



Effect of intraoperative nerve monitoring on postoperative vocal cord palsy rates after thyroidectomy: European multicentre registry-based study

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Background: Intraoperative nerve monitoring (IONM) of the recurrent laryngeal nerve (RLN) predicts the risk of vocal cord palsy (VCP). IONM can be used to adapt the surgical strategy in order to prevent bilateral VCP and associated morbidity. Controversial results have been reported in the literature for the effect of IONM on rates of VCP, and large multicentre studies are required for elucidation.

Methods: Patients undergoing first-time thyroidectomy for benign thyroid disease between May 2015 and January 2019, documented prospectively in the European registry EUROCRINE[®], were included in a cohort study. The influence of IONM and other factors on the development of postoperative VCP was analysed using multivariable regression analysis.

Results: Of 4598 operations from 82 hospitals, 3542 (77.0 per cent) were performed in female patients. IONM was used in 4182 (91.0 per cent) of 4598 operations, independent of hospital volume. Postoperative VCP was diagnosed in 50 (1.1 per cent) of the 4598 patients. The use of IONM was associated with a lower risk of postoperative VCP in multivariable analysis (odds ratio (OR) 0.34, 95 per cent c.i. 0.16 to 0.73). Damage to the RLN noted during surgery (OR 24.77, 12.91 to 48.07) and thyroiditis (OR 2.03, 1.10 to 3.76) were associated with an increased risk of VCP. Higher hospital volume correlated with a lower rate of VCP (OR 0.05, 0.01 to 0.13).

Conclusion: Use of IONM was associated with a low rate of postoperative VCP.

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Introduction

According to the literature, vocal cord palsy (VCP) rates range from 3 to 5 per cent in the early postoperative period following thyroidectomy, and permanent VCP is diagnosed in 1–2 per cent of patients^{1–3}. Hospital-specific variation may in part be related to the routine or targeted use of postoperative laryngoscopy, due to symptoms or intraoperative findings. The most common mechanism of injury of the recurrent laryngeal nerve (RLN) during thyroidectomy is traction at the suspensory ligament of the thyroid gland (Berry's ligament), which is in close anatomical relation to

the nerve. Transection or thermal damage during surgery leads to more serious RLN lesions^{4,5}. Depending on the mechanism of injury, global (type 1) or segmental (type 2), loss of RLN signal may occur during surgery, with VCP being transient or permanent. Early VCP was observed in 95 per cent of patients with segmental loss of signal, whereas VCP occurred in 70 per cent of patients who experienced the less severe global loss of signal^{4,6}.

Apart from causing voice impairment, VCP is associated with an increased risk of aspiration pneumonia^{7,8}. Bilateral VCP may lead to a mechanically based respiratory

insufficiency, which potentially requires tracheostomy^{7–9}. In past decades, intraoperative nerve monitoring (IONM) has been shown to contribute to intraoperative identification of the RLN^{10,11}. Identification of the nerve is essential to preserve its functional integrity during surgery^{12,13}. The advantage of IONM to reduce the risk of transient¹⁴ or permanent³ VCP has been substantiated in various comprehensive studies. However, meta-analyses^{12,15,16} have concluded that use of IONM did not contribute to reduced rates of VCP. Apart from the debate on the influence of IONM, thyroiditis (Graves' disease or Hashimoto's thyroiditis)^{17,18} and malignancy^{1,19} have a proven effect on postoperative rates of VCP. In addition to factors influencing the complexity of the individual surgical procedure, the experience and training of the operating surgeon play an important role, which is why hospital volume is a relevant factor when considering rates of postoperative VCP^{13,19}.

The aim of this large-scale multicentre study was to analyse the impact of IONM, and other factors, on the rate of postoperative VCP in a homogeneous patient cohort undergoing first-time thyroidectomy for benign thyroid disease.

Methods

Patients undergoing first-time surgery with thyroidectomy (bilateral thyroid lobe resection, 'total thyroidectomy') for underlying benign thyroid disease (nodular goitre, follicular adenoma, Graves' disease, Hashimoto's thyroiditis, Riedel's thyroiditis and other (unspecified) benign thyroid tumours) in hospitals using the EUROCRINE[®] database, between May 2015 and January 2019, were included in the study. As laryngoscopic assessment is essential to diagnose VCP⁷, patients who did not have postoperative laryngoscopy were excluded from the analysis. The number of RLN palsies was counted per patient.

