Prophylactic cranial irradiation for stage III non-small cell lung cancer patients treated with curative intent

Impact paragraph

Lung cancer is the leading cause of cancer deaths worldwide, making up 18% of all cancer-related deaths.[1] A common metastatic site in patients with stage III non-small cell lung cancer (NSCLC) is the brain, as approximately 30% of the patients develop brain metastases over time. Brain metastases can lead to neurocognitive disorders, loss of health-related quality of life, and have a major impact on the patients' overall survival.[2] Without treatment, the prognosis of NSCLC patients ranges from 2 to 6 months. Although a radical local treatment of brain metastases may be possible with radiosurgery or resection, the prognosis often remains poor. In order to improve health-related quality of life as well as overall survival, there is an unmet need to prevent the occurrence of brain metastases.[3] The aim of this thesis was to assess the clinical and cost-effectiveness of PCI added to usual care in patients with stage IIINSCLC compared to usual care only. This chapter provides an overview of the relevance of this thesis for the most important stakeholders and the dissemination of the findings.

Relevance for patients and clinicians

The findings of this thesis are relevant for patients with stage III NSCLC and clinicians in the field of lung cancer. Although our results showed that PCI did not demonstrate an overall survival benefit, it is beneficial in terms of reducing brain metastases and prolonging the progression-free survival.[4] Clinicians are hesitant to adopt PCI for stage III NSCLC patients in clinical practice because of the lack of a statistically significant overall survival benefit and the increased risk of late toxicity. However, individual patient preferences vary, and preventing progression, especially in terms of brain metastases (and the accompanying impact on their quality of life) may be valued more important than overall survival and the increased risk of toxicity by some patients. This trade-off may especially be favourable towards PCI for patient subgroups with a high brain metastases risk, such as those with a specific genetic profile (e.g. epidermal growth factor receptor activating mutations or anaplastic lymphoma kinase rearrangements. In clinical practice the treatment pathway of individual patients could therefore be determined through a shared decision-making process. Lastly, chapter five informs clinicians that there is an association between the number of PCI fractions and the risk of toxicity (i.e. PCI given in 10 fractions increased the risk of toxicity compared to 15 fractions), without conclusive evidence of impacting the brain metastases-free survival.[5]

Relevance for clinical guideline development

Based on the findings of this thesis, it may be reconsidered which outcomes are important to inform clinical guidelines in oncology. Guidelines such as the ESMO Magnitude of Clinical Benefit Scale and the PASKWIL criteria are currently focussed on overall survival.[6,7] However, the results of this thesis show that although PCI did not demonstrate a statistically significant overall survival benefit, it is beneficial in terms of reducing brain metastases and prolonging the progression-free survival.[4] Therefore, outcomes that are beneficial in other ways than prolonging life could be more emphasized in lung cancer guidelines. As it can be challenging to combine all relevant clinical endpoints or to separately weigh them against each other, and the QALY could therefore be considered as an alternative to capture all benefits and harms of potential new treatments. Lastly, the cost-effectiveness assessment of PCI in stage III NSCLC in chapter seven showed that Bayesian approaches, illustrated by the survival probability plot, seem more supportive for decision making than frequentist approaches, and could therefore also be used for clinical guideline development.

Relevance for researchers

The findings of this thesis are also relevant for other researchers. Chapters two and three provide the application of two meta-analysis approaches, one based on aggregate data and one based on individual patient data.[4,8] The results of these chapters inform researcher about the important advantages and limitations of both approaches and guides them in their consideration of which approach may be most suitable for their own research involving meta-analysis. For researchers interested in health-related quality of life, chapter six presents several health-related quality of life instruments.[9] As these instruments measure distinct but complementary aspects of health-related quality of life, it is important for researchers to understand how they are different but complementary (generic or disease-specific, patient or general population perspective) before choosing which instrument(s) to use for their own health-related quality of life research.

Dissemination

To disseminate the findings, conclusions and recommendations of the studies included in this thesis to all relevant stakeholders, it is important that these studies are published in international journals. Of the six studies that are described in this thesis, five have been published so far and the remaining one is currently submitted for publication. In addition, the results of the studies included in this thesis have been

presented at (inter)national conferences such as the European Lung Cancer Congress (ELCC), the World Conference on Lung Cancer (WCLC), the post-ESMO-WCLC symposium and the Lowlands health Economics Study Group (LolaHESG). Next to that, results were presented to researchers and health care professionals at cancer-research institute Gustave Roussy, radiotherapeutic institutes Zuidwest Radiotherapeutisch Instituut and Maastro, and internally to colleagues from the department of Clinical Epidemiology and Medical Technology Assessment (KEMTA) at MUMC+.

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