Optimizing prophylactic cranial irradiation for patients with lung cancer

Summary

Lung cancer is the leading cause of cancer related deaths. Brain metastases (BM) are very common in patients with lung cancer, and are associated with a decrease in quality of life (QOL) and overall survival (OS). Identifying risk factors for BM development can help clinicians to select patients who are at higher risk to develop BM during the disease course, and accordingly propose strategies to reduce the risk, such as administering prophylactic cranial irradiation (PCI). PCI is an effective method to reduce the incidence of BM in patients with lung cancer. However, it is associated with a risk of neurocognitive decline. Therefore, PCI should be selectively applied only to patients who are more likely to develop BM. Importantly, PCI is not the only cause that could give rise to neurocognitive impairment. Hence, revealing the risk factors for cognitive impairment is also very important, which can help improve the QOL by modifying the treatments, such as proposing hippocampal avoidance (HA)-PCI. Based on the above described rationales, I conducted serial studies to optimize PCI for patients with lung cancer in this thesis.

Chapter 1 is the first part of the thesis, where I provided a detailed background for this thesis, including lung cancer and its main pathology types, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and the differences between the two diseases. I described BM in lung cancer and its prognosis, together with currently known risk factors and the needs for further research. Next, I summarized how to reduce the incidence of BM by PCI, the pros and cons of PCI, and how to reduce the toxicity of PCI by HA-PCI. Last, I specified the definition of cognitive impairment and how to assess the cognitive function and QOL. I tried to solve the open questions described in chapter 1 in the subsequent chapters.

I started with evaluating the risk factors for BM in patients with SCLC and in patients with NSCLC. In **Chapter 2**, I conducted a propensity score matching multi-centric retrospective study in China to investigate whether thoracic twice-daily radiotherapy (TDRT) is associated with a higher incidence of BM compared with once-daily radiotherapy (ODRT) in patients with SCLC. It showed that TDRT increased the risk of BM without affecting the OS. Then, I systematically reviewed all the risk factors that have been reported for patients with SCLC in the current literature and conducted meta-analysis when applicable (**Chapter 3)**. It domenstrated that the most important risk factors were younger age, higher T stage, and extensive disease (ED). Six studies have investigated the association of thoracic radiotherapy fractionation (ODRT/TDRT) with BM development and showed conflicting conclusions. No qualified data were available to perform meta-analysis for this factor. Future studies are

warranted to confirm this issue. After that, I took a further step to NSCLC and investigated risk factors for BM in patients with radically treated stage III NSCLC, including radiomics features of the gross tumor volume (GTVs) on the planning CT scan for thoracic radiotherapy (**Chapter 4**). I developed a clinical model, three radiomics model (GTV, GTV of the involved lymph nodes [GTVn], GTV of the primary tumor [GTVp]), and a combined model. I compared their performance and clinical utility and found that the radiomics model of GTVn was the best one. Younger age, NSCLC non-squamous subtype, and larger GTVn were risk factors for BM. The GTVn volume and GTVn radiomics features were most prognostic for BM development in patients with stage III NSCLC. The GTVp and GTVn should be contoured separately in clinical practice.

The next part handles neurocognitive impairment and QOL in patients with SCLC and in patients with NSCLC. In **Chapter 5**, I systematically reviewed risk factors for neurocognitive decline in patients with lung cancer who were treated with PCI. To ensure the conclusions are reliable, I focused on reports from prospective clinical trials with adequate sample size. The main message is that high-quality data is lacking. Age, PCI dose, regimen and timing might be associated with cognitive impairment after PCI, but further research is needed.

With an overview on the status and pitfalls of current neurocognitive function related studies, I investigated the self-reported cognitive functioning (SRCF) and QOL in SCLC patients who were treated with PCI or HA-PCI from the phase III Dutch-Flemish randomized controlled trial (RCT), NCT01780675 (**Chapter 6**). The conclusion is: HA-PCI or PCI do not result in a difference in QOL and SRCF. Then, I pooled the two comparable phase III RCTs, the Dutch-Flemish NCT01780675 trial and the Spanish PREMER/NCT02397733, to investigate the impact of HA-PCI on SRCF and BM, including BM incidence and location (**Chapter 7**). It revealed that HA-PCI has no impact on SRCF, sparing the hippocampus did not lead to a higher incidence of isolated brain failure within or out of the hippocampal avoidance zone. Meanwhile, I also investigated the risk factors for cognitive impairment in patients with radically treated stage III NSCLC based on the longitudinal data from the phase III NVALT-11 trial (**Chapter 8**). I found that cognitive impairment is dynamic in individuals and can be classified into four types based on changes over time: sustained, reversible, recurring, and alternating, which was also confirmed in patients with SCLC (**Chapter 7**). Baseline cognitive impairment is the most important risk factor for subsequent cognitive functioning.

The last part of the thesis (**Chapter 9**) provides the main findings of each project and a general discussion on the findings, including the value of the findings, together with strengths and contributions of our studies, challenges we have met in conducting the studies, limitations

that need attention in each study, what we have done to mitigate the corresponding bias, how we can improve it in future work, and future perspectives.