Valorization
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Lung cancer is a highly aggressive disease causing significant morbidity and mortality worldwide. Lung cancer is yearly diagnosed in approximately 13,000 patients in the Netherlands (2016), and is the fourth most common type of cancer in men and women (IKNL). Pulmonary neuroendocrine tumors other than small cell lung cancer (SCLC), define a rare subgroup of lung cancers including the specific type of large cell neuroendocrine carcinomas (LCNEC) with an incidence of 3%. Patients suffering from LCNEC are known to have one of the worst prognoses in lung cancer. Overall survival for LCNEC is approximately 32 months when the disease has not metastasized and 8 months when it has metastasized at diagnosis.

Despite the first description of LCNEC already in 1991, standardized treatment incorporated into a guideline based on the evaluation of randomized clinical trials and/or meta-analyses for this disease is still lacking. In recent years, several new treatment options have emerged for non-small cell lung cancer (NSCLC) and pulmonary carcinoid, including targeted therapy countering the proliferative effects of driver mutations and/or upregulation of such pathways. Yet, the cornerstone of treatment for metastatic LCNEC remains to be (old) chemotherapy regimens evaluated in small cell lung cancer (SCLC) and/or NSCLC, which are not directly comparable. Amongst other, it is difficult to perform clinical trials regarding treatment in patients with LCNEC because of the depicted difficulty to diagnose this tumor. Concerns are particularly raised on the accuracy and precision of LCNEC diagnosed on a biopsy specimen, while this is of high importance to increase the feasibility of clinical trials evaluating treatment in LCNEC.

Therefore, temporal changes in the diagnosis and treatment of LCNEC in the Netherlands were investigated. In addition, we aimed to optimize the diagnosis of LCNEC on a biopsy specimen with additional markers. Furthermore, treatment of LCNEC when the disease has already metastasized was investigated using the experience of genomic profiling in LCNEC by others and related this experience to our knowledge on chemotherapy treatment outcome. With this approach, we were able to define suggestions regarding improvement on LCNEC diagnosis and treatment, possibly leading to an improved patient outcome in the future.

Relevance for the diagnosis of LCNEC

In chapter 3, it is shown that despite the lack of diagnostic criteria in the World Health Organization classification (2004) for LCNEC on a biopsy specimen, pathologists have been diagnosing LCNEC on biopsy specimen and have been doing this more often over the past years. This is also highlighted by our findings in chapter 4, were we show that
the occurrence of advanced LCNEC disease, usually diagnosed on a biopsy specimen, increased with over 2-fold in the Netherlands comparing 2003-2009 versus 2009-2012. In 2012, approximately 160 patients with LCNEC were diagnosed, about 1% of all lung cancer types. In Europe approximately 234,000 patients are yearly diagnosed with lung cancer of which it is estimated that 2340-7020 (1-3%) patients are suffering from LCNEC (white book figure 7d). Therefore, although the findings presented in thesis cannot be translated into a direct societal benefit, the results do emphasize that clinicians (pathologists and oncologists) will encounter LCNEC-patients more frequently. In chapters 4-6 and 8, we evaluated the diagnosis of LCNEC in daily practice. We observed that ambiguous diagnostic nomenclature is often, 20% of all neuroendocrine tumor diagnoses, used to describe diagnoses of neuroendocrine carcinomas not being SCLC on a biopsy specimen. Such nomenclature may be confusing for clinicians and can be interpreted in several ways leading to different treatment options. Also, we identified that although the diagnostic criteria for LCNEC are frequently not described in the original pathology reports (71%), this does not necessarily reflect the quality (accuracy) of the diagnosis. However, in up to 30% of LCNEC diagnoses, a diagnosis other than LCNEC was established by panel revision, including NSCLC, SCLC, and carcinoid diagnoses. Finally, we observed that LCNEC is often not recognized on a biopsy specimen because neuroendocrine morphology is absent or ambiguous to identify in such specimen. Collectively, all observed diagnostic problems regarding LCNEC can lead to suboptimal patient management and increase morbidity and mortality with associated economical costs.

