Chapter 8

General discussion and conclusions

Many questions about the diagnosis, clinical course, treatment and quality of life of the recurrent respiratory papillomatosis (RRP) patient remain unanswered today. This thesis provides answers to some of these questions in order to help the medical specialist to better understand, more accurately diagnose and more effectively treat RRP, and therewith improve the healthcare experience of the RRP patient. The underlying chapter presents this thesis' key findings, and identifies areas for future research on RRP.

Part I Diagnosis

Chapter 2, *"Narrow band imaging is a new technique in visualization of recurrent respiratory papillomatosis",* focuses on the diagnosis of RRP, and presents evidence that narrow band imaging (NBI), when used as an additional imaging technique during surgical interventions, helps surgeons to better visualize and more effectively remove papilloma. NBI increases the sensitivity in detecting RRP lesions from 80% to 97%. Chapter 2 is the first study which shows beneficial effects of using NBI in diagnosing RRP, where NBI enables the surgeon to make a better distinction between papilloma and healthy tissue, allowing for a more secure and complete removal of the papilloma. After the publication of chapter 2, NBI became a standard additional technique during microlaryngoscopy in RRP patients in the University Medical Center Groningen (UMCG). As a result, it has been observed that since then more RRP lesions have been detected during surgery. Hence, it is recommendable that NBI becomes a standard additional technique applied during surgical interventions in RRP patients.

During the study, it was also observed that RRP lesions do not regularly re-appear in the exact same location where an RRP lesion has previously been removed. On the other hand, if lesions are not surgically removed, an RRP lesion can grow further in its existing location. As such, a more secure and complete removal of the papilloma, enabled by the application of NBI as an additional technique, may decrease the recurrence rate of RRP. To test this hypothesis, a cohort study should be performed where recurrence and surgical interventions are compared between a group of RRP patients where both NBI and white light are used during surgical interventions, and a group of RRP patients where only white light is used.

Head and neck surgeons are increasingly using NBI for staging, and to determine the difference between benign and malignant tissue. The generally accepted

classification to distinguish between benign and malignant tissue is the IPCL classification of Ni et al., based on irregular microvasculair patterns staged in type I to Vabc (1). A limitation of this IPCL classification is that the study by which it was determined did not include patients with RRP. If the IPCL classification is applied to RRP lesions, lesions can incorrectly be classified as malignant, because RRP lesions are difficult to distinguish from invasive carcinoma under the IPCL classification (2). An early distinction between the two diseases is important because they require the removal of different margins. A revision of the IPCL classification may enable such distinction. There are two macroscopic parameters that can help distinguish between malignant and RRP lesions, which could be added to the IPCL. The first is the location of the lesions; while there usually is only one malignant lesion located in one area in which it expands, RRP is often located in multiple distinct areas in the upper airways. The second parameter is ulceration; malignant lesions often contain ulcerations, whilst this is uncommon in RRP lesions. The possibility of adding the aforementioned parameters to the IPCL classification is subject of ongoing research in the Department of Otorhinolaryngology / Head & Neck Surgery at the UMCG.

Part II Clinical course

Chapter 3, *"The clinical course of recurrent respiratory papillomatosis: a comparison between aggressiveness of HPV6 and HPV11",* looks at the clinical course of RRP patients. Chapter 3 shows that the number of surgical interventions performed on both HPV6 and HPV11 positive RRP patients reduces over the course of the disease. This is due to the natural course and surgical control of the disease. However, patients in the HPV11 group have on average more surgical interventions and more extra-laryngeal spread of papilloma in the respiratory tract than patients in the HPV6 group. The data further shows that even after as much as 34 years of clinical remission, RRP lesions can recur. It hence seems more appropriate to speak of 'clinical remission' in RRP patients than of 'curing' of RRP patients, a term often used in medical literature.

In addition, statistical analysis in chapter 3 shows that both HPV type and age of onset are correlated with the number of surgical interventions performed on an RRP patient. A statistical model was constructed to describe the aggressiveness of RRP. It shows that HPV11 positive RRP patients with an early age of onset are likely to undergo more surgical interventions than HPV6 positive RRP patients with an early age of onset. The opposite was seen in the late onset patients, where the RRP

patients with HPV6 had more surgical interventions than patients with HPV11. The turning point with respect to age of onset at which the model shows a quantitatively less favorable outlook for an RRP patient with type HPV6 than an RRP patient with type HPV11 is 22.4 years. The statistical model, and the insights on the differences between HPV6 and HPV11 positive RRP patients allow medical specialists to better inform RRP patients on disease prognosis, including the expected number of required surgical interventions. Because little is known about the drivers behind the aforementioned differences between the clinical course of RRP patients with HPV6 and HPV11 observed in chapter 3, more fundamental research is recommendable.

