M U N I

COMMENTARY TO HABILITATION THESIS[1]

The presented habilitation thesis in Otorhinolaryngology is an annotated collection of previously published scholarly works dealing with advanced diagnostics and conservative and surgical treatment of laryngeal diseases. This topic has recently received increasing attention worldwide due to advances in pharmaceuticals and technology.

The habilitation thesis is divided into two main parts. The first main part is theoretical. It summarizes current diagnostic methods of the larynx, the most common laryngeal pathologies and surgical and non-surgical treatment options. The second main part is experimental, devoted to the author's research. It is a collection of twenty-four previously published scholarly works. For better clarity, it is further divided into three chapters and other subchapters. The introduction to each chapter or subchapter summarizes the issues with a focus on clarifying the origins of the studies. Subsequently, the settings of individual studies and their results are briefly presented. Substantial findings are then recapitulated in the most important points at the end of each study.

The first and most extensive chapter is devoted to advanced diagnostics of laryngeal diseases. First part is focused on research of risk factors for recurrent respiratory papillomatosis (RRP). In a series of consecutive studies, we focused in detail on expanding the diagnostic by identifying possible risk factors that could contribute to the pathogenesis and progression of RRP. Human papillomavirus (HPV) causes RRP, but RPP prevalence is much lower than HPV prevalence. Thus, HPV infection is necessary, but not sufficient, to cause RRP and other factors are likely to contribute to its pathogenesis. The results of our case series and case-control studies indicate laryngopharyngeal reflux (LPR) and Epstein-Barr virus co-infection might be such risk factors activating latent HPV infection, enhancing cell proliferation and contributing to the pathogenesis and progression of RRP in up to one third of patients. Second part of the chapter is focused on diagnostic of reflux laryngitis and LPR. LPR is very common etiopathogenetic factor not only for laryngeal pathologies and its diagnostics is still not optimal. Recently, a 24-hour impedance was used as golden standard to detect LPR. However,

[1] The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant’s contribution in terms of both quality and content.

the evaluation criteria for impedance are not clearly defined. Thus, pathological pharyngeal impedance values needed to be clearly established to diagnose pathological LPR. More precise limit of the pathological result of 24-hour impedance (and pathological LPR) was set according to our results, which were achieved in prospective study by comparing the results of 24-hour impedance and immunohistochemical detection of pepsin in laryngeal mucosa biopsy as the most accurate diagnostic method of relevant LPR. Six or more pharyngeal reflux episodes registered during the 24-hour impedance was set as the cutoff for diagnosing pathological LPR. In another study, suitability of measuring pepsin in saliva using Peptest® as a possible screening LPR test was verified by comparing its results and the results of 24-hour impedance in the same patient. A positive Peptest® was highly supportive of a pathological LPR diagnosis. However, a negative test could not exclude LPR. Therefore, the Peptest® could serve as a screening test for physicians who cannot visualize the larynx, for whatever reason. In contrast, a negative Peptest® cannot rule out LPR. Therefore, when the Peptest® is negative, the patient should be examined and screened by otolaryngologist with the Reflux Finding Score, which had 57% sensitivity according to our findings, or the Reflux Sign Assessment, which is expected to have greater sensitivity. The last part of this chapter is dedicated to the use of new optical methods for the detection of laryngeal pathologies. It consists of research of optical diagnostic methods using filtered light or image adjustment and drug induced sleep endoscopy. We compared the results of different optical technologies and found both methods, narrow band imaging endoscopy and Storz Professional Image Enhancement System, are comparable in detection and analysis of superficial neoangiogenesis, typical for benign lesion and for precancerous or cancerous changes in larynx. In another study, we identified optical characteristics of rare laryngeal pathology pemphigus vulgaris which makes it possible to express a clear suspicion of this pathology, thus speeding up diagnosis and treatment. Furthermore, drug induced sleep endoscopy as a still relatively new endoscopic method has been successfully used to evaluate the failure of positive airway pressure therapy in patients with obstructive sleep apnea in our case series. It was possible to visualize the effect of overpressure on the individual sites of airway obstruction and thus set the optimal positive airway pressure. It also made it possible to detect cases of collapsing epiglottis that need to be primarily treated surgically which will improve the treatment outcomes of obstructive sleep apnea.

