SDHD-related head and neck paragangliomas & their natural course

Heesterman, B.L.

"Medicine is a science of uncertainty and an art of probability."

William Osler

8

General discussion

The natural course of head and neck paragangliomas

The primary aim of this thesis was to gain more insight in the natural course of SDHD-related head and neck paragangliomas and ultimately improve counseling, surveillance, and treatment strategies. The risk of occult and metachronous paragangliomas (*chapter 2 and 6*), tumor growth (*chapter 3, 4 and 5*), clinical progression (*chapter 4 and 6*), and survival of SDHD germline mutation carriers (*chapter 7*) were addressed. In this final chapter the acquired knowledge is further discussed.

Penetrance

The age-related penetrance has been estimated by several authors ($\approx$ 85-100% at age 70) [1–4]. However, due to the inclusion of primarily symptomatic patients, these studies are methodologically flawed. Not surprisingly, the estimated penetrance in a large multigenerational family that harbors the c.274G>T, p.Asp92Tyr missense mutation, was lower compared to the thus far reported numbers. Although, bias due to over-representation of symptomatic patients was reduced in this analysis, the question remains if the results can be extrapolated to other SDHD variants [1].

In this thesis the prevalence of occult paragangliomas in asymptomatic SDHD germline mutation carriers was studied (*chapter 1*). A head and neck paraganglioma was detected in nearly 60% of subjects. If subsequently, the chance that unaffected carriers eventually develop head and neck paragangliomas is considered (*chapter 6*, an adapted version of figure 6.0.2c is printed on the facing page), this number increases to approximately 95% after 20 years of follow-up (median age: 55 years, range 36-90). It should be noted that *chapter 6* was not set out to create a prediction model and the predictive value was not validated. In addition, in families with more affected members or severe disease, asymptomatic family members may be more inclined to pursue genetic testing.

Although the most accurately estimated penetrance will be obtained by including multiple families and applying a maximum likelihood approach [5]. It is, considering the hitherto published data and evidence provided in this thesis, safe to say that carriers of a paternally derived germline mutation in SDHD face a very high risk of developing head and neck paragangliomas. As already evident from previous studies and further reinforced by results reported in this thesis (*chapter 6*), most SDHD germline mutation

carriers will even develop multiple (synchronous or metachronous) head and neck paragangliomas [3, 6].