EUROCRINE[®] registry

Since May 2015, the European database EUROCRINE[®] has been available for registration of endocrine surgical procedures. The aim of EUROCRINE[®] is increase the quality of surgical treatment of endocrine disease, and to disseminate clinical standards and reduce the differences among hospitals that perform surgery on patients with endocrine disease²⁰.

Data variables

Data on vocal cord function and clinical parameters were collected prospectively. Clinical parameters included sex,

age, use of IONM, thyroiditis, and damage to the RLN during surgery (noted and reported by the operating surgeon). Hospital volume (defined by the total number of operations in this study performed per hospital), and surgeon qualification (consultant *versus* assistant surgeon) were registered and analysed. The primary endpoint of the study was postoperative VCP, and the secondary endpoint was the frequency of permanent VCP.

Statistical analysis

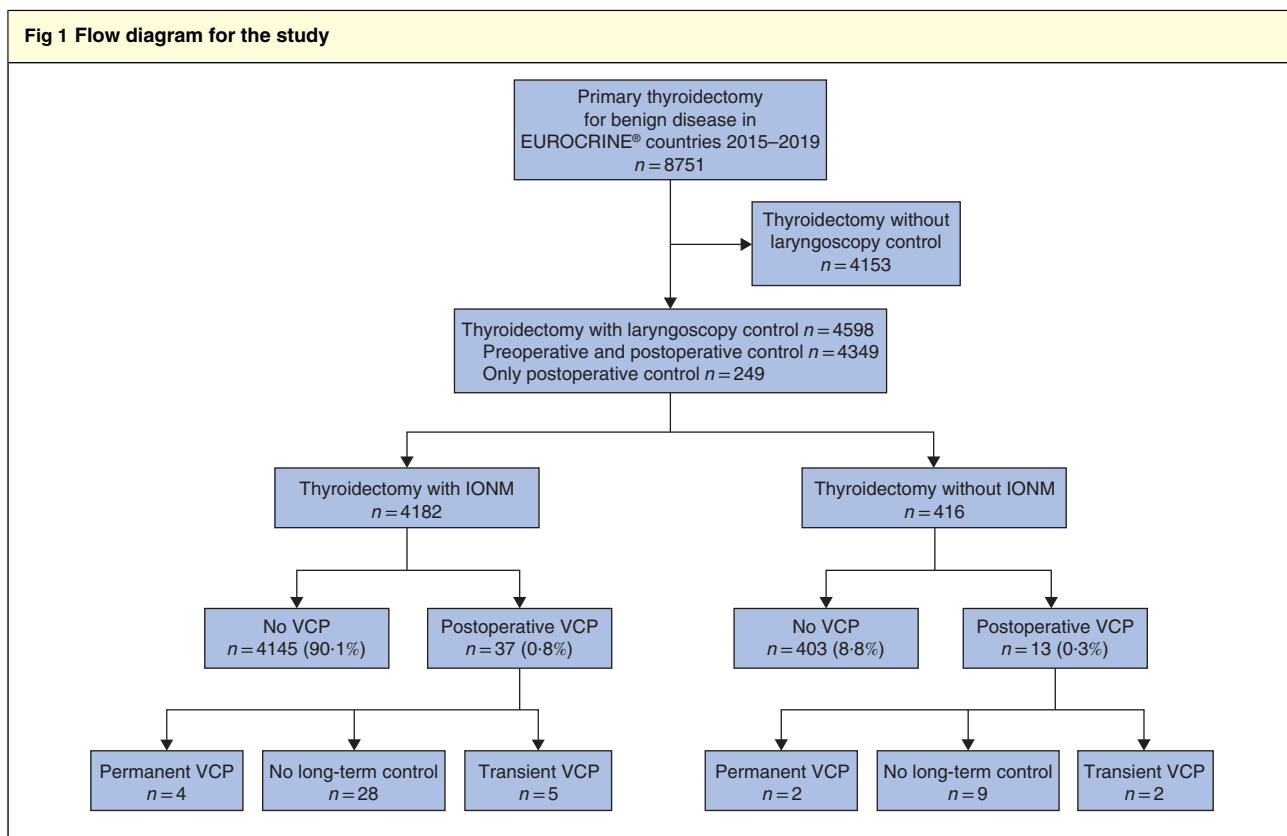
Data were documented and described using Excel[®] (Microsoft, Redmond, Washington, USA). Statistics were performed using R v.3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Comparisons between groups were performed with Fisher's exact test, the χ^2 test or Mann–Whitney *U* test. Categorical variables are presented as numbers with percentage, and continuous variables as median (range) or mean(s.d.) values.

