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Podium

1. Multi-modality Treatment of Anaplastic Thyroid Cancer: Outcomes of Yonsei Protocol

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Introduction: Anaplastic cancer is a rare variant of thyroid cancer. It is one of the most aggressive and rapidly progressing malignant human neoplasms with a grave prognosis. An aggressive treatment may be attempted for tumors at an early stage, but the optimal management of this disease remains controversial especially for cancer at advanced stage with distant metastasis. In this study, we report the outcome of multi-modality treatment protocol of Yonsei University Medical College (YUMC) in 46 cases of anaplastic thyroid carcinoma.

Materials and methods: From January 2015 to October 2018, 46 patients of ATC who were treated at the Thyroid Cancer Center, Gangnam Severance Hospital, Yonsei University College of Medicine were enrolled in this study. The patients were treated according to the YUMC protocol as follows: two cycles of chemoradiotherapy of paclitaxel and radiation of 60 Gy/30 fx were conducted, followed with resectability evaluation. If the cancer was resectable, surgery was performed, if not, more cycles of chemotherapy were continued. These patient's records were retrospectively analyzed with respect to clinical manifestations, extent of disease, distant metastasis, treatment modality and cause of death.

Results: Forty-six patients (28 females, 18 males, mean age 63.6 years) with histologically proven ATCs were enrolled. There were 12 (26.1%) stage IVb patients, and 34 (73.9%) stage IVc patients. Complete resection was possible in 14 (30.4%) patients. From the 46 patients, 17 (37%) were still alive. The median survival was 252 (58–1,021) days. When complete resection was possible, the patients showed significant better median survival [(281 (230–520) vs 150 (148–259)].

Conclusion: ATC is an aggressive cancer with advanced stage at time of presentation. Active multimodality treatment may be considered to prolong survival.

2. Usefulness of Stereotactic Radiotherapy for Locoregional Recurrence and Metastatic Thyroid Cancer

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Purpose: External beam radiotherapy (EBRT) is a well established treatment for local control and pain relief against cancer. However, conventional EBRT has been found to result with high rates of local progression and pain relapse. In addition, it often causes irreversible radiation-related toxicity. On the other hand, the advantage of stereotactic radiotherapy (SRT) using the CyberKnife®, compared to conventional EBRT, is that it minimizes

damage to the peripheral organs while enabling high-dose irradiation to the focal lesion. The objective of the present study was to investigate the feasibility and efficacy of SRT as salvage treatment for recurrences and metastatic lesions of the thyroid cancer.

Materials and methods: Between August 2011 and June 2019, 248 lesions in 77 patients with recurrences of thyroid cancer were treated by SRT using the CyberKnife®. The patients' medical records were retrospectively reviewed. The locoregional recurrences and metastatic lesions were evaluated by follow-up CT for therapeutic effectiveness, and the RECIST criteria were used to assess the overall patient response.

Results: Fifty patients were diagnosed as papillary cancer, 18 as follicular cancer, 5 as poorly cancer and 3 as anaplastic cancer. Adverse events were infrequent and mild. Sixty-eight locoregional recurrences, 51 bone metastases, 10 brain metastases and 6 lung metastases treated by SRT were evaluated for therapeutic effectiveness. One-year local control rates in locoregional, bone, brain and lung lesions were 96.6%, 97.8%, 100% and 100%, respectively.

Conclusion: Stereotactic radiotherapy using the CyberKnife® was found to be a feasible and effective treatment for recurrences and metastases of the thyroid cancer.

3. Perioperative Management of Pheochromocytoma: Experience from Australia and New Zealand

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Purpose/Introduction: Postoperative management after pheochromocytoma resection includes monitoring of blood pressure and blood sugar, and vigilance for hemorrhage. Some guidelines recommend 24–48 hours of continuous monitoring, usually necessitating ICU admission. We hypothesized that most patients undergoing pheochromocytoma resection do not require postoperative ICU admission. In this study, we describe current Australian and New Zealand perioperative management of pheochromocytoma and aim to elucidate factors that predict the need for intensive postoperative monitoring.