Chapter 3 looks at the aggressiveness of the RRP disease course based on the number of surgical interventions. Taking the decision to surgically intervene or not, and at what time is a fine balancing act. On one hand, papilloma needs to be removed as much as possible to achieve disease control. On the other hand, the number of surgical interventions on an RRP patient should be kept to a minimum to avoid scar tissue, which can cause irreversible damage to the vocal cords. Medical literature does not offer an optimal operating strategy for this dilemma, and treatment of a particular RRP patient and finding the right balance between disease control and minimizing side effects remains a challenge. In the UMCG, patients underwent microlaryngoscopy under general anesthesia only when the size of the papilloma was graded exophitic; if the papilloma was graded sessile no surgical intervention was done (3). This standardized practice prevented patients from undergoing surgical intervention for every papilloma, and therewith avoided causing scar tissue to protect the voice function.

The effectiveness of medical interventions in RRP patients is often analyzed by a comparison of the number of surgical interventions pre- and post-medication. Until now such studies have been done without a correction for the natural course of the disease. They often report a decrease in the number of surgical interventions post-medication, and conclude that this is a result of that medical intervention. However, chapter 3 shows that the natural disease course of RRP generally demonstrates a decrease in surgical interventions over time. A reduction in the number of surgical interventions would therefore be expected with any medication, or even without medication. As such, adjustments for the natural course should be made prior to drawing conclusions on the effectiveness of a medical intervention, in particular in studies without a control group.

Part III Treatment

Part III presents a letter to the editor (chapter 4) and two studies on the treatment of RRP. The first study in chapter 5**,** *"Safety of intralesional cidofovir in patients with recurrent respiratory papillomatosis: an international retrospective study on 635 RRP patients",* presents the findings of a worldwide retrospective research into the use and side effects of cidofovir (Vistide®, Gilead, Foster City, CA, USA). It concludes that the use of cidofovir differs between laryngology and other medical specialties. The cidofovir dosages administered to RRP patients in laryngology varies amongst centers, but is generally lower than cidofovir dosages used in other medical specialties. Also, the route of administration of cidofovir is different; in laryngology cidofovir is administered intralesionally on RRP patients, whereas in other medical specialties it is administered intravenously. Chapter 5 finds no clinical evidence for more nephrotoxic, neutropenic or oncogenic side effects in RRP patients after the use of intralesional cidofovir compared to RRP patients that did not use cidofovir. Following this retrospective worldwide multicenter study, Moore et al. showed there was no difference in the mean dysplasia score before and after treatment of intralesional cidofovir in RRP patients (4). Based on these findings, RRP patients can be informed that while nephrotoxicity, neutropenia, oncogenicity can arise from the use of cidofovir, these side effects have not been observed to occur more frequently in RRP patients treated with cidofovir compared to RRP patients not treated with cidofovir. After Gilead's warning in 2011 on side effects of cidofovir, otorhinolaryngologists generally stopped using cidofovir in RRP treatment. As of 2016, cidofovir is used on a regular basis in the United States of America again in the treatment of RRP, and also a few European hospitals have reintroduced the use of cidofovir in the treatment of RRP.

Besides cidofovir, many other medicines such as bevacizumab, celecoxib, HPV vaccine, gastroesophageal reflux disease medication, indole-3-carbinol, interferon, mumps vaccine and even traditional Chinese drugs have been applied in treatment of RRP patients (5,6). In 2012, Chadha et al. did a Cochrane systematic review on antiviral agents (7). They found one randomized controlled trial (RCT), and 24 uncontrolled trials or case series. It is remarkable that only one study has been performed on the efficacy of drugs on RRP which makes use of a control group. This RCT with 19 patients describes a significant improvement of VHI score in the cidofovir group versus the control group after 12 months (8). However, no differences between these two groups were found in respect of

the number of surgical interventions or Derkay scores (8). As such, caution should be applied when prescribing antiviral medicines, including cidofovir, because no convincing evidence has been found regarding the long-term effectiveness of antiviral medicines to decrease the burden of RRP patients. Given the above, it is recommendable that more studies are performed to analyze the effectiveness of the available medication in the treatment of RRP. Such studies should either include a control group, or be performed in the form of an RCT to enable more robust study conclusions. Also, more clinical studies should be performed on the dosage and route of administration (systemic or intralesional) of cidofovir in RRP patients.