To investigate the influence of different parameters on postoperative VCP, univariable analyses were performed, using the glm function in the stats R package to perform logistic regressions analysis. Variables with a $P < 0.250$ were included in a multivariable model. Resulting odds ratios (ORs) and their 95 per cent confidence intervals are reported. For comparison, continuous variables were standardized using the R scale function. The analysis was explorative; no adjustment for multiple testing was performed. The significance level was set at 5 per cent.

For an analysis of risk factors for permanent VCP, palsies persisting for more than 6 months after surgery were considered as permanent. Two theoretical models were analysed depending on whether patients with postoperative VCP lacked long-term follow-up or not: patients with postoperative VCP and lacking long-term control with laryngoscopy were assumed to have transient VCP in model 1, and to have permanent VCP in model 2. Owing to the small sample size of only six permanent palsies in total, the estimators of model 1 are not stable.

Results

A total of 8751 first-time thyroidectomies performed for benign disease were registered in EUROCRINE[®] during the study period. After excluding 4153 operations due to lack of postoperative laryngoscopy, 4598 operations were included in the present analysis (*Fig. 1*) from 82 different hospitals participating in EUROCRINE[®]. Some 94.6 per cent of analysed patients had both preoperative and postoperative laryngoscopy (*Fig. 1*). Postoperative laryngoscopy was performed a mean(s.d.) of 6(22) days after surgery.



The percentage values shown are based on the total number of included operations ($n = 4598$). IONM, intraoperative nerve monitoring; VCP, vocal cord palsy.

There were 3542 female patients (77.0 per cent) and the median (range) age of patients was 54 (3–92) years. The number of procedures entered into the register per hospital ranged from 1 to 683. The mean(s.d) duration of surgery was 112(45) min. Approximately three-quarters of the operations were carried out by a consultant surgeon (Table 1).

Subgroup with postoperative vocal cord palsy

The overall rate of VCP was 50 of 4598 (1.1 per cent). Hospitals with a lower patient volume were more likely to have a higher rate of postoperative VCP (Fig. 2). Except for one patient, VCP was unilateral. Among the 50 patients in the group with postoperative VCP, it was more common to have postoperative laryngoscopy only, rather than preoperative and postoperative laryngoscopy as assessment of vocal cord function (Table 1). The distribution of age and sex was similar in the patient groups with and without VCP. Median hospital volume was significantly lower in the group diagnosed with postoperative VCP (Table 1). The rate of thyroiditis on final histological examination was higher in the group with postoperative VCP: 25 of 50

(50 per cent) versus 1275 of 4548 (28.0 per cent) without VCP. The rate of IONM was lower in patients who had postoperative VCP than in those with a normal finding on postoperative laryngoscopy (74.0 versus 91.1 per cent respectively) (Table 1).

Of the 50 patients diagnosed with postoperative VCP, 37 did not undergo long-term laryngoscopy control. Of the remaining 13 patients who underwent long-term control, six had permanent pareses; seven pareses were transient (Fig. 1).

