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Autophagy and epigenetic implications in adrenocortical carcinoma

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Introduction: Treatment options of adrenocortical carcinoma (ACC) are limited and result in poor prognosis and high mortality. Long-non-coding RNA H19 is down-regulated in ACC, thus leading to high proliferation rate and high metastatic potential. Autophagy modulation mediated by epigenetic modification could represent a strategy to target cancer cells. Our aim is to detect H19 and autophagy markers expression in ACC. Furthermore, to check the ability of epigenetic modifications induced by histone deacetylase inhibitors to lead a change of the expression of H19 and autophagy related genes in H295R ACC cells.

Methods: Tumor samples from 14 ACC patients operated at Marburg University Hospital between 2000 and 2017 were processed by RT-qPCR to detect the expression of H19 and autophagy markers. Normal tissue was used as control. Cell viability of H295R monolayer was analyzed by xCelligence. H295R spheroids morphology was monitored by light microscopy.

Results: 13 patients showed a significant down-regulation of H19 and 1 patient a stable expression. Down-regulation of TFEB (transcription Factor EB) was the most correlating autophagy marker (12 patients). Beclin1 (BECN1), UVRAG (UV Radiation Resistance Associated Gene), MAP1LC3B (Microtubule Associated Protein 1 Light Chain 3 Beta),

SQSTM1 (p62) and PRKAA1_1 were down-regulated in the majority of the analyzed patients. The pan-deacetylase inhibitors panobinostat, SAHA and TSA caused a significant reduction of H295R cell viability, morphological changes and reduction of spheroids volume, dismantling of spheroid outer membrane and over-expression of H19. The autophagy transcripts were stable/over-expressed. P62 transcript was down-regulated.

Conclusion: H19 correlates with the suppression of autophagy markers in ACC patients. H295R cells treated with pan-deacetylase inhibitors showed a reduction of cell viability, morphological changes and over-expression of H19 and modulation of autophagy markers. Results represent new perspectives for the treatment of ACC.

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Hemodynamic instability during surgery for pheochromocytoma – a retrospective cohort analysis

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Introduction: Perioperative hemodynamic instability is one of the most commonly adverse events in patients undergoing adrenalectomy for pheochromocytoma. Aim of this study was to analyze perioperative episodes of severe hemodynamic instability in regard of postoperative complication and potential risk factors.

Methods: In this retrospective Analyses of the major tertiary university hospital, Tuebingen, Germany, we analyzed all consecutive Patients undergoing elective open or laparoscopic adrenalectomy from 2005 until 2018 for pheochromocytoma. Main Outcome Measures was perioperative severe Hypertension and Hypotension defined as rapid blood pressure increase or decrease of more than 30% respectively.

Results: A total of 64 patients underwent laparoscopic (n=49) or open (n=15) adrenalectomy. Preoperative alpha blockade was employed in 55 patients. Intraoperative episodes of severe hypertension and hypotension occurred in 21 and 59 patients respectively. In the latter, a mean of 5±2.9 episodes for severe hypotensive episodes and a mean of 1.9±1.3 episodes for hypertensive episodes occurred. Patients with more than five severe hypotensive episodes had a longer mean ICU stay (20.6h ± 19.4h vs 41.7h ± 42.1h, p=0.007) and median total hospital stay (8 days [2-24] vs. 7 days [4-25],

$p=0.01$). Postoperative complications were not correlated with peri-operative hemodynamic instability.

Conclusion: Predominantly hypotensive episodes rather than hypertensive episodes occurred during adrenalectomy, resulting in longer hospital stay and ICU time.

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Incidental appendiceal NET: When is oncological completion reoperation necessary?

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Introduction: Appendiceal neuroendocrine tumors (APPNET) are mostly found incidentally in histopathology after emergency appendectomy and various abdominal surgeries. Controversies regarding indication and extent of oncological completion reoperation remain due to the lack of reliable prognostic criteria and rarity of disease.

Methods: Retrospective single center chart analysis identified patients with APPNET operated between 2004 until 2019. Follow-up investigation was initiated.

Results: Of 1568 appendectomies performed histology revealed 15 APPNET (1%). 12 patients presented with acute appendicitis, 1 with tumor perforation, 1 with conglomerate mass of caecum and 1 with suspected ovarian malignancy. Mean age was 46y (16-85) at time of diagnosis. Median APPNET tumor size was 11 mm (2-68). Primary location was at the tip in 10, central in 2 and at the base in 1. Mesoappendix infiltration was confirmed in 6. 3 patients revealed goblet cell carcinoma (GCC), 1 with lymph node metastasis. Primary right hemicolectomy was performed in 2, secondary right hemicolectomy was performed in 5, including all 3 GCC patients. 2 patients denied reoperation. 6 patients underwent appendectomy only. During mean follow-up of 25 months (1-87) 2 GCC patients died with progressive disease. 1 GCC patient died of pulmonary metastases of unknown origin with concomitant prostate cancer, 1 with APPNET (G1) due to oral squamous cell carcinoma. The remaining 11 patients showed disease-free survival during follow up.

Conclusion: The present series identifies tumor type of GCC and Ki-67-index to be associated with poorer prognosis. Age, tumor size, perforation and complete resection at initial surgery also appear to be important factors determining necessity for reoperation in benefit-risk-evaluation. Due to rarity of the disease further studies are of importance to determine the necessity of oncological completion reoperation.

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Meta-analysis of Alpha Blockade versus no Blockade prior to Adrenalectomy for Pheochromocytoma

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Introduction: Pre-operative alpha blockade in pheochromocytoma surgery is recommended by all guidelines to prevent intra-operative cardio circulatory events. The aim of this meta-analysis was to assess the benefit of such pre-operative treatment prior to adrenalectomy for pheochromocytoma compared to no treatment.

Methods: A systematic literature search from was performed in MEDLINE, Web of Science and CENTRAL without language restrictions. Randomized and non-randomized comparative studies investigating pre-operative α -blockade in pheochromocytoma surgery were included. Two reviewers independently identified the relevant trials and extracted data on peri-operative safety, effectiveness and outcomes. Pooled results are displayed as odds ratio (OR) or mean difference (MD) with respective 95% confidence interval (95%-CI).