In the patients described in chapter 5, malignant tumors were observed to be more common amongst HPV negative RRP patients than in low-risk HPV positive RRP patients. The same was observed by Omland and coworkers, who concluded that there is a more common transition from RRP to malignancy in HPV negative RRP patients compared to RRP low-risk HPV positive patients. Omland and coworkers did not consider RRP misdiagnosis as a possible explanation for the observed phenomenon (9). Characteristics such as age, smoking and alcohol were not described in the group with a malignancy. No transformation phase to malignancy was shown in HPV negative RRP patients. Within the RRP patient group in the UMCG that developed a malignancy, there was only a short period (few months) between the diagnosis of RRP and the development of a malignancy in the same anatomical location. In addition, most of these patients were older than 50, and had a history of smoking and alcohol usage. Hence, there are two possibilities: either RRP in HPV negative patients can transform into malignancy, or more likely, the pathologic pre-cancer phase has similar features to RRP, causing misdiagnosis of patients in a pre-cancer phase. As RRP HPV negative patients are more likely to develop malignancy due to transformation or misdiagnosis, it is firstly recommendable that the RRP biopsies of every new RRP diagnosed patient are tested for both low-risk (mainly HPV6 and HPV11) and high-risk HPV types. Secondly, those RRP patients that have been determined to be HPV negative should receive more frequent follow-up visits than RRP positive HPV patients in order to detect malignancy at an early stage.

Chapter 6, *"Immunological response to quadrivalent HPV vaccine in treatment of Recurrent Respiratory Papillomatosis",* shows that HPV seroreactivity against the associated HPV type increased after administration of the quadrivalent vaccine

(Gardasil®, Merck & Co inc., Whitehouse Station, NJ, USA) in RRP patients. Children with HPV and RRP have lower neutralizing antibody titers than children who were exposed to HPV but did not develop RRP (10). Based on this observation, patients with higher neutralizing seroreactivity against HPV could theoretically have a form of protection against RRP. The quadrivalent vaccine contains virus L1 like particles of HPV6, HPV11, HPV16 and HPV18, and is administered to patients before exposure to HPV to prevent HPV related diseases. Chapter 6 shows that when administered to RRP patients *after* infection and activation, the quadrivalent vaccine induces higher seroreactivity than the natural infection in RRP patients. Hypothetically, this higher seroreactivity could influence the clinical course of RRP by intensifying an RRP patient's immune response and preventing re-infection. To further test this hypothesis, a randomized controlled trial could be used to analyze the effects of the quadrivalent vaccine on the clinical course of RRP patients, including the number of surgical interventions, Derkay score, and VHI.

Little is known with regards to the role the immune system plays in RRP patients. Healthy persons infected with HPV in general are able to mediate a T-cell immune clearance of HPV. However, patients who develop a symptomatic HPV related disease like RRP seem to develop a tolerance to the HPV infection instead of a cell-mediated immune clearance (11). More studies are required to better understand the immune deficiency that prevents effective clearance of HPV6 and HPV11 infection in RRP patients. This could lead to new therapeutic targets for the treatment of RRP (12).

Part IV Quality of life

Chapter 7, *"Change of Voice Handicap Index after treatment of benign laryngeal disorders",* describes the voice related quality of life of UMCG patients with one of seven benign laryngeal disorders including RRP. It observes significant improvement in the VHI after treatment in RRP patients, and in five of the six other benign laryngeal disorders studied in the UMCG.

In general, the VHI is considered an appropriate measure to determine quality of life for patients with benign laryngeal disorders. However, some caution has to be applied in the use of VHI for RRP patients. The VHI as used in this study entails the measurement of a patient's sentiment at two distinct moments in time: before, and 3 months after surgical intervention. Because of the recurrent and chronic

character of RRP, VHI scores can differ significantly depending on when the questionnaire is taken.