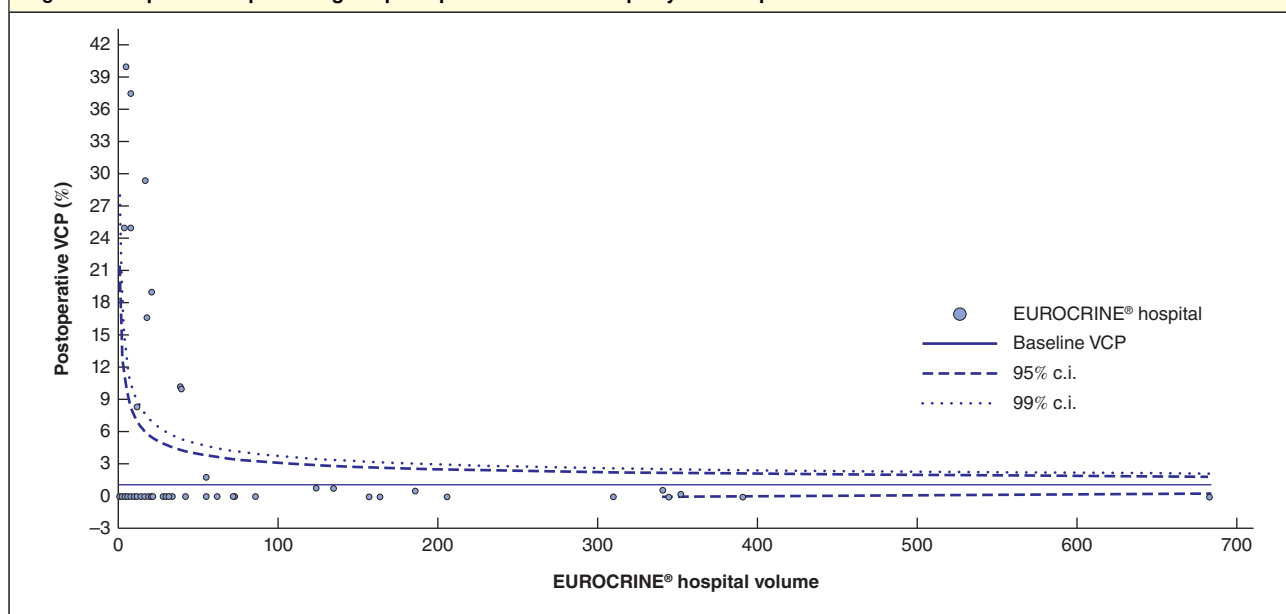
Intraoperative nerve monitoring

IONM was used in 4182 (91.0 per cent) of the 4598 operations. There were no differences in hospital volume or patient age in the groups with and without use of IONM (Table 2 and Fig. 3). In patients with IONM, RLN damage was noted more often than in patients without IONM (3.9 versus 1.9 per cent respectively) (Table 2). A higher rate of postoperative VCP was registered in the group without the use of IONM: 3.1 per cent versus 0.9 per cent in the group that had IONM (Table 2).

Table 1 Details of the study cohort of patients with and without postoperative vocal cord palsy

	Total (n = 4598)	Postoperative vocal cord paralysis		P‡
		No (n = 4548)	Yes (n = 50)	
Basic parameters				
Hospital volume*	10 (1–683)	310 (1–683)	17 (1–325)	< 0.001§
Age (years)*	54 (3–92)	54 (3–92)	50 (23–79)	0.228§
Sex				0.613
M	1056 (23.0)	1043 (22.9)	13 (26)	
F	3542 (77.0)	3505 (77.1)	37 (74)	
Intraoperative parameters				
Type of surgeon				0.576¶
Assistant	428 (9.3)	422 (9.3)	6 (12)	
Consultant	3507 (76.3)	3472 (76.3)	35 (70)	
Not specified	663 (14.4)	654 (14.4)	9 (18)	
Damage to recurrent laryngeal nerve noted				< 0.001
Yes	173 (3.8)	149 (3.3)	24 (48)	
No	4425 (96.2)	4399 (96.7)	26 (52)	
Intraoperative nerve monitoring				< 0.001
Yes	4182 (91.0)	4145 (91.1)	37 (74)	
No	416 (9.0)	403 (8.9)	13 (26)	
Postoperative parameters				
Histological result: thyroiditis				0.001
Yes	1300 (28.3)	1275 (28.0)	25 (50)	
No	3298 (71.7)	3273 (72.0)	25 (50)	
Laryngoscopy control type				< 0.001
Preoperative and postoperative	4349 (94.6)	4343 (95.5)	6 (12)	
Only postoperative	249 (5.4)	205 (4.5)	44 (88)	
Postoperative day of laryngoscopy†	6(22)	6(22)	19(33)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range) and †mean(s.d.). ‡Fisher's exact test, except §Mann–Whitney U test and ¶ χ^2 test.