Materials and methods: We collected retrospective data on patients undergoing excision of pheochromocytoma in thirteen centers around Australia and New Zealand between 2000 and 2018. Data collected included preoperative medical management, anesthetic management, vasopressor support, HDU or ICU admission and complications.

Results: A total of 211 patients were included in the study, 171 (81%) of whom were admitted to HDU/ICU postoperatively. Patient demographics and tumor characteristics were similar between centers, as was the dosage of preoperative alpha blockade and anesthetic management. There were significant differences in the proportion of patients admitted to HDU/ICU between centers. Of patients admitted to ICU, 70 (41%) required vasopressor support—54 (77%) of whom required only low dose noradrenaline that was weaned within 24 hours. Among patients admitted to the ward, there were no complications that required escalation of care.

Conclusion: Although not widespread practice in Australia and New Zealand, it appears safe for the majority of patients undergoing minimally invasive resection of pheochromocytoma to be admitted to the ward postoperatively.

4. Calcifications Formation on Ultrasonography after Fine Needle Aspiration in Benign Thyroid Nodules

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Purpose: The presence of calcification on thyroid ultrasonography is one of the important indicators of malignancy. However, fine needle aspiration (FNA) itself could lead to the formation of calcification that may mimic malignancy. The purposes of this study are to investigate the characteristics and development course of FNA-induced calcifications.

Materials and methods: From October 2008 to August 2017, 51 patients with 55 benign thyroid nodules that had new calcifications during sonographic follow-up after at least one history of FNA were enrolled. The patterns of calcification were as follows. Microcalcifications were defined as hyperechoic punctate foci of less than 1 mm; macrocalcifications included those large or coarse calcifications of more than 1 mm; mixed-calcifications were denoted by having both micro- and macro-calcifications. The clinical data included the sonographic features, FNA attempt, and time-to-calcification interval were evaluated. FNA was repeated to confirm benign lesion for any doubt lesion during follow-up.

Results: According to the patterns of calcification, 39 of 55 (70.9%) nodules had microcalcifications while 43 of 55 (78.2%) nodules had macrocalcifications. Twelve (21.8%) were pure microcalcifications, 16 (29.1%) were pure macrocalcifications, and 27 (49.1%) nodules showed mixed-calcifications. Nodules with mainly cystic content manifested most frequently as mixed-calcification (47.7%), while nodules with mainly solid content tend to show more macrocalcification (45.5%). None of the nodules became malignancy at follow-up cytology. The history of FNA was found to be performed average 478.71 days prior to the detection of calcification.

Conclusion: Long-term follow-up ultrasonography after FNA revealed calcifications that may be misdiagnosed as malignancy. Recognizing these important phenomena may aid in preventing unnecessary management or surgery.

5. Thyroid Function after Lobectomy for Papillary Thyroid Cancer

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Purpose/Introduction: Lobectomy for low-risk and selected intermediate-risk papillary thyroid cancer (PTC) provides excellent oncologic outcomes while keeps patients free from thyroid hormone supplementation. A retrospective study was conducted to determine the probability of and factors for developing hypothyroidism after lobectomy.

Materials and methods: The study population comprised of 318 patients who underwent lobectomy as initial, curative surgery for PTC from October 2010 to December 2017. They were followed-up every six months to have their thyroid function, as well as disease status, determined. Postoperative hypothyroidism was defined as an elevated serum TSH level. The following variables were collected to examine their relationship to the event; age, gender, body mass index, tumor size, preoperative serum levels of antithyroglobulin, thyroglobulin, TSH, free T3, and free T4. The cumulative incidence of hypothyroidism was estimated by the Kaplan–Meier method. Cox's proportional hazards model was used to determine factors associated with developing hypothyroidism.