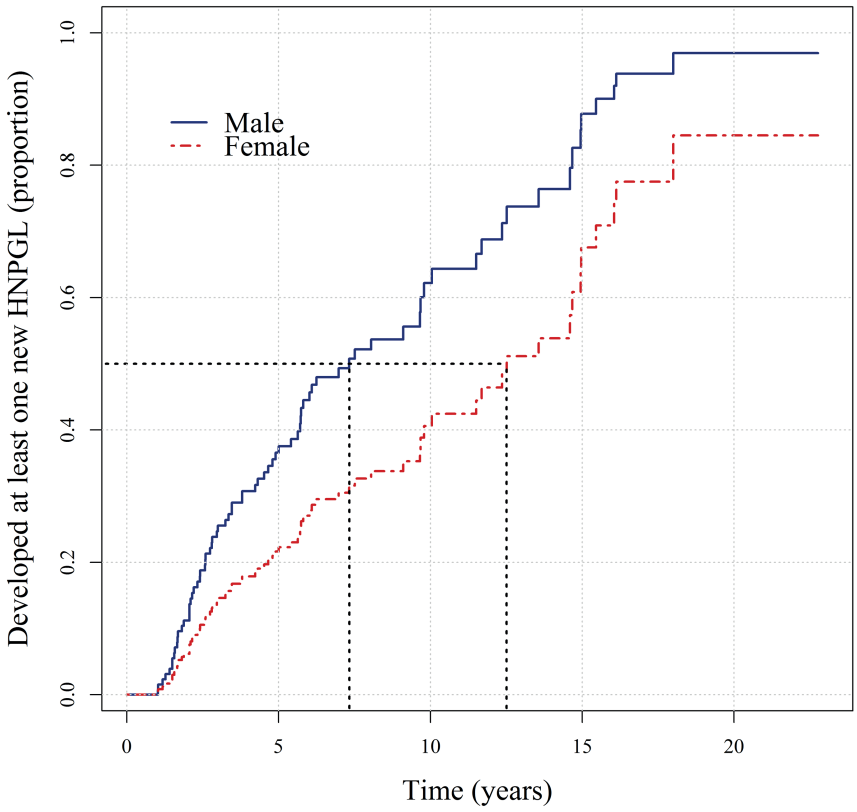

Figure 8.0.1: The cumulative proportion of subjects that developed at least one head and neck paraganglioma. In contrast to figure 6.0.2c, the results are represented for asymptomatic SDHD germline mutation carriers with no evidence of disease at baseline.

Growth of head and neck paragangliomas

Growth of head and neck paragangliomas has been previously addressed in several case series (12-48 paragangliomas), all demonstrating that progression is slow and many tumors (40-65%) remain stable for years [7–10]. Advances in imaging techniques, the use of measurement and tumor specific cut-off values for growth (*chapter 3*), and the inclusion of no less than 118 carotid and 66 vagal body paragangliomas enabled more accurate estimation of tumor growth (*chapter 4*). The use of time to event analysis (Kaplan-

Meier product limit estimator and multivariate Cox proportional hazards regression) provided the opportunity to factor in varying follow-up time and study predictors for tumor growth. Although the generally slow growth rate of head and neck paragangliomas (10.4% and 12.0% annually for carotid and vagal body tumors, respectively) was confirmed, growth will, with long follow-up, be observed in most cases (85% after 11 years). In accordance with a model of retarded growth, age and tumor volume were (independent) negative predictors for growth rate. This observation was further reinforced in *chapter 5*, decelerating tumor growth laws (Gompertz, logistic, Spratt and Bertalanffy equations) described growth of head and neck paragangliomas more accurately compared to a linear, exponential, or Mendelsohn model.

Clinical progression

Even though growth is generally slow and tumors may remain asymptomatic throughout life, the vast majority of SDHD germline mutation carriers will (eventually) develop clinical manifestations (figure 8.0.2). Accordingly, nearly 50% of patients managed with primary observation reported new symptoms during a median follow-up time of 8 years, of whom 26% was previously asymptomatic (*chapter 6*). Moreover, one-fourth was attributable to metachronous tumors. Consistent with decelerating growth, patients reported new symptoms less often with increasing age. Fortunately symptoms were generally mild (figure 8.0.3), and new cranial nerve deficits were reported in only 11% of patients. The relatively high fraction of patients experiencing new symptoms during follow-up, compared to results reported in *chapter 4* (new signs or symptoms were reported in approximately 25% of HNPGL), is readily explained by the fact that most SDHD germline mutation carriers are affected with multiple HNPGL.

Not surprisingly, symptomatic tumors were, with a median volume of 15.2 cm^3 (IQR: 6.4-24.3), considerably larger compared to asymptomatic tumors (median volume: 1.9 cm^3, IQR: 0.7-4.9). Moreover, with increasing volume, new symptoms developed more often.

Malignancy & mortality

The prevalence of malignant disease is low (3%), and even if metastases occur, disease may remain stable for years [11, 12]. In a review including 59 subjects with malignant