Results: A total of 4 retrospective comparative studies were included investigating 603 patients undergoing pheochromocytoma surgery. Mortality, cardiovascular complications, mean maximal intra-operative systolic and diastolic blood pressure and mean maximal intra-operative heart rate did not differ between patients with or without blocking. The certainty in evidence was very low due to the low study quality.

Conclusion: This meta-analysis demonstrates a lack of evidence for pre-operative alpha-blockade in surgery for pheochromocytoma. While the certainty of the available evidence is low, it does not show any benefit of pre-operative alpha-blockade. Randomised controlled trials are needed to evaluate if pre-operative alpha-blockade can be abandoned.

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Resection of the primary tumors before PRRT results in a prolonged survival in patients with neuroendocrine neoplasms stage IV.

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Introduction: Peptide receptor radionuclide therapy (PRRT) is an effective therapeutic option to treat metastatic neuroendocrine neoplasms (NEN) with high somatostatin receptor uptake.

Aim: Has a primary tumor (PT) resection before PRRT a beneficial outcome on survival?

Methods: Since 2004, all patients screened by ⁶⁸Ga somatostatin receptor (SSTR) PET/CT are included into a prospective database.

Retrospectively, we analyzed the data of 889 patients with advanced NEN (G1-G3, stage IV) treated with at least one cycle of PRRT. In 486/889 patients (55%, group 1), PT had been removed before PRRT. Group 2 involved 403 patients (45%) with no prior PT resection. Progression-free survival (PFS) and overall-survival (OS) was determined by ⁶⁸Ga somatostatin receptor (SSTR) PET/CT in all patients following RECIST and EORTC criteria.

Results: Most primary tumors were localized in pancreas (n = 335; 38%) and small intestine (n = 284; 32%). Both groups received a mean of 4 cycles of PRRT (p = 0.835) with a mean cumulative administered radioactivity of 21.6 ± 11.7 vs. 22.2 ± 11.2 GBq (p = 0.407).

Median OS group 1 was 134.0 months (CI: 118 -147) and OS group 2 was 67.0 months (CI: 60 – 80; HR 2.79); p < 0.001. Median PFS after first PRRT was in group 1 18.0 (CI: 15 – 20) months as compared to group 2 with 14.0 (CI: 15 - 18; HR 1.21) months; p = 0.012.

Conclusion: Patients with an advanced pancreatic or small intestine neuroendocrine neoplasms stage IV benefit from a primary tumor resection before PRRT.

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Is ACR-TIRADS able to improve the management of thyroid nodules and to avoid diagnostic lobectomies?

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Introduction: There is a large diagnostic delta between the prevalence of thyroid nodules and the incidence of thyroid carcinoma. To improve the results of thyroid ultrasound, risk stratification models such as the American College of Radiology: Thyroid Reporting and Data System (ACR-TIRADS) were established. Depending on the individual score, fine-needle aspiration cytology (FNA) or thyroid surgery is recommended. The aim of this study was to correlate the ACR-TIRADS results with histopathological findings.

Methods: Between 01/2018 and 08/2019, 141 patients (72% female, 28% male, mean age 52.4 years) with 172 thyroid nodules were preoperatively examined with ultrasound including the ACR-TIRADS score and were subjected to thyroid surgery.

Results: Histopathological reports described thyroid carcinoma in 21 of 141 patients (14.9%), with papillary thyroid carcinoma as the most common form (67%). Nodules were classified as ACR-TIRADS 2, 3, 4 and 5 in 7%, 31.4%, 58.7% and 2.9%. Cancer prevalence was 3.7% in TIRADS 3 and 14.9% in TIRADS 4. In TIRADS 5, thyroid malignancies were detected in 4 of 5 patients (80%). In TIRADS 2 nodules, no malignancy was observed.

Conclusion: TIRADS 2 and TIRADS 3 nodules can safely be monitored by ultrasound. TIRADS 4 nodules should be further clarified with FNA and in selected cases, thyroid surgery should be considered. For TIRADS 5 nodules with a high risk of malignancy, thyroid lobectomy with frozen section is recommended. Overall, the diagnostic value of ACR-TIRADS risk stratification system is encouraging, but more efforts have to be made to specify the various histopathological results of TIRADS 4 nodules.

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Lack of diagnostic value of positive Tc-99m-MIBI scintigraphy without previous fine needle biopsy in patients undergoing thyroid surgery

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Introduction: Thyroid scintigraphy with Tc-99m-MIBI in patients with cold thyroid nodules has a high negative and moderate positive predictive value in patients with an unclear result of a fine needle biopsy (FNB) of a thyroid nodule. The predictive value of Tc-99m-MIBI without preceding FNB is unclear. Therefore the aim of the present study was to assess the predictive value of a preoperatively positive Tc-99m-MIBI scintigraphy in patients undergoing thyroid surgery for thyroid nodules.

Methods: We retrospectively investigated all 8610 patients who underwent thyroid surgery in our institution between 2012 and 2017.

186 patients were operated on a Tc-99m-MIBI positive nodule. Of these, 145 patients had no previous FNB and were therefore subject of our investigation. 29 were excluded from further analysis, 15 due to incorrect scintigraphic methodology, 14 due to the presence of a parathyroid adenoma ipsilateral. 116 patients met inclusion criteria and were included in the further analysis.

Scintigraphy was assessed based on the written scan report and compared to the final pathology report.

Results: 14/116 (12.1%) patients showed a thyroid carcinoma in the histological analysis. However, only 7/116 (6.0%) had a carcinoma in the target lesion (i.e. the Tc-99m-MIBI positive nodule), whereas 7/116 (6.0%) patients had a carcinoma in a non-target lesion only. This results in a per-patient positive predictive value (PPV) of 12.1% and a target lesion PPV ± 95% Confidence Interval of 6.0% ± 4.7 in patients without an FNB-based indication for Tc-99m-MIBI.