Results: The female/male was 230/88. The median duration of follow-up was 33.6 months. The probability of developing hypothyroidism was 33.2% (95% CI: 28.0–38.7%) at six months after surgery. The multivariable analysis identified age ≥ 55 years and the preoperative serum level of TSH ≥ 2.0 μ U/mL were associated with postoperative hypothyroidism, and their hazard ratios were 1.56 (95% CI: 1.03–2.36) and 3.71 (95% CI: 2.46–5.65), respectively.

Conclusion: One out of every three patients who undergo lobectomy for PTC would eventually have to take hormone replacement therapy at 6 months after surgery. Sharing the evidence with patients would facilitate to make their expectations in line with reality.

6. Prospective Cohort Study of Objective Cardiac Changes in Pheochromocytoma and Paraganglioma and their Reversal following Curative Surgery

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Purpose of the study: Cardiac and vascular dysfunction in pheochromocytoma and paraganglioma (PCC and PGL) patients were known for reversal to normalcy after surgical cure, but much were reported as case reports. Subclinical cardiac changes were presumed, but not objectively assessed. Hence their reversal after surgical cure remains uncertain. This study aimed to assess the cardiac changes in pheochromocytoma and paraganglioma patients and their reversal following curative surgery.

Materials and methods: This prospective cohort study included untreated PCC/PGL patients ($n = 15$) as exposed subjects and essential hypertensive volunteers ($n = 15$) as unexposed subjects. Exposed subjects underwent conventional and speckle tracking echocardiography at diagnosis, after α -blockade, at 7 days and 3 months postadrenalectomy/paraganglioma excision. Unexposed subjects had similar echocardiography at diagnosis and after 3 months of anti hypertensive medications. The echo parameters of PCC/PGL patients, in pre and postoperative period were compared by unpaired t test, to assess the recovery pattern of same.

Results: Unlike unexposed subjects, PCC/PGL patients had systolic and diastolic dysfunction (Table 1), worsened strain curves, representing sub clinical cardiac dysfunction (Table 2). After α -blockade, most echo parameters (Table 3) including the left ventricle strain indices (Table 4) were improved and continued to improve after surgical cure.

Discussion: This study is the first to objectively document the sub clinical cardiac changes. Pheochromocytoma/paraganglioma patients had clinical and sub clinical cardiac dysfunction, which were worse when compared with unexposed. Improvement in cardiac indices is apparent with α -blockade and continues to improve after surgical cure.

Annexure

Table 1: Comparison of echocardiographic baseline parameters between exposed and unexposed groups

	PCC/PGL $n = 15$	Unexposed $n = 15$	p value
Septal wall thickness (mm)	11 ± 1.4	9.2 ± 1.3	0.001
Poster wall thickness (mm)	12 ± 2.5	9.1 ± 0.9	0.0002
Aorta diameter (mm)	31 ± 4	28 ± 3.6	0.039
LVEDD (mm)	42 ± 2.4	45.7 ± 3.2	0.001
LVEDV (mL)	91 ± 12	72.3 ± 9.3	0.0001
LVESV (mL)	34.4 ± 9.5	30.2 ± 4.3	0.130
LVEF (%)	58.4 ± 6	60 ± 4	0.39
E/A	1.6 ± 0.7	1.08 ± 0.28	0.012
Septal e'	0.08 ± 0.03	0.11 ± 0.02	0.003
Lateral e'	0.13 ± 0.03	0.16 ± 0.03	0.010

Table 2: Comparison of speckle tracking echo baseline parameters between exposed and unexposed groups

	PCC/PGL <i>n</i> = 15	Unexposed <i>n</i> = 15	<i>p</i> value
Longitudinal myocardial strain (%)	-14.4 ± 3	-21.2 ± 2	0.0001
Circumferential myocardial strain (%)	-25.3 ± 3.2	-22 ± 2.1	0.002

Table 3: Echocardiographic parameters in PCC/PGL patients (*n* = 15) and their changes after surgical cure