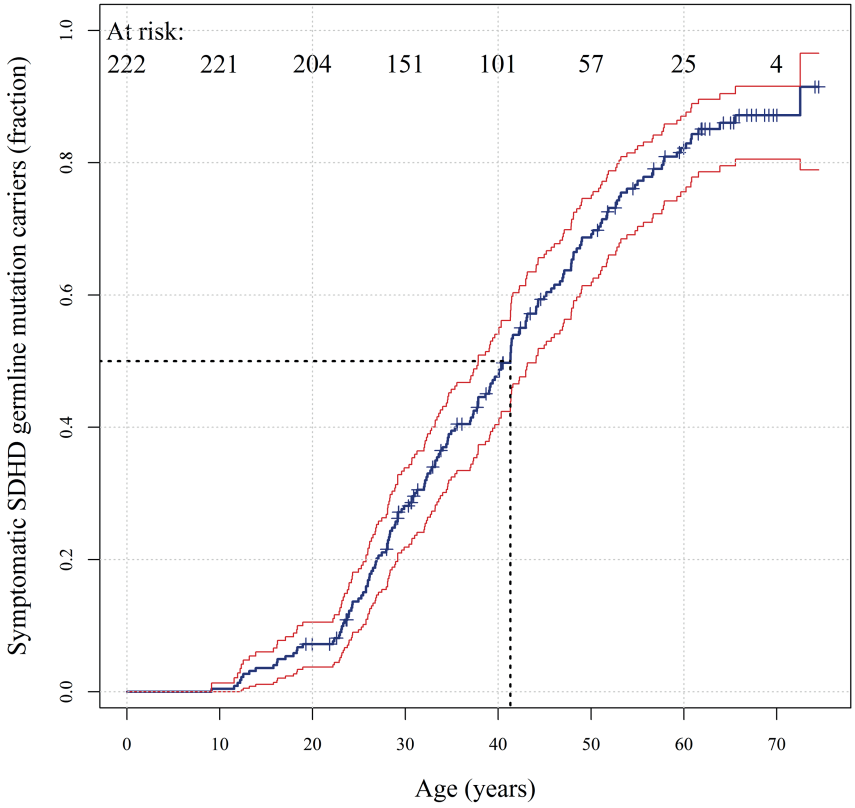

Figure 8.0.2: The fraction of symptomatic SDHD germline mutation carriers was estimated by means of survival analysis (Kaplan-Meier product limit estimator). One hundred forty-five (65%) subjects presented with symptoms, and an additional 24 (11%) subjects became symptomatic during follow-up (*chapter 6*). The age at onset of symptoms was known in 79%. In the remaining cases, symptoms were assumed to be present for 2 years prior to diagnosis (the effect of changing this assumption is limited, data not shown). Asymptomatic SDHD germline mutation carriers were censored at the age of their last PGL-related visit to the LUMC. If the relative under-representation of unaffected carriers is taken into account, by adding fictitious unaffected SDHD-germline mutation carriers (so that the penetrance is ≈90% at age 70), the estimated fraction of symptomatic subjects changes to approximately 80% at age 70.

paraganglioma, the 5 year survival rate was approximately 12% if distant metastases were present and nearly 80% if metastatic spread was restricted to regional lymph nodes. Unfortunately, the genetic status of patients was not reported. However, considering only 2 of the 10 patients diagnosed with malignant disease in our own series died of metastatic disease (*chapter 7*), the prognosis of SDHD-related malignant paragangliomas

is probably more favorable. Moreover, mortality in SDHD germline mutation carriers is not increased compared to the general population (*chapter 7*).

Management of SDHD germline mutation carriers

Seeing that survival of SDHD mutation carriers is not (substantially) reduced and the risk of metastatic transformation low, management of SDHD germline mutation carriers should be focused on the preservation of quality of life, rather than curative treatment. But how do we achieve this?

From previous research we know that the quality of life of SDHD germline mutation carriers is decreased compared to an age adjusted reference population, if patients experience paraganglioma-related symptoms. However, this is not true for SDHD germline mutation carriers without clinical manifestations (i.e., unaffected or asymptomatic) [13]. Should we thus treat all paragangliomas shortly after diagnosis? Not to achieve complete removal, but to prevent clinical progression? Surgery is generally recommended for pheochromocytomas, extra-adrenal sympathetic paragangliomas, and tympanic (Fish type A & B) paragangliomas (*chapter 1*). However, if tumors arise at other locations (or are no longer confined to the tympanomastoid compartment) surgery does not necessarily improve the natural course.

