-12-96.

[36] Ibrahim JG, Chu H, Chen M-H. Missing Data in Clinical Studies: Issues and Methods. JCO 2012;30(26):3297–303. https://doi.org/10.1200/JCO.2011.38.7589.

[37] Bennett AV, Jensen RE, Basch E. Electronic Patient-Reported Outcome Systems in Oncology Clinical Practice. A Cancer Journal for Clinicians 2012;62(5):336–47. https://doi.org/10.3322/caac.21150.