The second chapter is devoted to the treatment of benign and malignant laryngeal pathologies including its consequences and complications. Evolution of voice after transoral laser

cordectomy (TLC) for precancerous lesions and early glottic cancer was observed with a focus on choosing the best treatment modality for each patient depending on the extent of the tumor and patient characteristics. To date, the time period for voice recovery after TLC has not been examined. It is highly important for voice professionals to know when their voice will return. Our study showed that the evolution of voice quality after TLC depended on the extent of the resection. Precancerous lesions and early glottic cancers that required limited surgery without muscular infiltration showed good voice quality outcomes. Thus, TLC should be offered for these lesions, even when the patient is a voice professional. However, patients should be informed that voice quality improvements require more than 6 weeks, and good voice quality can only be presumably achieved in 3–6 months after surgery. In contrast, when a more extensive cordectomy is planned, the patient should be informed that voice deterioration is expected, and if voice quality is essential for the patient, radiotherapy should be recommended. We also monitored voice of patients in other studies. One study determined long term effect of vocal fold augmentation using autologous fat applied via direct microlaryngoscopy and calcium hydroxylapatite injected officebased and compared the two techniques. Both techniques yielded good 5-year results for the treatment of vocal fold insufficiency. In 10% of our patients, re-intervention was required at between 2 and 3 years after surgery. At 5 years after injection, the results did not differ between the two procedures. In another study, we found out whether there is an effect of voice therapy with or without transcutaneous electrical stimulation on recovery of injured macroscopically intact recurrent laryngeal nerve after thyroid surgery. A total of 149 patients were included in the analysis. Adding transcutaneous electrical stimulation to voice therapy provided no beneficial effect on the recovery of vocal fold movement. Therefore, its indications should be re-evaluated; it is questionable whether stimulation should be routinely recommended considering the time demands for both the patient and the physiotherapist. The chapter also contains work, in which the first results of a new surgical procedure effectively solving collapse of epiglottis in a series of patients with obstructive sleep apnea are described.

The third chapter is devoted to research of new methods helping with preventing of laryngeal complications not only during thyroid and parathyroid surgery. It was found that individualised timing of radio-guided parathyroidectomy using multi-phase SPECT/CT significantly increases in vivo sensitivity and accuracy and reduces operating time. Its use in this individualised mode thus helps the surgeon more. This is due to some parathyroid adenomas that wash radionuclide out earlier than was previously thought. We also found that

bipolar tissue thermofusion BiClamp® is an effective and safe system that significantly reduced the risk of postoperative bleeding and shortened the operation time without increasing the risk of perioperative recurrent laryngeal nerve injury during 1156 thyroid and parathyroid surgeries.

At the end of the habilitation thesis, further planned research in each of the researched areas is outlined.

[1][2] ***FORMANEK, M.*(corresponding author)***, D. JANCATOVA, P. KOMINEK, P. MATOUSEK a K. ZELENIK. Laryngopharyngeal reflux and herpes simplex virus type 2 are possible risk factors for adult-onset recurrent respiratory papillomatosis (prospective case-control study). *Clinical Otolaryngology* [online]. 2017, **42**(3), 597–601. ISSN 1749-4478. Dostupné z: doi:10.1111/coa.12779

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
70	100	80	100

[2] ***FORMANEK, Martin*(corresponding author)***, Debora FORMANKOVA, Pavel HURNIK, Adela VRTKOVA a Pavel KOMINEK. Epstein-Barr virus may contribute to the pathogenesis of adult-onset recurrent respiratory papillomatosis: A preliminary study. *Clinical Otolaryngology* [online]. 2021, **46**(2), 373–379. ISSN 1749-4478. Dostupné z: doi:10.1111/coa.13681

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
70	100	80	100

[3] ***FORMANEK, Martin*(corresponding author)***, Pavel KOMINEK, Debora JANCATOVA, Lucia STANIKOVA, Radoslava TOMANOVA, Jana VACULOVA, Milan URIK, Ivo SLAPAK a Karol ZELENIK. Laryngopharyngeal Reflux Is a Potential Risk Factor for Juvenile-Onset Recurrent Respiratory Papillomatosis. *Biomed Research International* [online]. 2019, **2019**, 1463896. ISSN 2314-6133. Dostupné z: doi:10.1155/2019/1463896

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
70	100	80	100

[2] Bibliographic record of a published scientific result, which is part of the habilitation thesis.