The incidence of postoperative cranial nerve dysfunction and other serious complications have already been discussed in *chapter 1* and are printed alongside results obtained in *chapter 6* on the next page. As already mentioned on multiple occasions throughout this thesis, the risk of iatrogenic damage to cranial nerves is considerable and exceeds the prevalence of cranial nerve dysfunction attributable to tumor progression (*chapter 6*). Due to slow progression and simultaneous compensation, neurological deficits resulting from tumor growth may go unnoticed. In younger patients sufficient compensation usually also occurs following surgery, although the rehabilitation period is prolonged if multiple cranial nerves are affected and interventions such as vocal cord medialization may be required. However, in elderly patients compensation is generally slow and often incomplete [9, 14, 15].

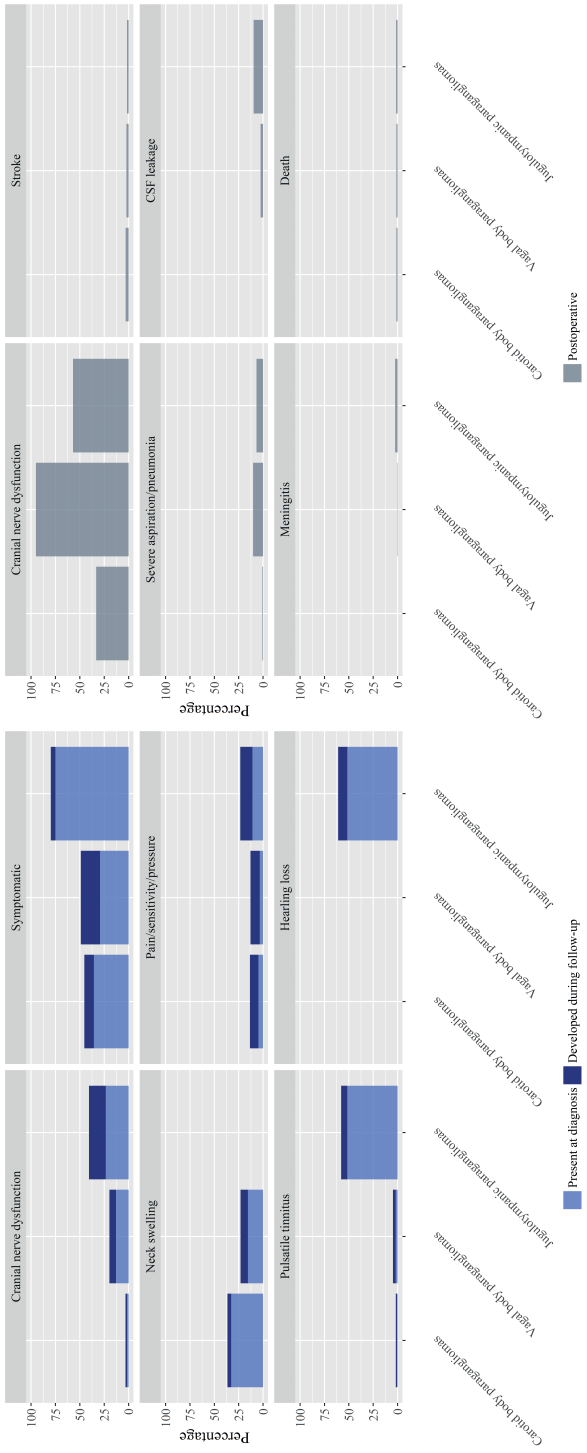

Figure 8.0.3: The reported risk of cranial nerve paralysis and (most common) symptoms attributable to tumor progression are reprinted from *chapter 6* (table 6.0.3 and 6.0.4). The risk of postoperative cranial nerve damage and other serious complications are obtained from literature [16–26].

