Optimizing prophylactic cranial irradiation for patients with lung cancer

Addendum I

Impact

Haiyan Zeng

Scientific contribution

In **Chapter 2**, I revealed that TDRT is a risk factor for developing BM after PCI in patients with SCLC in China. This is an inspiring finding that might motivate more in vitro and in vivo studies to further investigate the underlying mechanisms, as well as more prospective studies in China or Asia to further confirm it and in the end, probably change the clinical practice.

In **Chapter 3**, I systematically reviewed all the risk factors that have been reported in the literature and made a comprehensive summary, which can support the design of future studies evaluating BM prevention strategies for patients with SCLC. I raised to the community that it is of foremost importance to assess the quality of data before pooling everything together to perform a meta-analysis. I proposed a simple and effective method to evaluate the quality of data: only studies of the same type using the same method with proper statistical analysis should be pooled together under the premise that the patients belonged to the same category. This will avoid misleading conclusions from heterogeneous data.

In **Chapter 4**, I used the planning CT of thoracic radiotherapy, which is a part of clinical care and no additional contouring is necessary, and therefore extracting radiomics features from GTVs is feasible in clinical application for all patients with a radiotherapy treatment plan. I was the first one to separate GTVp and GTVn to analyze their associations with BM development. I found that GTVn radiomics features provided higher predictive value for BM development than GTVp and GTV. Therefore, I proposed to separate GTVp and GTVn in clinical and research practice and to further validate these findings in the ongoing NVALT28 trial.

The association of GTVs with BM should also be investigated in patients with SCLC, for which I have set up an international collaboration platform with multiple centers and collected 400 patients (South Korea, China, Barcelona, Zuyderland, Viecuri, Laurentius, MUMC, Rotterdam, Eindhoven, Utrecht, Amsterdam). In addition, I have obtained a research grant from BeiGene. Furthermore, we have designed a prospective clinical trial on this project to participate in the Eighth Multidisciplinary Collaborative Clinical Trial Workshop in Shenzhen, China (Joined online because of the COVID-19 pandemic), with such a relevant reach out to win the Outstanding Clinical Trial Concept Award.

In **Chapter 5**, I found that until now not enough validated data has been published to evaluated risk factors associated with neurocognitive decline after PCI in patients with lung cancer. None of the included clinical trials were judged to be at low risk of bias. This systematic review has relevance for the clinical community, since neurocognitive decline is common after PCI, both in SCLC and NSCLC. I also provided an overview on areas where future PCI-neurocognition research should focus on, which would be very helpful to improve future clinical trials and studies.

In **Chapter 6**, I found that there was no significant difference in cognitive decline and QOL between PCI and HA-PCI arms in patients with SCLC. As a result, the benefit of sparing the hippocampus in the context of PCI is still subject of debate.

In **Chapter 7**, I pooled the two most recent comparable clinical trials and provided the most robust evidence thus far that HA-PCI is safe in terms of reducing BM incidence and that HA-PCI has no impact on SRCF. Additional neuroprotective agents such as memantine should be investigated to further preserve the neurocognitive function.

In **Chapter 8**, I quantitatively showed that cognitive impairment at baseline is the most important risk factor for subsequent cognitive impairment, irrespective of having received PCI or not. These findings could identify patients who may benefit from interventions that are increasingly investigated. I also found that cognitive impairment is dynamic in individuals. I was the first one to propose that the cognitive impairment can be classified into four types based on changes over time: sustained, reversible, recurring, and alternating. The classification in the four types of impairment is very innovative and prompt for further clinical trials which may in the future lead to the early recognition, selection of patients for neuroprotective strategies and therefore mitigation of problems.

Patient care impact

1. If validated in the NVALT28 trial, patients with NSCLC, especially those at higher risk for developing BM (adenocarcinoma, larger GTVn), shall periodically undergo brain MRI to detect BM earlier, with hopefully better survival and quality of life. Furthermore, if also validated in

SCLC, my data could also select patients that do not have to undergo potentially neurotoxic PCI.