Parameters	At diagnosis	After α -blockade	Postoperatively		<i>p</i> value*
			7–10 days	3 months	
Septal thickness (mm)	11 ± 1.4	10.9 ± 1.7	10.6 ± 1.5	9.8 ± 1.2	0.017
Poster wall thickness (mm)	12 ± 2.5	11 ± 1.7	10.3 ± 1.6	9.9 ± 1.5	0.006
LVEDD (mm)	42 ± 2.4	43.3 ± 3.1	45.6 ± 4	47.2 ± 3.1	0.001
LVEDV (mL)	91 ± 12	96 ± 10.5	98.1 ± 13	102 ± 13.2	0.02
LVESV (mL)	27 ± 9.5	32.3 ± 7.3	38.2 ± 8.4	41 ± 4.3	0.0001
LVEF (%)	58.4 ± 6	59.7 ± 8.3	61.9 ± 3.8	64 ± 4.5	0.007
E/A	1.08 ± 0.28	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.3	0.005
Septal e'	0.08 ± 0.03	0.07 ± 0.01	0.05 ± 0.02	0.04 ± 0.02	0.0002
Lateral e'	0.13 ± 0.03	0.12 ± 0.02	0.11 ± 0.01	0.09 ± 0.02	0.0002

*p value calculated between echo parameters at diagnosis and at 3 months postsurgery

Table 4: Speckle tracking echo parameters in PCC/PGL patients (*n* = 15) and their changes after surgical cure

	At diagnosis	After α -blockade	Postoperatively		<i>p</i> value*
			7–10 days	3 months	
Longitudinal myocardial strain (%)	-14.4 ± 3	-15.6 ± 1.1	-17.1 ± 1.4	-19.2 ± 2	0.0001
Circumferential myocardial strain (%)	-25.3 ± 3.2	-24.6 ± 1.2	-23.2 ± 1.3	-22.1 ± 2	0.0027

*p value calculated between echo parameters at diagnosis and at 3 months postsurgery

7. Prediction of Vocal Cord Paresis and Recovery after Loss of Signal during Thyroid Surgery

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Purpose/Introduction: Injury to the recurrent laryngeal nerve is the most dreaded complication during thyroid surgery. Intraoperative nerve monitoring (IONM) is now standard in most endocrine surgery units to assist with identification and verification of nerve function during operation. When the nerve signal is lost (LOS), it may be indicative of a nerve injury. There are only a few studies that estimates the predictive value of loss of signal to vocal cord paresis (VCP) and describe the vocal cord recovery time, important for patient follow-up postoperatively. Here we study patients with LOS correlated to vocal cord paresis and their vocal cord recovery time.

Materials and methods: In this retrospective cohort study, patients who had undergone thyroid surgery with IONM during the period 01-01-2015 to 13-06-2019 at the Endocrine Surgical Unit at Royal North Shore Hospital were included. Patients who had not undertaken both preoperative and postoperative laryngoscopy were excluded. We studied incidence and type of LOS, type I (focal) and type II (global) and time to vocal cord recovery.

Results: Two thousand and one hundred and forty two patients were operated with IONM during the period, putting 3,539 nerves at risk. LOS incidence per nerve at risk was 3.1% and LOS type I was more common (55%) than type II (45%). The mean recovery time for LOS type I was 9.8 weeks and 5.9 weeks for LOS type II (*p* < 0.05). The positive predictive value of LOS to a postoperative VCP was 87% and for a permanent VCP (>6 months) 0.07%.

Conclusion: We conclude that LOS is a strong predictor of postoperative VCP but weak predictor of permanent VCP. In our cohort, LOS type I is more common but patients with type II LOS recover significantly faster.

8. Epithelial–Mesenchymal Transition and its Association with PD-L1 and CD8+ T Cells in Thyroid Cancer

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Purpose: Recently, an association between programmed cell death-ligand 1 (PD-L1) and the mesenchymal signature of tumors has been established. However, the relationship between PD-L1 expression and epithelial–mesenchymal transition (EMT) has yet to be investigated in thyroid cancer. To address this issue, we examined the expression of CD8, PD-L1 and the EMT markers e-cadherin and vimentin in a cohort of papillary thyroid cancer (PTC) patients, and investigated the association of these with clinicopathologic characteristics and disease-free survival (DFS).