Should we, considering these risks, refrain from treatment in all cases? And if we do so, is there any added value of (presymptomatic) genetic testing or surveillance? Although one could argue that genetic testing is still useful in terms of exclusion of disease in genuinely healthy subjects, the added value of surveillance is limited if not (in selected cases) followed by intervention. Should surveillance thus be limited to pheochromocytomas and extra-adrenal sympathetic paragangliomas, considering these tumors are generally treated even in the absence of symptoms? Even though growth data can be utilized to improve mathematical modeling (*chapter 5*), ultimately surveillance is only valuable if mathematical modeling is applied to select cases that benefit form early intervention.

In addition to surgery, radiotherapy is increasingly used as primary treatment modality. Although the risk of cranial nerve dysfunction and major complications following irradiation, is significantly less compared to surgery, serious complications may occur in addition to more frequent side effects such as mucositis and fatigue (*chapter 1*) [16, 26, 27]. The efficacy of radiotherapy should be viewed in light of the generally favorable natural course of paragangliomas, unfortunately comparative studies between radiotherapy and primary observation are lacking. However, if the local control rates reported in literature (absence of tumor progression in approximately 80 - 100% during a mean follow-up time of at least 8 years) are compared with the estimated fraction of growing tumors ($\approx$ 80% after 8 years of follow-up, *chapter 4*), it is evident that irradiation effectively induces growth arrest or at least significant growth retardation. Nonetheless, it would be valuable to estimate this effect more accurately by applying radiotherapy after an initial period of primary observation.

Evidence in favor of radiotherapy over surgery is increasing, although surgery may be preferred in case of small carotid body tumors. However, it remains uncertain if the harms of treatment outweigh the advantages. Therefore, a "wait and scan" strategy is often applied, enabling the selection of tumors that will most likely benefit from intervention, while preventing overtreatment. Currently intervals of 1-2 years are maintained, 5 years if there is no evidence of disease. Justification for the latter was provided in *chapter 6*. The median time before the detection of new head and neck paragangliomas was 14.6 years. Even if the negative correlation between number of head and neck paragangliomas present at baseline and risk of developing new tumors is taken into consideration, an

interval of 5 years is sufficient. Particularly, in view of the generally slow growth rate of paragangliomas.

The prediction model created in *chapter 4*, facilitates a more personalized approach to "watchful waiting". By factoring in, age, tumor location, and volume, the likelihood of observing growth beyond the measurement error (*chapter 3*) can be estimated. Hence, the number of unnecessary scans and the chance that growth is overlooked as a result of too small scanning intervals will be reduced.

The proposed model provides the opportunity to predict the occurrence of growth in the near future with fairly good accuracy. Ideally, we would however be able to foresee long-term prospective growth and clinical behavior, and thereby select cases that will benefit from treatment with certainty. In addition, such knowledge would enable further elongation of surveillance intervals. If the evolution of tumor volume over time is accurately described by mathematical models, both the age at onset and long-term tumor growth can be calculated. In *chapter 5* several decelerating tumor growth laws were fitted to observed growth data, yielding excellent results (median R^2 0.996 - 1.00). Although observed growth was captured by the mathematical models almost perfectly, validation of the predictive value is required. Naturally, it is not feasible to verify the accuracy of the calculated age at onset. However, if future growth can be predicted with sufficient precision, estimated age at onset can be utilized to optimize screening. Considering the theoretical justification as well as the generally realistic predicted age at onset and predicted volume at age 90, the Bertalanffy model will probably be best suited to estimate past and predict future growth of head and neck paragangliomas.

In conclusion, important steps toward unraveling the natural course of SDHD-related head and neck paragangliomas and predicting future progression were made. The acquired knowledge, enables direct optimization of counseling and surveillance and may furthermore support the decision to continue a conservative approach or in contrast, opt for intervention.