Fig 2 Funnel plot of the percentage of postoperative vocal cord palsy and hospital volume

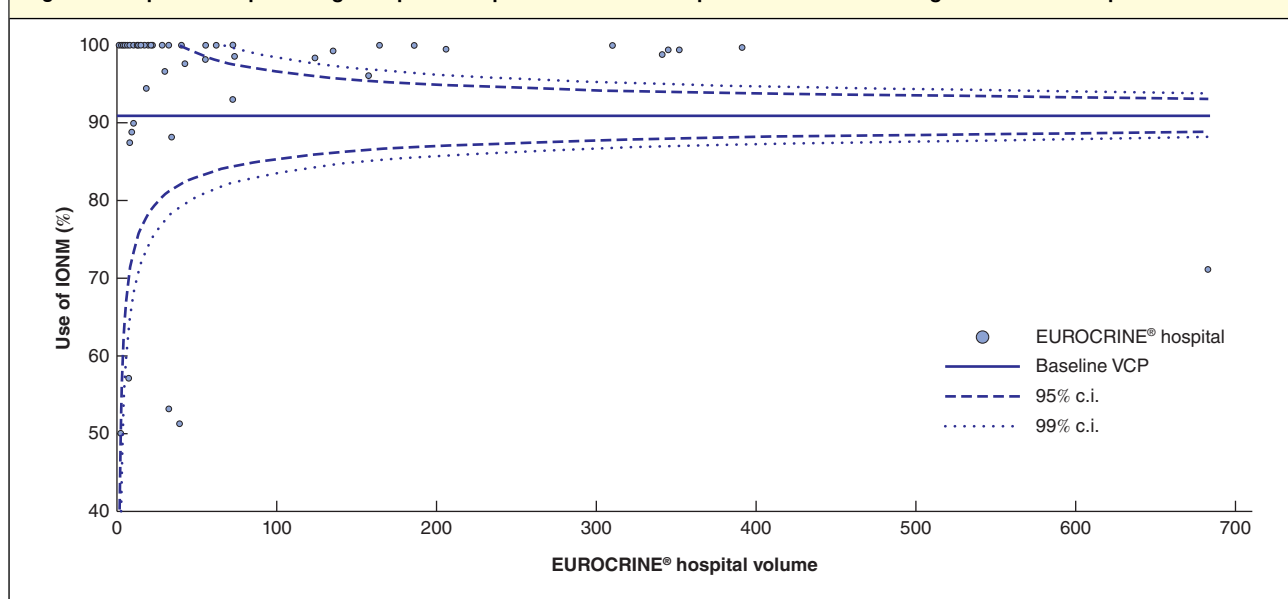
VCP, vocal cord palsy.

Table 2 Details of patients who had thyroidectomy with and without intraoperative nerve monitoring