[4] ***FORMÁNEK, M.*(corresponding author)****, H. KUČOVÁ, K. ZELENÍK a P. KOMÍNEK. Současné možnosti terapie juvenilní recidivující respirační papilomatózy. *Cesko-Slovenska Pediatrie*. 2015, **70**(3), 174–178.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
70	50	70	50

[5] ***FORMANEK, Martin*(corresponding author)****, Debora JANCATOVA, Pavel KOMINEK, Radoslava TOMANOVA a Karol ZELENIK. Comparison of Impedance and Pepsin Detection in the Laryngeal Mucosa to Determine Impedance Values that Indicate Pathological Laryngopharyngeal Reflux. *Clinical and Translational Gastroenterology* [online]. 2017, **8**, e123. ISSN 2155-384X. Dostupné z: doi:10.1038/ctg.2017.49

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
60	100	80	100

[6] ZELENIK, Karol, Viktoria HRANKOVA, Adela VRTKOVA, Lucia STANIKOVA, Pavel KOMINEK a ***Martin FORMANEK*(corresponding author)****. Diagnostic Value of the Peptest(TM) in Detecting Laryngopharyngeal Reflux. *Journal of Clinical Medicine* [online]. 2021, **10**(13), 2996. Dostupné z: doi:10.3390/jcm10132996

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	80	40	80

[7] KOMÍNEK, P., P. MATOUŠEK, **M. FORMÁNEK** a K. ZELENÍK. Alergie nebo reflux? Extraezofageální reflux z pohledu otorinolaryngologa. *Alergie*. 2013, **15**(3), 176–182.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
15	5	10	5

[8] STANIKOVA, L., R. WALDEROVA, D. JANCATOVA, **M. FORMANEK**, K. ZELENIK a Pavel KOMINEK. Comparison of narrow band imaging and the Storz Professional Image Enhancement System for detection of laryngeal and hypopharyngeal pathologies. *European Archives of Oto-Rhino-Laryngology* [online]. 2018, **275**(7), 1819–1825. ISSN 0937-4477. Dostupné z: doi:10.1007/s00405-018-4987-3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	30	15	10

[9] STANIKOVA, Lucia, **Martin FORMANEK**, Pavel HURNIK, Peter KANTOR, Pavel KOMINEK a Karol ZELENIK. Diagnosis of Laryngeal Pemphigus Vulgaris Can Be Facilitated Using Advanced Endoscopic Methods. *Medicina-Lithuania* [online]. 2021, **57**(7), 686. ISSN 1010-660X. Dostupné z: doi:10.3390/medicina57070686

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	20	20	10

[10] MASAROVA, M., J. SEKO, M. PLASEK, **M. FORMANEK**, O. JOR, V. NOVAK, P. KOMINEK a P. MATOUSEK. Význam spánkové endoskopie při titraci přetlakové ventilace - první výsledky. *Ceska a Slovenska Neurologie a Neurochirurgie* [online]. 2021, **84**(2), 183–187. ISSN 1210-7859. Dostupné z: doi:10.48095/cccsnn2021183

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	50	10	30

[11] STANIKOVA, Lucia, Karol ZELENIK, **Martin FORMANEK**, Jana SEKO, Radana WALDEROVA, Peter KANTOR a Pavel KOMINEK. Evolution of voice after transoral laser cordectomy for precancerous lesions and early glottic cancer. *European Archives of Oto-Rhino-Laryngology* [online]. 2021, **278**(8), 2899–2906. ISSN 0937-4477. Dostupné z: doi:10.1007/s00405-021-06751-3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	30	20	30

[12] ***FORMÁNEK, M.*(corresponding author)***, K. ZELENÍK, J. DVORÁCKOVÁ a P. KOMÍNEK. Chondrosarkom prstencové chrupavky. *Otorinolaryngologie a Foniatrie*. 2013, **62**(3), 136–139.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
100	60	90	50