Future perspectives

As already alluded to in the previous section, the predictive value of mathematical models (especially the Bertalanffy equation) needs to be validated. However, it is not merely

future growth but clinical behavior that will truly support a well-founded treatment decision. It is therefore essential to relate the evolution of clinical manifestations to tumor progression. Considering the estimated volume of symptomatic versus asymptomatic tumors, the transition point will probably be reached if tumors become approximately 5-15 cm^3 in size (*chapter 4*). For further investigation, a prospective study design is best suited, preferably including patients with a single tumor, or at least without multiple ipsilateral tumors as it complicates correct attribution of symptoms. Seeing that SDHD germline mutation carriers are often affected with multiple head and neck paragangliomas, the inclusion of sporadic cases or subjects with a mutation in other susceptibility genes is required. Thereby, a final point of interest is stipulated: can the results reported in this thesis, be generalized to all paraganglioma patients or even beyond the two dutch founder mutations in SDHD? Naturally, the risk of developing paragangliomas and survival are at least specific to germline mutation in SDHD. It is however likely that the observed growth rates and created prediction model are applicable to head and neck paragangliomas beyond the investigated population, although external validation is required.

References

1. E. F. Hensen, J. C. Jansen, M. D. Siemers, et al. "The Dutch founder mutation SDHD.D92Y shows a reduced penetrance for the development of paragangliomas in a large multigenerational family." In: *Eur. J. Hum. Genet.* 18.1 (2010), pp. 62–66.
2. D. E. Benn, A. P. Gimenez-Roqueplo, J. R. Reilly, et al. "Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes". In: *J. Clin. Endocrinol. Metab.* 91.3 (2006), pp. 827–836.
3. H. P. H. Neumann, C. Pawlu, M. Peczkowska, et al. "Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations." In: *JAMA* 292.8 (2004), pp. 943–51.
4. C. J. Ricketts, J. R. Forman, E. Rattenberry, et al. "Tumor risks and genotype-phenotype-proteotype analysis in 358 patients with germline mutations in SDHB and SDHD". In: *Hum. Mutat.* 31.1 (2010), pp. 41–51.
5. J. A. Rijken, N. D. Niemeijer, E. P. M. Corssmit, et al. "Low penetrance of paraganglioma and pheochromocytoma in an extended kindred with a germline SDHB exon 3 deletion." In: *Clin. Genet.* 89.1 (2016), pp. 128–32.
6. L. T. van Hulsteijn, A. C. den Dulk, F. J. Hes, J. P. Bayley, J. C. Jansen, and E. P. M. Corssmit. "No difference in phenotype of the main Dutch SDHD founder mutations". In: *Clin. Endocrinol. (Oxf).* 79.6 (2013), pp. 824–831.
7. J. C. Jansen, R. van den Berg, A. Kuiper, A. G. van der Mey, A. H. Zwinderman, and C. J. Cornelisse. "Estimation of growth rate in patients with head and neck paragangliomas influences the treatment proposal." In: *Cancer* 88.12 (2000), pp. 2811–2816.
8. A. Langerman, S. M. Athavale, S. V. Rangarajan, R. J. Sinard, and J. L. Netterville. "Natural History of Cervical Paragangliomas: Outcomes of Observation of 43 Patients". In: *Arch. Otolaryngol. - Head Neck Surg.* 138.4 (2012), pp. 341–345.
9. M. L. Carlson, A. D. Sweeney, G. B. Wanna, J. L. Netterville, and D. S. Haynes. "Natural History of Glomus Jugulare: A Review of 16 Tumors Managed with Primary Observation". In: *Otolaryngol. – Head Neck Surg.* 152.1 (2014), pp. 98–105.
10. S. C. Prasad, H. A. Mimoune, F. D'Orazio, et al. "The role of wait-and-scan and the efficacy of radiotherapy in the treatment of temporal bone paragangliomas." In: *Otol. Neurotol.* 35.5 (2014), pp. 922–31.
11. L. T. van Hulsteijn, O. M. Dekkers, F. J. Hes, J. W. A. Smit, and E. P. M. Corssmit. "Risk of malignant paraganglioma in SDHB-mutation and SDHD-mutation carriers: a systematic review and meta-analysis". In: *J. Med. Genet.* (2012), pp. 768–776.
12. J. W. Bradshaw and J. C. Jansen. "Management of vagal paraganglioma: Is operative resection really the best option?" In: *Surgery* 137.2 (2005), pp. 225–228.
13. L. T. Van Hulsteijn, A. Louisse, B. Havekes, et al. "Quality of life is decreased in patients with paragangliomas". In: *Eur. J. Endocrinol.* 168.5 (2013), pp. 689–697.
14. J. L. Netterville and F. J. Civantos. "Rehabilitation of cranial nerve deficits after neurotologic skull base surgery." In: *Laryngoscope* 103.11 Pt 2 Suppl 60 (1993), pp. 45–54.