Conclusion: Without previous FNB, a positive Tc-99m-MIBI scintigraphy has a very low PPV. It should therefore not be used as the only basis for indicating thyroid surgery.

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Intermittent versus continuous neuromonitoring in complex non-malignant thyroid surgery: A retrospective study.

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Introduction: In spite of the advances in thyroid surgery, the postoperative paralysis of the recurrent laryngeal nerve remains a dreaded complication. The current study compares intermittent (I-IONM) to continuous neuromonitoring (C-IONM) in terms of paresis rate, postoperative bleeding, length of operating time, and placement of wound drains in complex, benign thyroid surgery.

Methods: IONM and CIONM assisted operations on 613 nerves at risk were examined retrospectively. Cases included resections as a result of recurrent nodules, thyroid or parathyroid operations after previous cervical surgery (anterior approach), Graves' disease, and complex parathyroid operations (primary and recurrent). Also included were primary and revisional operations in cases of planned thyroidectomy with loss of signal during the neuromonitoring of the first side. The results were compared in a contingency table, the chi square test was applied to determine the significance ($p < 0.05$). Operating time and length of hospital stay were analyzed with the aid of t-tests for independent sampling.

Results: In the total collective there was a significant difference in the early postoperative rates of paresis ($p = 0.020$). In the individual collectives the significance was confirmed in the patients with previous cervical surgery ($p = 0.030$) and the collective of patients with recurrent goiters ($p = 0.023$). The rate of permanent paralysis after I-IONM assisted operations was with 1.5% not significantly higher as after C-IONM assisted operations (1%; $p = 0.619$).

In the C-IONM collective there were significantly more drains placed. The operating times and rate of postoperative bleeds did not differ significantly.

Conclusion: The use of C-IONM leads in this study to a significant reduction in the rate of early postoperative paresis of the recurrent nerve compared to the use of I-IONM in complex benign thyroid and parathyroid surgery. In relation to the rate of permanent paralysis, there is an insignificant trend toward the benefits of C-IONM usage.

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First results of the NEKAR study: Clinical Presentation, treatment and outcome of parathyroid carcinoma

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Introduction: Parathyroid carcinoma (PC) is a rare malignancy for which diagnostic workup and treatment is not established. The aim was to describe the clinical presentation and treatment of PC; to determine clinical parameters of prognosis.

Methods: Retrospective cohort study of 83 patients diagnosed with PC from 29 tertiary care centers in Germany, Switzerland and Austria. Disease-specific (DSS) and recurrence-free survival was estimated with the Kaplan-Meier method. Risk factors for recurrence were identified by Cox proportional hazards modelling with adjustment for age and sex. 39 tumors underwent central histopathological review.

Results: Renal failure (40%), gastrointestinal symptoms (24%), osteopenia (23%) and psychic symptoms (19%) were the most common symptoms at diagnosis. Serum concentrations of calcium (median 3.34 mmol/l; 1.6–6.0) and parathyroid hormone were strongly increased (median 566 pg/ml; 32–8900). Initial surgical treatment was heterogeneous (parathyroidectomy (PTx) 23%; PTx and hemithyroidectomy 24%; en-bloc resection 16%; others 37%) and complications of surgery were frequent.

While DSS was high (81/83), recurrence of PC was observed frequently (32/83) with 75% of these patients showing local recurrence. In univariate analysis the rate of recurrence was significantly reduced when extended initial surgery had been performed ($p < 0.04$). In multivariate analysis a significantly lower rate of recurrence was observed for low T-status (OR=2.65, 1.02–6.88, $p=0.045$), N0 (OR=6.32, 1.33–30.01, $p=0.02$), Ki-67<10% (OR=14.07, 2.09–94.9, $p=0.007$) and postoperative biochemical cure (OR=0.023, 0.001–0.52, $p=0.018$). This was not different when the groups of patients with and without histopathologic reevaluation were compared.

Conclusion: Despite a favorable prognosis, PC is associated with a high rate of recurrence leading to repeated surgery and complications. A critical awareness for this rare disease is recommended and extended surgery may be warranted when the suspicion of PC is reasonable.

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Influence of parathyroidectomy on kidney graft function in secondary and tertiary hyperparathyroidism

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Introduction: The timing of parathyroidectomy remains controversial in kidney transplant candidates with renal hyperparathyroidism. The aim of this retrospective study was to identify the influence of early versus late post-transplant parathyroidectomy compared to pre-transplant parathyroidectomy on renal graft function and morbidity.

In detail we questioned, whether early parathyroidectomy (within one year) after kidney transplantation has a negative impact on kidney graft function and whether low post PTX serum parathyroid hormone levels endanger kidney graft function and patient survival.

Methods: The timing of parathyroidectomy remains controversial in kidney transplant candidates with renal hyperparathyroidism. The aim of this retrospective study was to identify the influence of early versus late post-transplant parathyroidectomy compared to pre-transplant parathyroidectomy on renal graft function and morbidity.

In detail we questioned, whether early parathyroidectomy (within one year) after kidney transplantation has a negative impact on kidney graft function and whether low post PTX serum parathyroid hormone levels endanger kidney graft function and patient survival.

Results: Kidney graft function was not compromised by parathyroidectomy nor did the time interval between kidney transplantation and parathyroidectomy affect graft function in our patients. Morbidity and mortality after parathyroidectomy were low and not different in kidney graft recipients when compared to patients receiving parathyroidectomy already prior to kidney transplantation.

Conclusion: Controversial opinions exist regarding the optimal time for parathyroidectomy in renal hyperparathyroidism. Since parathyroidectomy had no negative effect on graft function in our patients, whether performed prior to or early or late after kidney transplantation, surgical cure of renal hyperparathyroidism should be performed as soon as possible to prevent secondary complications.

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Surgery for primary hyperparathyroidism in Germany, Switzerland and Austria – analyzing the EUROCRINE database

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Introduction: EUROCRINE is an endocrine surgical register documenting diagnostic processes, indication for surgical treatment, type of surgical procedures and use of resources and outcomes.