Materials and methods: CD8, PD-L1 and EMT status was assessed in 74 patients with PTC via immunohistochemistry. The relationship between PD-L1 and EMT was further investigated in three thyroid cancer cell lines (8505C, K1 and FTC-133).

Results: Programmed cell death-ligand 1 positivity was significantly higher in PTC patients with mesenchymal phenotypes ($p = 0.012$). Kaplan–Meier analysis revealed that PD-L1 ($p = 0.045$), CD8+ ($p = 0.038$) and EMT status ($p = 0.038$) were all significant predictors for DFS. Sub-analysis confirmed that the poorest DFS was evident in PD-L1 positive patients with EMT features and negative CD8 expression ($p < 0.0001$). IFN γ -mediated upregulation of PD-L1 significantly promoted an EMT phenotype in two thyroid cancer cell lines, assessed via Western blot and live cell imaging.

Conclusion: Our findings suggest that PD-L1 signalling plays a role in stimulating EMT in thyroid cancer. Epithelial–mesenchymal transition, CD8 and PD-L1 expression may serve as valuable predictive biomarkers in patients with PTC. The combination of EMT inhibitors with immunotherapies targeting the PD-1/L1 axis may be beneficial in cancer patients with mesenchymal metastatic tumors.

9. CRISPR/Cas9 Mediated BRAF Mutation and its Influencing Factors in Papillary Thyroid Carcinoma Cells

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Background and objective: BRAF mutation is the most common and important mutation in thyroid carcinoma. Many studies have focused on the biological behavior of thyroid carcinoma after BRAF mutation, but how this mutation happened was still poorly defined. Our study aims to observe whether the BRAF mutation could be induced by CRISPR/Cas9, also to find the factors which might affect the BRAF mutation.

Materials and methods: CRISPR/Cas9 plasmid was constructed, it expressed Cas9 protein and BRAF g-RNAs which targeting at the upstream and downstream of the BRAF15th exon V600 position. After transfection into the TPC cell line and enrichment with puromycin screening, the BRAF mutation rate was calculated. Besides, the changes of mutation rates were further observed after giving potassium iodide, TSH, thyroxine, estradio, lactic acid, H₂O₂ and hypoxia.

Results: The BRAF mutations including mismatch, insertion and deletion could be observed in the targeting region of the 15th exon. The mutation rates was 16.7%. Besides, it also could be up regulated by TSH, estradio, lactic acid and hypoxia with the mutation rates of 41.7%, 53.8%, 21.7%, 53.8%, respectively, but only the differences in estradio and hypoxia groups have statistic significances ($\chi^2 = 5.58, p = 0.018$; $\chi^2 = 6.55, p = 0.011$, respectively).

Conclusion: BRAF mutation could be induced by CRISPR/Cas9 in papillary thyroid carcinoma cells, it also could be up regulated by hypoxia and estradio.

Keywords: BRAF mutation, CRISPR/Cas9, Thyroid carcinoma.

10. Synergistic Anti-cancer Effect of Histone Deacetylase Inhibition and Blockade of the Glycolytic Pathway

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Background: Advanced cancer has been shown to have a higher percentage of epigenetic changes are more often events than genetic mutations. Preclinical models have showed that combination of the HNHA (N-hydroxy-7-(2-naphthylthio)heptanamide) and 2DG (2-deoxy-D-glucose) is a play crucial role in ATC (cancer stem-like cell, anaplastic thyroid cancer). The aim of this research is to study that caspase cleavage dependent apoptosis by combination therapy of HNHA and 2DG in ATC.

Materials and methods: ATC cell lines were exposed to HNHA and 2DG alone or combined, and cell viability was determined by MTT assay. Synergistic anticancer effects of the combination therapy on cell cycle and intracellular signaling pathways were estimated by flow cytometry and immunoblot analysis. The ATC cell lines xenograft model was used to examine the antitumor activity *in vivo*.