	Total (n = 4598)	Intraoperative nerve monitoring		P‡
		No (n = 416)	Yes (n = 4182)	
Basic parameters				
Hospital volume*	10 (1–683)	157 (1–683)	310 (1–683)	0.147§
Age (years)*	54 (3–92)	53 (18–78)	54 (3–92)	0.321§
Sex				0.032
M	1056 (23.0)	78 (18.8)	978 (23.4)	
F	3542 (77.0)	338 (81.3)	3204 (76.6)	
Intraoperative parameters				
Type of surgeon				< 0.001¶
Assistant	428 (9.3)	35 (8.4)	393 (9.4)	
Consultant	3507 (76.3)	368 (88.5)	3139 (75.1)	
Not specified	663 (14.4)	13 (3.1)	650 (15.5)	
Damage to recurrent laryngeal nerve noted				0.041
Yes	173 (3.8)	8 (1.9)	165 (3.9)	
No	4425 (96.2)	408 (98.1)	4017 (96.1)	
Postoperative vocal cord paralysis				< 0.001
Yes	50 (1.1)	13 (3.1)	37 (0.9)	
No	4548 (98.9)	403 (96.9)	4145 (99.1)	
Postoperative parameters				
Histological result: thyroiditis				0.004
Yes	1300 (28.3)	143 (34.4)	1157 (27.7)	
No	3298 (71.7)	273 (65.6)	3025 (72.3)	
Laryngoscopy control type				< 0.001
Preoperative and postoperative	4349 (94.6)	357 (85.8)	3992 (95.5)	
Only postoperative	249 (5.4)	59 (14.2)	190 (4.5)	
Postoperative day of laryngoscopy†	6(22)	11(23)	6(22)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range) and †mean(s.d.). ‡Fisher’s exact test, except §Mann–Whitney U test and ¶ χ^2 test.

Fig 3 Funnel plot of the percentage of operations performed with intraoperative nerve monitoring in relation to hospital volume



IONM, intraoperative nerve monitoring; VCP, vocal cord palsy.

Table 3 Univariable and multivariable logistic regression analysis of risk factors for postoperative vocal cord palsy

	Univariable analysis		Multivariable analysis	
	Odds ratio	P	Odds ratio	P
Damage to recurrent laryngeal nerve noted (no)	27.25 (15.21, 48.67)	< 0.001	24.77 (12.91, 48.07)	< 0.001
Use of intraoperative nerve monitoring (no)	0.28 (0.15, 0.54)	< 0.001	0.34 (0.16, 0.73)	0.005
Patient age	0.99 (0.97, 1.01)	0.340		
Patient sex (M)	0.85 (0.46, 1.66)	0.609		
Surgeon type (assistant)				
Consultant	0.71 (0.32, 1.88)	0.439		
Not specified	0.98 (0.35, 2.90)	0.951		
Standardized hospital volume	0.05 (0.01, 0.08)	< 0.001	0.05 (0.01, 0.13)	< 0.001
Thyroiditis (no)	2.57 (1.46, 4.50)	0.001	2.03 (1.10, 3.76)	0.023

Values in parentheses are percentages. Reference groups are shown in parentheses.

Table 4 Univariable logistic regression analysis of risk factors for permanent vocal cord palsy

	Model 1*		Model 2†	
	Odds ratio	P	Odds ratio	P
Damage to recurrent laryngeal nerve noted (no)	5.23 (1.01, 3.79)	< 0.001	33.77 (18.15, 63.36)	< 0.001
Use of intraoperative nerve monitoring (no)	0.19 (0.04, 1.43)	0.062	0.28 (0.14, 0.59)	< 0.001
Patient age	0.72 (0.34, 1.60)	0.410	0.85 (0.63, 1.15)	0.279
Patient sex (M)	0.30 (0.05, 1.60)	0.138	0.76 (0.40, 1.56)	0.440
Surgeon type (assistant)				
Consultant	1.9×10^6 (2.3×10^{-59} , n.a.)	0.992	0.56 (0.25, 1.50)	0.209
Not specified	1.05×10^7 (1.2×10^{-58} , n.a.)	0.991	0.97 (0.35, 2.91)	0.951
Standardized hospital volume	0.13 (9.1×10^{-3} , 0.58)	< 0.001	0.01 (1.47×10^{-3} , 0.04)	< 0.001
Thyroiditis (no)	1.27 (1.17, 6.51)	0.783	2.22 (1.20, 4.07)	< 0.001

Values in parentheses are percentages. Reference groups are shown in parentheses. Thirty-seven postoperative palsies without follow-up are assumed *transient and †permanent. n.a., Not assessable.