2. Patients with lung cancer, even in the absence of PCI, can have neurocognitive impairment. Therefore, patients shall periodically perform neurocognitive assessments, including neuropsychological tests and self-reported questionnaires, to better evaluate their cognitive function and to make individualized treatment strategies accordingly to reduce the risk of neurocognitive impairment.

3. Clinicians shall avoid prescribing twice-daily PCI or concurrent PCI with chemoradiotherapy to reduce the neurotoxicity.

4. Radiation oncologists shall delineate GTVn and GTVp separately in radiotherapy practice for better prognostic value.

Societal impact

1. If confirmed in a future trial, thoracic TDRT can be replaced by ODRT for patients with SCLC in China or Asia, especially where too many patients are waiting for radiotherapy within limited radiotherapy accelerators.

2. More financial and logistic investments are needed to conduct high quality clinical trials, such as encouraging participants to come back for brain MRI scanning and neurocognitive functioning assessments by offering reimbursements.

3. Suggestions on how to improve BM and cognitive function related trials will help the society conduct better studies with more reliable conclusions, therefore improve the daily care for patients with cancer.

4. Highly selective PCI can avoid unnecessary irradiation and subsequent neurotoxicities for patients who are not likely to develop BM, and consequently reduce the economy and health care burden for society and the family.

5. Optimizing PCI will reduce the risk of neurotoxicity and improve the QOL for patients with lung cancer.

Industrial impact

1. The findings of this thesis could result in several subsequent studies, both in the laboratory for mechanism research and in the clinical setting for clinical trials, which might further improve healthcare. For example, if HA-PCI plus memantine will be found to preserve neurocognitive function significantly, memantine will result a higher need in the market. And facilities and technicians that enables the application of HA-PCI techniques will also have a higher market share.

2. The series of projects in this thesis show that we are a very professional and productive team capable of conducting multiple studies and clinical trials. Based in Maastro, a nationally and internationally renowned radiotherapy center that explicitly wants to make the connection between patient care, education and effective scientific research, and Maastricht University Medical Centre+ (MUMC), distinguished nationally and internationally top clinical patient care, research, and education, our team has made great contributions in patients care and academy.

3.The radiomics findings will stimulate more related studies, not only in patients with NSCLC, but also in SCLC, esophageal cancer, breast cancer, and for any solid tumors at any sites of the body that need radiotherapy during the whole disease course; not only in radiomics field, but also can be extended to other fields of computer science and data science that dealing with big data, such as deep learning, machine learning, and artificial intelligence.

4. The neurocognitive findings will inspire more cognition related trials in clinical settings, encourage neuropsychologists to develop and improve neuropsychology tests, promote the

using of patient-reported EORTC questionnaires, and stimulate the medicine industry to develop related agents.

5. The findings on the pitfalls of risk of bias assessment tool will help the Cochrane improve the assessment tools for systematic review and meta-analysis.

Cultural impact

1. The series of projects in this thesis involves patients and international collaborators from multiple centers worldwide. I developed a broad network worldwide with different culture backgrounds, such as Chinese, Belgium, Dutch, Italian, American, Spanish, and Iranian. By working closely together, I learned about each other's' culture and I connected multiple centers. This is very helpful for global networks and collaborations in the future.

2. The projects in this thesis involve experts from multiple disciplines, such as radiation oncologists, oncologists, radiologists, computer scientists, data scientists, neuropsychologists, statisticians, and epidemiologists. A diverse interdisciplinary collaboration enables us to broaden our knowledge and bridge professional gaps between disciplines.

3. In addition, I also have learnt a third language, Dutch, and have improved my English level. This benefits me a lot to improve my 4-years life abroad.

Dissemination

Three oral presentation at ESTRO annual conferences (2021, 2023).
One poster at WCLC 2021.
One ePoster at WCLC 2022.
One poster at ESMO 2022.
Multiple presentations within MAASTRO.
Multiple peer-reviewed publications, including some high-impact journals.