Aim was to analyze the data of surgery for PHPT in German speaking countries.

Methods: All operations for primary hyperparathyroidism, performed from 2015 to September 2019 were analyzed.

Results: 3076 patients from 30 institutions in Germany (n=11; 1641 patients), Switzerland (n=14; 919 patients) and Austria (n=5; 516 patients) were analyzed. 19.25% were asymptomatic, 40.35% showed bone manifestations, 34.3% fatigue and/or neuropsychiatric symptoms and 13.6% kidney stones. 27 patients (0.88%) had a hereditary disease (MEN1 n=24; MEN2A n=1; FHPT n=2) but 985 patients (32%) have not been genetically tested. Sestamibi and ultrasound were performed in 77.9% and 93.6%, CT and PET in 8.8% and 6.7%, respectively. Sensitivity and PPV were 78.16% and 90.09% for ultrasound, 73.82% and 90.68% for sestamibi, 75.4% and 90.91% for CT-scan and 91.37% and 94.24% for PET, respectively. Serum calcium decreased from 2.80±0.24 preoperatively to 2.34±0.21 after surgery. Intraoperative PTH- monitoring [IOPTH] was correct in 82.6%, false positive in 0.46% and false negative in 3.15%. 440 operations (14.3%) were performed without IOPTH. Focused parathyroidectomy was performed and finished in 1368 patients (44.5%), unilateral exploration was performed in 950 patients (30.9%) of which 129 were converted from focused surgery. Bilateral neck exploration was performed in 887 (28.8%; conversion from focused/UNE in 208). Mean operative time was 68.9±45.4 minutes. Recurrent laryngeal nerve palsy was observed in 76 patients (2.47%) after

surgery and in 21 patients (0.68%) at follow-up. Histology revealed parathyroid cancer in 13 patients (0.42%).

Conclusion: EUROCRINE database documents a low complication rate in parathyroid surgery. Although performed in only 6.7%, PET has highest sensitivity and PPV for preoperative localization.

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Testing the use of autofluorescence for intraoperative detection of parathyroid glands

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Introduction: Thyroid surgery continues to pose the risk of post-operative and permanent hypoparathyroidism. Therefore it is of great importance to intra-operatively spare the parathyroid glands (PGs). We tested a device that can perform real time fluorescence imaging during surgery, in order to see if that could help surgeons with the aforementioned task.

Methods: 34 patients who underwent thyroid or parathyroid surgery were included. We assumed 2 PGs per operated side. Combined with the patients with primary hyperparathyroidism where the surgeon just looked for one, there were 111 potential PGs to be found. An intraoperative evaluation of the PGs with autofluorescence was performed, in most cases to verify the PGs already found by the surgeon, but also in cases where the surgeon could not find the PG, or to check the already removed thyroid and the operation field for PGs.

Results: Of the 111 PGs potentially to be found, 75 were first identified by the surgeon. 73 (97%) of those could be verified with the device. 6 PGs could only be found with the aid of autofluorescence. In 2 cases the surgeons identified a PG that showed no enhanced signal and in 5 cases there was only a slight difference in autofluorescence between thyroid and PG. In one case neither the surgeon nor the device could detect a PG on the resected thyroid, but the frozen section analysis showed one on the specimen. Of the 6 Patients with parathyroid adenoma that were tested, 3 showed only a weak autofluorescence signal. There also was one case with a false positive autofluorescence signal where the Histologic exam showed brown fat tissue.

Conclusion: Autofluorescence is a helpful device in detecting regular PGs in situ as well as on the resected specimen. Surgeons experienced the device as helpful and reassuring. To evaluate the clinical benefit for avoiding post-operative or permanent hypoparathyroidism, prospective studies are needed. Parathyroid adenoma did not respond as expected.

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Utility of 18 Flour-Cholin-PET-CT plus 4D-CT to localize “negative” parathyroid adenomas – intraoperative correlation and 12 month postoperative results

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Introduction: To characterize the diagnostic performance of 18F-Fluoroethylcholine(FCH)-PET-CT combined with 4D-CT to localize parathyroid adenomas (PA) in primary hyperparathyroidism (pHPT) when ultrasound (US) and MIBI-Scan (MS) are either inconclusive or completely fail to localize the adenoma - as determined by the results of cervical exploration and one year follow up.

Methods: Beginning in 07/2017 18-FCH-PET and 4D-CT was employed in patients with biochemically proven pHPT in whom US and MS delivered either incongruent or negative findings. All patients were offered cervical exploration with intraoperative on site PTH-monitoring (IO-PTH) and followed for 12 months postop.

Results: From 07/2017 to 05/2019, 354 patients presented with the diagnosis of pHPT. 230 were scheduled for cervical exploration with PAs localized by either US or US plus MS. 124 patients had FCH-PET-CT because US plus MS did not localize PA (53) or gave discordant results (70); one had a nondiagnostic US only. FCH-PET-CT suggested PA(s) in 118 of 124 cases (95%). Of these 124 cases 106 already had surgery, confirming FCH findings to have accurately localized PA(s) to the respective side of the neck in 104 cases; to be false neg. in 2 and false pos. in 1, for a global sensitivity of 0,98; accuracy of 0,97 and PPV of 0,99. 41 of the 53 pts. with negative findings despite US and MS already had surgery and FCH-PET-CT was true pos. in all but 2 cases (1 false pos. and 1 false neg.; sensitivity 0,98; accuracy 0,95; PPV 0,98). The 12-month postoperative follow up (currently matched by 38/48) suggested that no PA(s) were missed.

Conclusion: Data from this ongoing clinical investigation suggest FCH-PET-CT to have a clinically meaningful diagnostic utility when US and MIBI fail to localize a PA. This allows for planned unilateral and focused as opposed to bilateral explorations in almost all cases. We, therefore, suggest FCH-PET-CT and 4D-CT for the localisation of negative PA(s).