[13] ZELENIK, Karol, **Martin FORMANEK**, Radana WALDEROVA, Debora FORMANKOVA a Pavel KOMINEK. Five-year results of vocal fold augmentation using autologous fat or calcium hydroxylapatite. *European Archives of Oto-Rhino-Laryngology* [online]. 2021, **278**(4), 1139–1144. ISSN 0937-4477. Dostupné z: doi:10.1007/s00405-020-06479-6

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	30	30	20

[14] MASAROVA, M., J. SEKO, J. KUBICKOVA, O. JOR, V. NOVAK, M. KOTULEK, P. MATOUSEK, **M. FORMANEK**, K. ZELENIK a P. KOMINEK. Epiglotopexe v léčbě obstrukční spánkové apnoe. *Ceska a Slovenska Neurologie a Neurochirurgie* [online]. 2021, **84**(1), 95–97. ISSN 1210-7859. Dostupné z: doi:10.48095/cccsnn202195

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	30	10	30

[15] ***FORMÁNEK, Martin*** a Karol ZELENÍK. Přímá laryngoskopie. In: CHROBOK, Viktor, Pavel KOMÍNEK, Jan PLZÁK, Petr ČELAKOVSKÝ a Karol ZELENÍK. *Otorinolaryngologie a chirurgie hlavy a krku*. 1. vydání. Havlíčkův Brod: TOBIÁŠ, 2022. s. 428-430. Medicína hlavy a krku. ISBN 978-80-7311-205-9.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
80	100	80	100

[16] ZELENIK, Karol, Pavel KOMINEK, Lucia STANIKOVA a ***Martin FORMANEK*(corresponding author)***. Local Bevacizumab Treatment of Juvenile-Onset Respiratory Papillomatosis Might Induce Multiple Tracheal Pyogenic Granulomas. *Laryngoscope* [online]. 2021, **131**(2), E518–E520. ISSN 0023-852X. Dostupné z: doi:10.1002/lary.28928

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	50	30	50

[17] ***FORMANEK, Martin*(corresponding author)***, Radana WALDEROVA, Sarka BANIKOVA, Irina CHMELOVA, Debora FORMANKOVA, Karol ZELENIK a Pavel KOMINEK. Effect of voice therapy with or without transcutaneous electrical stimulation on recovery of injured macroscopically intact recurrent laryngeal nerve after thyroid surgery. *European Archives of Oto-Rhino-Laryngology* [online]. 2020, **277**(3), 933–938. ISSN 0937-4477. Dostupné z: doi:10.1007/s00405-020-05806-1

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	100	70	100

[18] ***FORMANEK, Martin*(corresponding author)***, Vladimir DEDEK, Michal KOLACEK, Martin HAVEL, Karol ZELENIK a Pavel KOMINEK. Individualised Timing of Radio-Guided Parathyroidectomy Using Multi-Phase SPECT/CT Increases In Vivo Sensitivity and Accuracy and Reduces Operating Time: A Randomised Clinical Trial. *Diagnostics* [online]. 2021, **11**(4), 677. Dostupné z: doi:10.3390/diagnostics11040677

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
60	100	60	100

[19] HAVEL, Martin, Vladimir DEDEK, Michal KOLACEK a **Martin FORMANEK**. Quantitative analysis in parathyroid adenoma scintigraphy. *Nuclear Medicine Communications* [online]. 2022, **43**(1), 1–7. ISSN 0143-3636. Dostupné z: doi:10.1097/MNM.0000000000001474

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	30	20	30

[20] PNIAK, Tomas, **Martin FORMANEK**, Petr MATOUSEK, Karol ZELENIK a Pavel KOMINEK. Bipolar Thermofusion BiClamp 150 in Thyroidectomy: A Review of 1156 Operations. *Biomed Research International* [online]. 2014, **2014**, 707265. ISSN 2314-6133. Dostupné z: doi:10.1155/2014/707265

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	50	50	30

[21] ***FORMANEK, M*. *(corresponding author)***, T. HRBAC, V. PROCHAZKA, L. CABALOVA a P. KOMINEK. Carotid body paraganglioma, a very rare pediatric tumor. *Ceska a Slovenska Neurologie a Neurochirurgie* [online]. 2020, **83**(4), 436–437. ISSN 1210-7859. Dostupné z: doi:10.14735/amcsnn2020436

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	100	70	100