15. C. G. Jackson. "Glomus tympanicum and glomus jugulare tumors". In: *Otolaryngol. Clin. North Am.* 34.5 (2001), pp. 941–970.
16. C. Suárez, J. P. Rodrigo, W. M. Mendenhall, et al. "Carotid body paragangliomas: a systematic study on management with surgery and radiotherapy." In: *Eur. Arch. Otorhinolaryngol.* 271.1 (2014), pp. 23–34.
17. K. E. van der Bogt, M.-P. F. M. Vrancken Peeters, J. M. van Baalen, and J. F. Hamming. "Resection of carotid body tumors: results of an evolving surgical technique." In: *Ann. Surg.* 247.5 (2008), pp. 877–884.
18. C. D. Lees, H. L. Levine, E. G. Beven, and H. M. Tucker. "Tumors of the carotid body. Experience with 41 operative cases". In: *Am. J. Surg.* 142.3 (1981), pp. 362–365.
19. D. Kotelis, T. Rizos, P. Geisbüsch, et al. "Late outcome after surgical management of carotid body tumors from a 20-year single-center experience". In: *Langenbeck's Arch. Surg.* 394.2 (2009), pp. 339–344.
20. A. Dardik, D. W. Eisele, G. M. Williams, and B. A. Perler. "A contemporary assessment of carotid body tumor surgery." In: *Vasc. Endovascular Surg.* 36.4 (2002), pp. 277–283.
21. G. Ghilardi, E. M. Bortolani, P. Pizzocari, P. L. Vandone, and M. De Monti. "[Paraganglioma of the neck. Analysis of 32 operated cases]." In: *Minerva Chir.* 46.20 (1991), pp. 1109–17.
22. M. Makeieff, I. Raingeard, P. Alric, A. Bonafe, B. Guerrier, and C. Marty-Ane. "Surgical management of carotid body tumors." In: *Ann. Surg. Oncol.* 15.8 (2008), pp. 2180–6.
23. Z. Wang, Z. Zhang, Q. Huang, J. Yang, and H. Wu. "Surgical management of extensive jugular paragangliomas: 10-year-experience with a large cohort of patients in China". In: *Int. J. Surg.* 11.9 (2013), pp. 853–857.
24. T. K. Nicoli, S. T. Sinkkonen, T. Anttila, A. Mäkitie, and J. Jero. "Jugulotympanic paragangliomas in southern Finland: a 40-year experience suggests individualized surgical management". In: *Eur. Arch. Oto-Rhino-Laryngology* (2016), pp. 1–9.
25. Y. Oestreicher-Kedem, S. Agrawal, R. K. Jackler, and E. J. Damrose. "Surgical rehabilitation of voice and swallowing after jugular foramen surgery." In: *Ann. Otol. Rhinol. Laryngol.* 119.3 (2010), pp. 192–8.
26. C. Suárez, J. P. Rodrigo, C. C. Bödeker, et al. "Jugular and vagal paragangliomas: Systematic study of management with surgery and radiotherapy." In: *Head Neck* 35.8 (2013), pp. 1195–204.
27. C. C. Boedeker. "Paragangliomas and paraganglioma syndromes." In: *GMS Curr. Top. Otorhinolaryngol. Head Neck Surg.* 10 (2011), Doc03.