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What is the gain of calcium stimulation in c-cell disease? A matched-pair analysis comparing calcium vs. pentagastrin

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Introduction: Calcitonin stimulation testing aims at defining the underlying type of c-cell disease (CCD) in order to customize appropriate timing and extent of surgery or consider observation. The importance of stimulation testing is widely accepted in hereditary CCD and the follow-up of MTC, while its role in sporadic forms is controversial. Importantly, calcium (Ca²⁺) stimulation testing lacks comparison to established recommendations based on reliable cut-off values using pentagastrin (Pg). This study investigates the correlation of Ca²⁺- and Pg-stimulation testing in CCD.

Methods: In a matched-pair analysis, Pg- and Ca²⁺-stimulation testing for calcitonin (Ct) was compared in 295 patients with c-cell hyperplasia (CCH) and with medullary thyroid cancer confined to the thyroid (Tx N0 M0) undergoing primary surgery. All patients demonstrated biochemical cure (Ct < 2.0 pg/ml) postoperatively.

Results: In CCH, preoperative Ca²⁺-stimulation testing resulted in Ct levels exceeding the 10- fold mark, in males 16- fold, and females 10.1- fold. Contrary, in CCH with Pg- stimulation, median Ct increase was only 3-fold in females and 6.9-fold in males. In MTC, response to Ca²⁺-stimulation was again higher compared to Pg. In females, Ct peaked 12.8- fold vs. 9.6 with Ca²⁺, and in males, Ct increase was 6.1- fold vs. 4.4 with Pg.

Conclusion: Ca²⁺-stimulation in CCH leads to exceedingly higher Ct concentration compared to Pg in 89% of patients. Contrary, Ca²⁺-stimulation in MTC leads to higher Ct concentration compared to Pg in only 43% of patients. The 15-minute value in Ca²⁺ Test can be omitted

without compromise in accuracy. Credible cut-off values, in comparison to basal Ct concentration, could only be established for males with Ca2+ - stimulation testing to allow for CCD differentiation, while Ca2+ - stimulation does not add any value in CCD in the remaining population, except for the rare exclusion of extrathyroidal Ct source).

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Lenvatinib plus Pembrolizumab - a breakthrough therapy for metastatic poorly differentiated and anaplastic thyroid carcinoma. First results from an ongoing study.

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Introduction: Despite extensive multimodal therapy, survival of metastasized poorly differentiated thyroid carcinomas (PDTC) and anaplastic thyroid carcinomas (ATC) rarely exceeds months. The tumors are highly proliferative, and frequently display increased mutational burden (TMB) and elevated PD-L1 levels.

Methods: Clinicopathological data of 8 patients with metastasized ATC (n=6) or PDTC (n=2), who received a combination of lenvatinib (started at 24/20 mg/d) and the immune checkpoint inhibitor pembrolizumab (200 mg/3w), were retrospectively analyzed. These results are presented and founded the rationale for an ongoing prospective phase II trial (ATLEP). All tumors were characterized by WES and PD-L1 expression.

Results: To date 20 patients with stage IV ATC/PDTC were treated w. lenvatinib and pembrolizumab (8 in the retrospective cohort, 12 in prospective trial). Maximum duration of treatment has now reached 30 months and most patients are still on treatment (5/8 in the retrospective cohort, 11/12 in the trial). In the retrospective cohort, ORR at 3 months was 75% (6 PR, 1 SD, 1 PD); with 2 long term remissions of more than 2 years. 3/8 initial patients had complete remissions at one year of treatment. Current PFS in this cohort is 13.8 months (1, 4, 9, 10, 13, 14, 25, 30 months). Grade III/IV toxicities evolved in 3/8 patients, but resolved after reduction or discontinuation of TKI (2/8). OS and PFS have not been

reached, since the majority of patients is under continued therapy (at 30, 16, 15, 10 and 9 months). All patients with long-term remission (≥ 24 months) as well as those with CR had increased TMB or PD-L1 TPS > 50%. The first interim analysis of the ongoing phase II ATLEP-trial confirms these results with an ORR of 80% at 3-months of treatment.

Conclusion: These results suggest the combination of lenvatinib and pembrolizumab to be safe and effective in patients with stage IV ATC/PDTC. For the first time complete and lasting response is seen in these patients, who commonly face a dismal prognosis.

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Metastasised papillary carcinoma of the thyroid located cervically and in a separate intrathoracic goitre, with a secondary renal carcinoma.

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Introduction: We present the case of a 66-year old female patient initially admitted with a goitre with a suspicious nodule on the right, for elective hemithyroidectomy. During this surgery, a frozen section of suspicious lymph nodes revealed metastases of a papillary carcinoma; subsequently a thyroidectomy and central neck dissection were performed. The complete histological result of the tissue removed in this surgery led to the diagnosis of a metastasised papillary carcinoma (pT1a, pN1a (3/14), R0). Consequently the patient went through radioiodine therapy with Mbq Iodine-131. To evaluate the therapeutic success, a FDG-PET-CT scan was performed, revealing an accumulation of radioglucose inside the thorax, leading to the assumption of separate thyroid tissue located in the mediastinum. Surgery was recommended to remove this tissue by VATS. Beforehand, a CT scan of the thorax was carried out, revealing yet another suspicious tumour, located in the left kidney; this tumour was deemed highly suspicious of a renal carcinoma (T1b, Nx, Mx). The mediastinal tumour was thereafter removed; the histological evaluation of the tissue removed in this second surgery revealed a further localisation of the papillary thyroid carcinoma (new classification: pT3a (m), pN1a (2/4), R0). Hence the question arises where the papillary carcinoma of the thyroid originated from: the cervical goitre or the mediastinal one.

Methods: Not applicable

Results: Not applicable

Conclusion: Not applicable

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New treatment options for anaplastic thyroid cancer- modulation of autophagy

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Introduction: Anaplastic thyroid carcinoma (ATC) responds for the majority of death of thyroid carcinoma (TC), so there is an urgent need for new treatment options. Molecularly targeted therapies, e.g. tyrosine kinase inhibitors (TKI) and histone deacetylase inhibitors (HDACi) gained importance in the last years. Currently, it has been found that targeted autophagy can be used as a strategy for cancer prevention, because it is involved in tumor suppression and tumor cells survival and therefore may play a role in regulating drug resistances and the dedifferentiation process of TC.