Final considerations

Because RRP is a rare disease and RRP patients are spread across many hospitals, general hospitals treat very small numbers of RRP patients. Centralizing the care of RRP patients in tertiary centers will enforce more uniformity in the treatment of RRP. In addition, a higher number of RRP patients treated within certain centers will justify higher investments in equipment, such as equipment necessary for NBI. One way to achieve more centralization of RRP care is by agreeing amongst laryngologists to refer RRP patients to specialized tertiary centers in a country, in the realization of which laryngology associations can play a role. Finally, research on RRP can also benefit from centralization and cooperation between international RRP centers, as demonstrated in this thesis. An international network of RRP centers could enable such cooperation.

As prevention is better than cure, many countries have vaccine programs for cervix cancer nowadays. The fact that some countries use a bivalent vaccine whilst other use a quadrivalent HPV vaccine, creates an opportunity for a comparative study of the incidence in female RRP patients in these countries. Additionally, countries without a vaccine program can function as a control group. This study would allow testing the hypothesis that the RRP incidence amongst women in the countries where quadrivalent vaccines have been administrated decreases the most, because quadrivalent vaccines also protect against the RRP-related HPVs, HPV6 and HPV11. If the study would confirm the hypothesis, it could be considered to administer quadrivalent vaccines to both boys and girls in order to reduce or even eradicate RRP, and other HPV related diseases.

There is at present no curative treatment for RRP patients, and management of RRP remains a challenging task for otorhinolaryngologists. The disease burden on patients is high due to the unpredictable clinical course, the many hospital admissions and related voice problems. This thesis provides medical specialists with more insights on RRP to enable improvements in its diagnostics and treatment. Furthermore it has identified opportunities for future research, which is required to further build on the knowledge and insights on RRP to be able to optimally inform and treat the RRP patient.

References

(1) Ni XG, He S, Xu ZG, Gao L, Lu N, Yuan Z, et al. Endoscopic diagnosis of laryngeal cancer and precancerous lesions by narrow band imaging. J Laryngol Otol 2011 Mar;125(3):288-296.

(2) Lukes P, Zabrodsky M, Lukesova E, Chovanec M, Astl J, Betka JA, et al. The role of NBI HDTV magnifying endoscopy in the prehistologic diagnosis of laryngeal papillomatosis and spinocellular cancer. Biomed Res Int 2014;2014:285486.

(3) Dikkers FG. Treatment of recurrent respiratory papillomatosis with microsurgery in combination with intralesional cidofovir - a prospective study. Eur Arch Otorhinolaryngol 2006;263:440-443.

(4) Moore JE, Garcia A, Sanyal S, Saunders S, Portnoy JE, Hu A, et al. Degrees of dysplasia based on viral typing in patients with cidofovir use and recurrent respiratory papillomatosis. J Voice 2013 Nov;27(6):765-768.

(5) Carifi M, Napolitano D, Morandi M, Dall'Olio D. Recurrent respiratory papillomatosis: current and future perspectives. Ther Clin Risk Manag 2015 May 5;11:731-738.

(6) Okubo K, Saito K, Fukuda H, Watanabe K, Ogawa K, Shiotani A. Traditional Chinese Medicine for treatment of laryngeal papillomatosis. J Altern Complement Med 2010 Apr;16(4):427-433.

(7) Chadha NK, James A. Adjuvant antiviral therapy for recurrent respiratory papillomatosis. Cochrane Database Syst Rev 2012 Dec 12;12:CD005053.

(8) McMurray JS, Connor N, Ford CN. Cidofovir efficacy in recurrent respiratory papillomatosis: a randomized, double-blind, placebo-controlled study. Ann Otol Rhinol Laryngol 2008 Jul;117(7):477-483.

(9) Omland T, Lie KA, Akre H, Sandlie LE, Jebsen P, Sandvik L, et al. Recurrent respiratory papillomatosis: HPV genotypes and risk of high-grade laryngeal neoplasia. PLoS One 2014 Jun 11;9(6):e99114.

(10) Stern Y, Felipovich A, Cotton RT, Segal K. Immunocompetency in children with recurrent respiratory papillomatosis: prospective study. Ann Otol Rhinol Laryngol 2007 Mar;116(3):169-171.

(11) Rodman R, Mutasa S, Dupuis C, Spratt H, Underbrink M. Genetic dysregulation in recurrent respiratory papillomatosis. Laryngoscope 2014 Aug;124(8):E320-5.