Chapter 10

Summary
Recurrent Respiratory Papillomatosis (RRP) is a rare disease, caused by human papillomavirus type 6 (HPV6) or 11 (HPV11). The disease presents as wart-like tumor growth (papillomas) throughout the airways, resulting in voice problems and eventually a compromised airway. As there is no curative therapy for the disease, patients depend on repeated surgical removal of the papillomas. The disease has an unpredictable course and severity is very different between patients. An overview of the disease characteristics is given in chapter 1. This thesis provides insights in confounders of the clinical course of RRP and the psychosocial wellbeing of patients.

Part I: Clinical course

Before, it was thought that RRP only occurred in newborns and young adults. Chapter 2 describes the age of onset of RRP. Six hundred and thirty-nine patients from twelve European hospitals were included. A mixture model was selected using the Bayesian information criterion. The analysis revealed that instead of a bimodal distribution of age of onset, there is a trimodal distribution. RRP generally starts at the age of 7, 35 and 64 years. The elder patient group with a mean age of onset of 64 years is new entity, which is not accounted for in foregoing research.

In chapter 3.1 we report on a cohort of 55 RRP patients, with either HPV6 (n=42) or HPV11 (n=13) associated disease. We observed that the disease course significantly worsens when the age of onset is lower. HPV11 patients have a significantly worse disease course compared to HPV6 patients at an age younger than 22. This effect reverses after the age of 22, although differences between HPV6 and HPV11 are smaller. Overall HPV11 associated RRP is characterized by a statistically significant wider spread of the papillomas, especially distally from the larynx. None of the included patients developed malignancy from RRP.

Not many studies on therapy in RRP take into account the natural decrease of the needed number of surgical interventions. Many therapies are therefore considered as effective, while this is accountable to the natural course. For this a response letter was edited as response to one of such articles to ask
for attention for the need to correct for the clinical course in these articles (chapter 3.2). As the method of correcting for the natural course is applicable on existing data, it is unnecessary to re-expose patients to different therapies. It would be better to reanalyse results of these articles with this correction.

Many therapies other than surgery to treat RRP have been tried with variable success. One of the proposed therapies is therapeutic use of the quadrivalent HPV vaccine (Gardasil®). Theoretically the vaccine could (re)activate the immune system in RRP patients and therefore prevent further spread of the papillomas by reinfection. In chapter 4 a pilot study was performed to determine the immunological response on Gardasil® in 6 HPV6/11 positive RRP patients. First we show that seroreactivity on the associated HPV type (HPV6 or HPV11) rose significantly after vaccination, indicating reactivation of the humoral immune system even though patients had active disease. Although this pilot study was not designed to assess the clinical course of RRP or papilloma spread after vaccination, a decrease of the number of surgical interventions was seen in the majority of patients. However, this study lacked the power to draw firm conclusions. Given the course of disease in the 6 included patients, power analysis revealed that 29 vaccinated patients and 29 controls are needed in a two-year double-blind placebo controlled randomized controlled trial. To confirm the improvement by this therapy, this will be subject of future studies.

One of the factors that is generally assumed to worsen the clinical course of RRP is gastroesophageal reflux disease (GERD). It would theoretically provoke viral activity due to irritation, increasing the risk to induce papilloma growth. Many centres treating RRP patients had therefore included anti-reflux therapy in their general treatment protocols. To evaluate the influence of GERD on the clinical course of RRP a systematic review (PRISMA) of the literature was performed (chapter 5). This analysis revealed that till now no study proved that GERD influences the number of surgical interventions, severity of disease (as measured by different scoring systems) and histopathological parameters. One study showed that patients with papilloma in the anterior and posterior commissure benefitted from perioperative anti-reflux therapy. Anti-reflux decreased the chance of laryngeal web formation. However, the quality of that study (as defined by the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institute of Health) describing this effect
was moderate. It was also shown in chapter 5 that the incidence of objectified GERD in AoRRP patients is higher than in the general population.

Part II: Psychosocial aspects of RRP

Due to the unpredictable and frequently severe clinical course of RRP, it is thought that the disease causes a high psychosocial burden on patients. Few have studied this, most of those that did found voice-related quality of life (QoL) problems in many patients. In these studies it was unclear how RRP affected other domains of QoL. In chapter 6 aspects of QoL in 91 Dutch and Finnish RRP patients are described. Analyses revealed that patients were on average slightly more depressed than the general population; they had more voice problems and a lower general health perception. Paradoxically, RRP patients had a better health-related QoL and less anxiety than the average population. The factors that were negatively associated with parameters of QoL were country of origin, gender, current age, age of onset of RRP, and presence of comorbidity. The number of surgical interventions the patient underwent and the duration of disease did not have a significant effect on any of the QoL parameters. Only a few patients received psychosocial support. Although most patients experienced voice problems, only two out of five received speech therapy, which number seems low.

In chapter 7 an instrument to screen for severity and nature of distress is investigated (in Dutch and Finnish). On the Distress Thermometer and Problem List (DT&PL) patients can indicate the severity of distress they experience. Additionally, they can provide information about problems inducing this distress as well as their desire for professional care for the problems they experience. Other versions of the DT&PL have been used in the daily care of patients with chronic and malignant diseases. We showed that the RRP adapted version of the DT&PL is valid, useful and appreciated by patients. The tool is easy to use in the in- and outpatient clinic.

For mutual understanding it is important that patients and partners have extensive knowledge of the disease and its course. Provision of information is very important for this. In chapter 8 we report on a quality and readability assessment of online English written patient information. The analysis was
designed as if a patient or layperson would search for information. Relevant information was collected using three different search engines and seven different search terms. Quality and readability were assessed. Fifty-one English websites were included. Mean quality of the included websites was considered poor and information presented on average difficult to read. Improvement of English online information is needed.

Finally, a discussion is presented including suggestions for future directions of research of this debilitating disease.