Methods: Fourteen tumor samples from patients affected by ATC were analysed by RT-qPCR. Normal tissue resected from eight patients was used as control. Spheroids from ATC cell line C643 were established. Spheroid growth was monitored by contrast phase light microscopy after treatment with panobinostat and sorafenib. Autophagy markers were analysed by RT-qPCR.

Results: All patients were characterized by a significant down-regulation of the autophagy transcripts BECN1 and MAP1LC3B. Only one patient showed a stable expression of MAP1LC3B. C643 spheroids treated for 48h with 10 nM panobinostat and 100 µM sorafenib showed an alteration of their morphology and outer membrane dismantling. Additionally, spheroids treated with panobinostat showed a necrotic inner area. 24h treatment with 10 nM panobinostat or 100 µM sorafenib caused a significant over-expression of BECN1 and MAP1LC3B in C643 spheroids.

Conclusion: ATC is characterized by an extreme low expression of autophagy markers BECN1 and MAP1LC3B. This could highlight an impaired autophagy process in these tumors. The treatment with panobinostat and/or sorafenib is able to restore and increase the expression of both markers. Furthermore, both compounds trigger the alteration of spheroids morphology highlighting cell death mechanism. Autophagy markers could represent valid bio-markers. The restoration of autophagy could be a target for the treatment of patients affected by ATC.

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Metastatic papillary microcarcinoma - a rare identity

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Introduction

Thyroid papillary microcarcinoma (PTMC), defined as a thyroid tumor measuring 1 cm or less, is usually an indolent tumor. The incidence of PTMC has increased dramatically in recent years. In our clinical analysis some PTMC are aggressive with lymph node metastasis.

Methods

We retrospectively analysed 141 patients with PTMC (2007 - 2018, 7. / 8. Auflage TNM classification) and compared positive lymph node metastasis (LND) in this classification.

Results

In 8 patients (6%) of our collective had a positive lymph node metastasis. 6 patients had a central lymph node metastasis and 2 a lateral lymph node metastasis. All patients with lateral lymph node metastasis had a multifocal PTMC and also lateral lymph node metastasis in time of diagnosis. Also the tumor were bigger than 5 mm and has a desmoplastic stromal reaction (DSR).

Conclusion

The mPTMC with lymph node metastasis is a rare but maybe aggressive disease. Lymph node involvement is part of the initial diagnosis. Risk factors for LND were tumor size > 0,5 cm, multifocality and additional desmoplastic stromal reaction.

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Prognostic impact of BRAF V600E mutations in papillary thyroid microcarcinomas

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Introduction

Prognosis of papillary thyroid microcarcinoma (PTMC) is considered to be excellent and active surveillance instead of conventional thyroid lobectomy is currently performed in an increasing number of patients. Nevertheless, some PTMC show a more aggressive behavior with the incidence of lymph node metastases. For example. The aim of this study was to evaluate the impact of BRAF V600E mutations on clinicopathological findings and the prognosis of PTMC.

Methods

From July 2014 to September 2019, 170 patients undergoing thyroid surgery were diagnosed with papillary thyroid cancer.

In 93 of 170 cases PTMC was detected (78.5% female, 21.5% male, mean age 48.8 years).

The indications to perform thyroid surgery were mostly benign thyroid disorders (89%) such as multinodular goiter or Graves disease and PTMC was diagnosed incidentally.

Results

Surgery included total thyroidectomy in 64.5%, lobectomy in 19.3% and an additional lymph node dissection in 16.2%.

The mean tumor size was 4.8 mm (1 – 10 mm).

In 59 of 93 patients BRAF V600E mutation was examined. In 34 patients, a BRAF V600E mutation was found.

In all of 25 patients without the BRAF mutation no lymph node metastases could be detected. 12 of the BRAF positive patients were N0 (35%), 6 N1 (17,6%) and 16 Nx.

Three PTMC were in the stage T3, one PTMC in the stage T4. The T4 carcinoma and one T3 carcinoma were BRAF positive. BRAF was not determined in the two other T3 carcinomas.

Conclusion

BRAF V600E mutations in PTMC carry a higher risk for lymph node metastases and a potentially more aggressive behavior. For this subgroup of patients, active surveillance should not be recommended. In patients without a BRAF mutation, no lymph node metastases were observed.

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Basics and side effects in thermal spread of different local ablative technologies in treating thyroid nodules.

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Introduction

In case of benign thyroid nodules thermal ablation is nowadays a possible alternative to radio iodine ablation or thyroid surgery. Many physicians are interested in the new technologies. The background basics are not considered by all therapists so far.

Methods

A protein phantom (changing the colour above 65 ° C) based on thyroid tissue was used to document the thermal effects and side effects of standardized available ablation probes. The results were documented on video images and still pictures.

Results

In contrast to the so far known effect on liver tissue the denatured tissue spread in thyroid differs on the structure of the nodule (cystic vs. mixed vs. solid). The used technique (HIFU, RFA or Microwave) has also an effect on the transformed tissue.

Conclusion

The knowledge of the thermal spread and effect of different technologies used in thermal ablation in thyroid nodules is necessary to avoid side effects like skin burn or neural damage.

Local ablative techniques are needed to be analyzed in their effect. Treatment without training and knowledge of the basics might endanger patients.

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Complete (paralysis) and incomplete recurrent laryngeal nerve injury (paresis) after thyroid and parathyroid surgery: Clinical impact

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Introduction

Injury of the recurrent laryngeal nerve and consequent disorder of vocal fold movement is a typical complication in thyroid and parathyroid surgery. During postoperative laryngoscopy we observed not only a complete standstill (vocal fold paralysis), but also a hypomobility (paresis). In this presentation, we focus on the difference in symptoms and IONM data between vocal fold paralysis and vocal fold paresis.