Risk factors for early postoperative vocal cord palsy

Univariable analysis revealed a significant impact of the use of IONM, hospital volume, damage to the RLN noted (as reported by the operating surgeon) and thyroiditis on postoperative VCP (Table 3). Multivariable regression analysis confirmed the impact on VCP for these factors (Table 3). The strongest effect on the risk of VCP in multivariable analysis was documented for damage to the RLN noted during surgery and hospital volume, followed by use of IONM and thyroiditis. When RLN damage was noted during surgery, the risk of postoperative VCP was 25-fold higher than in patients without observed or suspected damage. When IONM was not used, the risk of postoperative VCP was threefold higher than when it was used. The presence of thyroiditis was associated with a twofold greater risk of postoperative VCP than in patients without thyroiditis. A reduction in hospital volume by one standard deviation (211 patients) resulted in a 22-fold higher risk of postoperative VCP. Surgeon qualification, patient sex and patient age did not influence the rate of VCP.

Risk factors for permanent vocal cord palsy

Among the 50 patients with postoperative VCP, 37 (almost three-quarters) did not have long-term follow-up by laryngoscopy. Risk factors for permanent VCP in model 1 (assumed transient VCP) and model 2 (assumed permanent VCP) were RLN damage noted during surgery and hospital volume. Thus, independent of potential long-term laryngoscopic follow-up, these factors were relevant for the risk of permanent VCP.

The risk of permanent VCP was 5–34-fold higher when suspected RLN damage was documented during the operation. A reduction in hospital volume by one standard deviation (211 patients) resulted in a 7.7-fold increase in the risk of permanent VCP, if the VCP in the 37 patients without laryngoscopic follow-up was considered transient. If the VCP in the 37 patients without follow-up was considered permanent, the risk would have increased by 100-fold (Table 4). In model 2 (patients without follow-up assumed to have permanent VCP), thyroiditis and the use of IONM were also associated with a decreased risk of permanent

VCP (Table 4). Age, sex and type of surgeon did not influence the risk of permanent VCP.

Discussion

This analysis found that postoperative laryngoscopy to exclude VCP after thyroidectomy was not standard in the countries and clinics participating in EUROCRINE®. Of 8751 patients who had a thyroidectomy, only 4598 were investigated with postoperative laryngoscopy. This lack of standard use of postoperative laryngoscopy is in agreement with the American Thyroid Association guidelines²¹, which recommend laryngoscopy neither before (unless there are risk factors or suspicion or proven thyroid malignancy) nor after (unless voice abnormality is documented) surgery. In contrast, German Association of Endocrine Surgeons (CAEK) guidelines^{22,23} recommend preoperative and postoperative laryngoscopy, independent of preoperative suspected or proven malignancy. In the present study, patients without postoperative laryngoscopy were excluded from analysis, as VCP could not be assessed objectively.

In addition to the CAEK guidelines, Dionigi and co-workers²⁴ recommend that postoperative laryngoscopy be performed on postoperative day 2, owing to its high sensitivity for VCP, based on patient compliance. In the present cohort, a high proportion of patients with documented postoperative VCP had only postoperative laryngoscopy, and not systematic preoperative and postoperative assessment. The underlying reason for this may be that hoarseness noted after surgery led to the suspicion of VCP, which resulted in verification of the suspected diagnosis by laryngoscopy rather than a routine investigation, as recommended by CAEK.

The use of targeted postoperative laryngoscopy, due to loss of signal during IONM or for other clinical reasons, leads to overestimation of the rate of VCP in these patients³. Furthermore, approximately three-quarters of patients diagnosed with postoperative VCP did not have long-term follow-up for potential permanent paresis. Therefore, the present study does not allow for a precise analysis of risk factors of permanent VCP.

IONM was used in over 90 per cent of operations, a high proportion compared with that in other studies in the field^{2,3,19}. Considering that thyroid redo surgery and operations for malignant disease were excluded from the present analysis, this finding emphasizes that in recent years IONM has commonly been done in clinics using the EUROCRINE® database for routine procedures. Moreover, IONM was used independently of hospital volume of the participating centres. In the present study, use of IONM had a significant impact on the rate of postoperative

VCP (0.9 per cent *versus* 3.1 per cent without use of IONM). Among other reasons, IONM facilitated detection of intraoperative RLN damage (3.9 per cent *versus* 1.9 per cent without use of IONM). However, information on RLN damage may be biased by the information given by the loss of signal during IONM, as the detection of RLN damage without the use of IONM is restricted to severe RLN injury, such as by transection or thermal damage.