Ways to solve the reported diagnostic problems are proposed in this thesis. 1) we should aim to increase the awareness of the diagnostic problems regarding LCNEC, but not limited to, among pathologists and clinicians. We aimed to do this in the Netherlands by organization of several neuroendocrine tumor workshops during the Pathologen Dagen (2017) and the yearly pulmonary oncology course (Wengen op de Wadden). 2) Implementation of standardized reporting protocols may increase unanimity in diagnostic nomenclature and for this reason the recently introduced national PALGA module for lung biopsies has been evaluated and we have provided feedback for the criteria relevant for LCNEC. 3) in this thesis, an adjustment to the current World Health Organization (WHO) classification is proposed (chapter 8) suggesting further implementation of neuroendocrine markers on biopsy specimen to recognize LCNEC in otherwise undifferentiated NSCLC. And finally, 4) RB1 protein marker staining on a biopsy specimen may be a useful diagnostic tool to separate a subgroup of LCNEC possibly requiring NSCLC type (cisplatinum-paclitaxel/gemcitabine) chemotherapy.
Relevance for the treatment of LCNEC

Treatment of LCNEC is subject of debate, according to expert opinion cisplatinum-etoposide chemotherapy (i.e., ‘SCLC type’) is the favored treatment for metastatic LCNEC. In chapter 9 we have shown that, based on the thus far worldwide largest cohort of LCNEC patients analyzed, NSCLC type chemotherapy is not inferior to SCLC type chemotherapy and may even have a more favorable outcome. Best treatment outcome was observed for the NSCLC type regimen platinum-gemcitabine and platinum-paclitaxel chemotherapy. To the contrary, platinum-pemetrexed chemotherapy, currently used as first-line treatment for non-squamous NSCLC, showed inferior results in LCNEC. These results are important for patients, clinicians as well as the treatment advice given by (inter) national guidelines, as both platinum-etoposide and platinum-pemetrexed are frequently administered to patients with LCNEC (>65% in 2012) and this requires further consideration. In chapter 10 and chapter 11 of this thesis, we underline the relevance of the recently identified genomic signatures in LCNEC separating a ‘NSCLC type’ identified by RB1 wildtype gene and a ‘SCLC type’ identified by RB1 gene mutation. Patient with LCNEC of a NSCLC type (i.e. RB1 wildtype) showed superior overall survival when treated with a NSCLC type chemotherapy regimen. These results should be considered as hypothesis generating, however, the results are encouraging as they provide a rational for personalized treatment, based on genomic profiles in patients with LCNEC disease additional to well-known and treatable oncogenes (e.g. EGFR).

Summary and future envisioned activities to implement results in daily practice

In summary, this thesis describes several possibilities allowing optimization of the diagnosis of LCNEC on a biopsy specimen and chemotherapy treatment in metastatic disease. Combined these results can be of benefit to patients, clinicians, care financers, and public health services by increasing accuracy of the diagnosis and improving treatment outcomes in patients suffering from LCNEC. These results can also be of interest to pharmaceutical companies investigating (new) drug combinations possibly applicable to LCNEC.
This thesis may provide a reference point. For the results described in this thesis to be of a real benefit to society through application in routine care practice, we should undertake several steps soon:

- A prospective study evaluating the adjusted diagnostic criteria for undifferentiated NSCLC on biopsy specimen should be initiated possibly linking PALGA and IKNL data prospectively.

- A European randomized clinical trial evaluating cisplatinum-gemcitabine (or paclitaxel) versus platinum-etoposide chemotherapy should be performed. Included patients could be stratified based on *RB1* status.

- Basic translational research should be encouraged in LCNEC evaluating response of chemotherapy drug combinations in different molecular LCNEC subtypes through establishment of cell lines and mice models.