Methods

Data were prospectively collected and analyzed in a single high-volume thyroid center between 2012 and 2016. Vocal fold paresis was defined as hypomobility in abduction or adduction, a reduction in range and speed of vocal fold movement. Vocal fold paralysis was defined as asymmetry and missing purposeful vocal fold movement.

Results

The study included 4,707 surgeries and 7,992 at-risk nerves at risk. Vocal fold paralysis was diagnosed in 374 patients (4.68% of 7,992 nerves at risk) and vocal fold paresis in 114 patients (1.43%). Exclusively in the paralysis group, 36 patients (0.45%) developed permanent loss of vocal fold function ($P < .001$). In follow-up, vocal fold paresis patients regain normal vocal fold function significantly earlier than vocal fold paralysis (mean duration: 6.96 ± 6.506 vs 10.77 ± 7.827 weeks) and presented with significantly less symptoms like hoarseness, diplophonia, dysphagia, and dyspnea (68.8% vs 95.9%). We found one case of bilateral motility disorder, in which one side showed a hypomobility, the other side complete paralysis, clinically the patient was not impaired as dramatically as other patients were from bilateral paralysis.

Conclusion

After thyroidectomy, vocal fold paresis must be distinguished from vocal fold paralysis as patients present with less severe symptoms and and less symptoms in total.

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Delayed discharge and hospital readmission after total thyroidectomy due to postoperative hypocalcemia – a retrospective analysis

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Introduction

Hypocalcemia after total thyroidectomy is the most frequent complication resulting in patient discomfort, prolonged hospital stay and increased

cost. Aim of this study was to assess the impact of postoperative hypocalcemia on delayed hospital discharge and readmission after total thyroidectomy in a health care system with hospital charge standard fees based on the type of illness stay.

Methods

Retrospective analysis of patients undergoing total thyroidectomy from 2005 until 2017. Outcome measures were delayed hospital discharge and 30 day readmission due to postoperative hypocalcemia.

Results

Of 1047 patients finally analysed 252 (24.1%) and 121 (11.6%) developed a biochemical and symptomatic hypocalcemia during the initial hospital stay respectively. Treatment with oral calcium was necessary in 146 patients (13.9%), intravenous calcium in 26 patients (2.5%) and vitamin D in 43 patients (4%). A delayed discharge beyond day two after surgery was attributable to postoperative hypocalcemia in 31 patients (3%). Hospital readmission due to hypocalcemia was necessary in three patients (0.3%). Significant clinical risk factors for delayed discharge and readmission were not identifiable.

Conclusion

While postoperative hypocalcemia after total thyroidectomy is a frequent complication, delayed discharge and readmission presents a rather minor problem.

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Implementation of transoral endoscopic thyroidectomy (TOETVA) in a tertiary referral care center

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Introduction

Transoral endoscopic thyroidectomy via a vestibular approach (TOETVA) has become a worldwide accepted minimally invasive surgical procedure. This analysis aims to document the implementation and development of a standard procedure in a university hospital setting.

Methods

The indications, surgical procedure and complications of all patients, operated in a 10-month period were analyzed.

Feasibility criteria for transoral technique were small thyroid nodules in a small thyroid gland, without defining a clear threshold. Parathyroidectomy was performed in patients with clearly localized inferior adenoma in at least two localization studies.

Results

In a 10 months period, 21 patients (19 female, 2 male) were operated for thyroid pathology ($n=18$; 85.7%) and primary hyperparathyroidism ($n=3$; 14.3%), respectively.

Operative time was mean \pm SD 131.29 \pm 18.9 minutes in the first 7 patients, 89.00 \pm 16.29 minutes in patient 8-14 and 76.57 \pm 19.22 minutes in the last 7 patients. Analyzing each procedure separately, operative time for hemithyroidectomy was 102.54 \pm 24.05 minutes, for thyroidectomy 122.50 \pm 19.00 minutes and for parathyroidectomy 70.00 \pm 13.33 minutes, respectively. Intermittent intraoperative neuromonitoring was used in all patients undergoing thyroid surgery. Temporary recurrent laryngeal nerve palsy was observed 3 patients (14.28%), temporary hypoparathyroidism in no patient. In one patient with papillary thyroid carcinoma (pT1b) a central neck dissection was performed. A standard procedure, based on the published technique and processes was developed. All data was documented in the EUROCRINE database (“myEUROCRINE” module).

Conclusion

TOETVA and transoral parathyroidectomy can be safely implemented in an experienced surgical unit with a steep learning curve and acceptable complication rate.

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24**Outcome after surgical intervention versus thermal ablation in thyroid nodules causing local problems**

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Introduction

Hemithyroidectomy or nodule excision is a well established procedure to treat local problems caused by thyroid enlargement. Recently Radiofrequency-ablation (RFA) has come up as a non-surgical alternative to treat these problems. Outcome data has not been published in Germany so far.

Methods

30 case of RFA were compared to 30 consecutive case of cases of surgical intervention. A standardized questionnaire with eight possible items (Thy-pro) was used prior to the treatment and six months afterwards. The maximum of eight points was possible. The outcome was recorded.

Results

The RFA group had an average score of 4,5 items as well as the surgical group prior to the treatment. The average volume in the RFA-group was 33ml (5-144ml) compared to 32,5ml (12-142ml) in the surgical group. After six months the RFA patients reached 1,8 points in average with the questionnaire compared to 0,4 points in the surgical group ($p < 0,05$).

Conclusion

RFA as well surgical removal improves local complaints in patients suffering from local problems due to thyroid enlargement. Surgical removal reaches the goal of improvement significantly better than RFA.

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25**Short term outcomes of surgery for Graves' disease – a plea for total thyroidectomy with continuous intraoperative neuromonitoring**

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Introduction

Surgical treatment of Graves' disease (GD) has a potentially increased incidence of postoperative bleeding, recurrent laryngeal nerve palsy (RLNP) and postoperative hypoparathyroidism. The aim of this study was to evaluate the current surgical strategy for the treatment of GD and its short-term outcomes.