An RCT by Barczynski and colleagues¹⁴ showed that use of IONM led to a reduction in the rate of transient VCP. However, the study did not show an effect on permanent VCP¹⁴. In contrast, a retrospective observational multicentre study by Bergenfelz *et al.*³ of Swedish departments showed that the use of IONM led to a reduced rate of permanent VCP. As an advantage, the multivariable analysis in this study³ crucially included information on whether postoperative laryngoscopy was used routinely or targeted due to patient symptoms and signs. In the present study, the effect of IONM on the postoperative VCP rate was analysed, and found to be significant. In addition, two theoretical models for permanent VCP were analysed, and gave a strong indication that IONM also influenced postoperative rates of VCP. However, the fact that 37 patients with documented postoperative VCP did not have long-term follow-up did not allow precise estimation of the rate of permanent VCP, and hence the precise impact of IONM.

A weakness of this study is that it did not assess whether continuous or intermittent IONM was used. Intermittent IONM can be used to identify the RLN, follow its anatomical course, and assess RLN function before and after resection of the thyroid lobe. This technique enables the surgeon to change strategy in patients with suspected RLN palsy, and therefore prevents bilateral VCP (according to the International Neural Monitoring Study Group (INMSG) 2018 recommendation^{7,9}). In contrast, continuous IONM additionally permits real-time evaluation of RLN function and enables the surgeon to react to electromyographic signal changes (so-called combined events)²⁵⁻²⁷ with a change of surgical strategy, depending on information on the effect on RLN function indicated by continuous IONM. Owing to the documentation structure of EUROCRINE®, the exact surgical management prompted by intermittent or continuous IONM information cannot be retrieved. Data on which operations with loss of signal were terminated as a lobectomy rather than the intended thyroidectomy were not included during the analysed time period. However, as the use of IONM was associated with a reduced VCP rate, this implies that the INMSG recommendations^{7,9} for intermittent and continuous IONM were practised successfully in hospitals that used the EUROCRINE® database for quality control.

However, postoperative laryngoscopy cannot be replaced by IONM to evaluate the rate of VCP, as the literature is inconclusive regarding the value of IONM^{15,16}.

Apart from IONM, factors influencing postoperative VCP rates are thyroiditis (Graves' disease or Hashimoto's thyroiditis)^{17,18} and malignancy^{1,19}. Especially in thyroid malignancy, deliberate resection of the RLN for oncological reasons is inevitably associated with permanent VCP. Thyroid redo surgery may be associated with increased rates of RLN palsy of up to 20 per cent^{1,2}. The *a priori* exclusion of thyroid reoperation and surgery for malignant disease excluded these factors from the present analysis. As already described by other authors^{17,18}, the present study has confirmed that thyroiditis increases the rate of postoperative VCP. In contrast, for permanent VCP, thyroiditis is debatable as a risk factor based on the theoretical models calculated for the present cohort.

In the present analysis, hospital volume (defined by the total number of operations in the study that were entered in the registry per hospital) had a significant impact on postoperative VCP, with lower volume being associated with an increased risk of VCP. However, the fact that hospitals joined EUROCRINE[®] at different time points might have biased the results, as hospitals with a higher volume (and greater experience) might be represented with an incorrectly low patient number in the registry. However, hospital volume significantly influenced postoperative VCP, as well as permanent VCP development. Surgeon qualification (consultant *versus* assistant) did not significantly influence VCP rates.

Postoperative laryngoscopy is not used as a standard to evaluate vocal cord function during first-time thyroidectomy for benign disease in a number of European countries and hospitals. The use of IONM is common during thyroidectomy in this subgroup of patients, and is associated with a reduced risk of early postoperative and permanent VCP. The impact of hospital volume on the risk of VCP after thyroidectomy is significant.

Collaborators

Members of the EUROCRINE[®] Council: P. Riss, S. van Slycke, M. Iacobone, L. Brunaud, A. Bergenfelz, T. Clerici, J. Villar, M. Raffaelli, D. Scott-Coombes.

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