Methods

Patients who underwent thyroid resection for GD were identified from the prospective StuDoQ/Thyroid registry. Patients' data were retrospectively analysed regarding demographics, surgical procedures and short-term perioperative outcomes.

Results

1808 patients with GD (81.3% female) with a median age of 44 (range 14–85) years were enrolled in a 25-months period by 78 departments. 34.6% (n=691) of patients had an endocrine orbitopathy and 6 (0.1%) patients a thyrotoxic crisis. Total thyroidectomy was performed in 93.4% (n=1688) of patients. Intraoperative neuromonitoring (IONM) was used in 98.9% (n=1789) of procedures. In 98.3% (n=1777) patients at least one parathyroid gland was visualized and in 21.7% (n=375) of patients' parathyroid glands were autografted. The rates of unilateral and bilateral transient RLNP were 3.9% (n=134/3429 Nerves at risk) and 0.1% (n=4/3429 NAR). It is of note that the rates of RLNP were higher after the use of intermittent compared to continuous IONM (4.1% vs. 3.4%, $p < 0.05$). The rate of transient postoperative hypoparathyroidism was overall 29% (n=525). It was significantly higher in patients who underwent parathyroid autotransplantation compared to patients without (43.5% vs. 25.2%, $p < 0.05$). Reoperations for postoperative bleeding (1.3%) or wound infections (0.2%) were rare.

Conclusion

Total thyroidectomy with IONM is safe and the current operative standard for GD. The use of continuous IONM and a more restrictive attitude to autotransplant parathyroid glands might further minimize complication rates in thyroid surgery for GD.

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26**Thyroid surgery: continuous quality improvement in a 40 years period including 40.257 operations: merits and limits**

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Introduction

Continuous quality improvement that aim at better therapeutic approaches require accurate documentation and analysis of outcomes; improving patient care also implicitly requires quality control.

Methods

Starting with 1979, diagnostic, surgical procedures, surgical team, complications, and follow-up findings for every patient were entered into a computerized documentation system, that was adapted for the specific requirements of thyroid surgery.

Results

Between 1979 and 2018, 40.257 Patients were operated in our surgical department. According to 5-years periods, postoperative recurrent nerve injury rates were 6,1/5,9/4,7/3,4/3,3/4,0/4,8/4,7 %. Recovery rates improved significantly in %: 55/55/71/69/81/87/88/84, but could not

exceed definitely 90%. Despite of quality control, not all surgeons improved their results over years. Data will be shown. Furthermore, we analyzed hypoparathyroidism and hemorrhage as well as change of diagnosis and surgical procedures over decades. Details will be presented.

Conclusion

Quality control can improve the global outcome and identify the variability in individual performance of surgeons. This cannot be eliminated by merely confronting actors with comparative data; hence, it is important to search for the underlying causes.

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Transoral Thyroid Surgery vestibular approach. Preliminary results.

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Introduction

Various approaches for endoscopic and minimally invasive thyroid operations have been reported, with some becoming popular to date. The aim is to reduce and prevent visible scars in the neck. This led to the transoral endoscopic thyroidectomy vestibular approach (TOETVA) technique. After implementation of TOETVA in three specialized endocrine centres in 2017 we now report on our preliminary results with this promising technique.

Methods

We evaluated the transoral technique performed in well selected patients in Germany and Austria since 2017. Transoral operations have been performed by 4 Endocrine Surgeons. In some patients an additional retroauricular access was used to retrieve bulky thyroid specimens. TOETVA was performed in patients with single thyroid nodules, sporadic primary hyperparathyroidism, isthmic nodule or thyroglossal duct cyst. TOETVA was performed using 3 laparoscopic ports, laparoscopic instruments inserted at the oral vestibule. Patients characteristics, surgical outcome and complications were determined.

Results

74 transoral procedures were performed in 72 patients. An additional retroauricular access was necessary in 10 patients. Overall, median operation time was 205min (range: 96-370min). Permanent recurrent laryngeal nerve palsy occurred in one patient (1%, 101 nerves at risk). No conversion to conventional open surgery was necessary. Long term mental nerve injury occurred in two patients. No infection and no permanent hypoparathyroidism were identified.

Conclusion

Transoral thyroid and parathyroid surgery via the vestibular approach is of interest in an increasing number of specialized centres. It is feasible and safe. The rate of thyroid surgery specific complications seems to be equal

to conventional thyroid surgery, while procedure related problems must be evaluated. Combination with an additional extracervical approach might be a promising alternative to allow for transoral surgery also in thyroid specimen of more than 40ml.

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Volume and outcome correlates in the learning curve of a complex technology: continuous neural monitoring guided thyroid surgery at a tertiary surgical center

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Introduction

Continuous intraoperative nerve monitoring (CIONM) provides superior monitoring of the functional status of RLN. It is increasingly acknowledged as a useful tool to recognize impending nerve injury to abort the related maneuvers and thus to prevent nerve injury during thyroid surgery.

Methods

All patients with intact preoperative RLN function who underwent thyroid surgery between January 2011 and December 2018 under CIONM were included in this observational study conducted at a tertiary surgical center.

Results

There were 3003 patients with 5253 NAR. Vocal fold palsy (VFP) rate at the 2nd postoperative day was 1.5 % (78 NAR); 9 of whom (0.13 %) were false negative. Permanent VFP rate was 0.02 % (1 NAR). After a 2-year period standardly using CIONM a considerable decrease of VFP rate at 2nd postoperative day (6.28 % to 1.3 %) was observed. After loss of signal (LOS), a continuously increasing number in NAR with intraoperative recovery of electromyographic signal with incomplete palsy or even intact vocal fold function was documented. False negative events were rare, and of temporary nature; however no criteria were identified to predict these.

Conclusion

CIONM is a complex technology with convincing merits when used in a high volume practice, demonstrating a learning curve of CIONM application during thyroid surgery. Growing experience with CIONM enables the surgeon to identify impending nerve injury as it unfolds, release distressed nerves by reversing causative maneuvers, and verify functional nerve recovery of after LOS with evidence of improved outcome even in experienced surgeons' hands.

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