Results: Consequently, our results are suggest that combination therapy of HNHA and 2DG is synergistically decreased cell viability in ATC cell, and also significantly induced apoptotic cell death in this cells, as showed by the cleavage of caspase-3. HNHA and 2DG combination was reduced antiapoptotic factor in these cells. Thus, combination therapy with HNHA and 2DG most significantly reduced tumor volume in ATC cell xenografts.

Discussion and conclusion: The current study suggests that HNHA and 2DG combination treatment was more effective than treatment with the HNHA or 2DG alone. These findings may offer a new therapeutic approach to ATC include the cancer stem-like cells.

11. Two Distinct E3 Ligases Target Thyroid Transcription Factor 1 for its Ubiquitination and Degradation in Thyroid Follicular Normal Epithelial and Carcinoma Cells, Respectively

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Background: Thyroid transcription factor-1 (TTF1/NKX2.1) is a homeodomain-containing transcription factor, belonging to NKX2 family. TTF1 is expressed in both thyroid follicular normal epithelial cells and follicular thyroid carcinoma cells. In normal thyroid cells, it regulates the tissue-specific expression of genes, such as thyroglobulin (TG), thyroid peroxidase (TPO), and thyrotropin receptor (TSHR). Reduction of TTF1 levels have been shown contribute to the oncogenesis of thyroid carcinoma. However, the mechanism of TTF1's metabolism in thyroid normal and carcinoma cells have not been revealed. Ubiquitin E3 ligases play key roles in mediating ubiquitination and degradation of intracellular proteins. Here we identify two distinct ubiquitin E3 ligases are responsible for TTF1 degradation in thyroid normal cells and carcinoma cells, respectively.

Materials and methods: Thyroid follicular epithelial cells (HTori3) and follicular thyroid carcinoma cells (FTC133) were used to investigate phorbol myristate acetate (PMA)-induced TTF1 ubiquitination and degradation by immunoblotting and *in vitro* ubiquitination assay. Different E3 ligases were tested to identify the ones regulating TTF1 stability by immunoblotting and co-immunoprecipitation. Cells migration and proliferation were investigated by a wound healing assay and cell counting.

Results: Phorbol myristate acetate induced TTF1 protein degradation in dose- and time-dependent manners in both HTori3 and FTC133 cells, without altering TTF1 mRNA levels. Proteasome inhibitor MG-132, not lysosome inhibitor leupeptin, attenuated TTF1 degradation in both cell types, suggesting that PMA induces TTF1 degradation in the proteasome. Overexpression of HECW1 E3 ligase induced TTF1 degradation and ubiquitination in normal thyroid follicular epithelial Htori3 cells, but not in carcinoma FTC133 cells. Overexpression of ubiquitin E3 ligase subunit FBXL19 increased TTF1 ubiquitination and degradation in FTC133 cells, while it had no effect on TTF1 levels in Htori3 cells, suggesting that TTF1 stability is controlled by different ubiquitin E3 ligases in thyroid normal and carcinoma cells, respectively. Furthermore, we found that lysine 151 residue is a key ubiquitin acceptor site within TTF1 in both cell types. Overexpression of TTF1 increased TG and NIS mRNA levels, cell migration and cell proliferation in HTori3 cells, while the effects were reversed by the overexpression of HECW1.

Conclusion: This is the first study that investigates TTF1 stability in any system. This study reveals an undiscovered molecular mechanism by which TTF1 ubiquitination and degradation is regulated by different E3 ligases in thyroid normal and tumor cells. The data may provide new therapeutic targets specifically to treat thyroid cancer by modulating TTF1 stability.

12. Comprehensive Gene Expression Profile between Follicular Thyroid Cancer and Benign Thyroid Tumor

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Introduction: Distinguishing between follicular thyroid cancer (FTC) and follicular thyroid adenoma (FA) or adenomatous goiter (AG) is a great challenge for even an experienced pathologist. Follicular thyroid cancer cannot be diagnosed if which has no extrathyroidal extension or no vascular invasion. Molecular markers may potentially support a diagnosis between FTC and FA or AG. The purpose of this study was to investigate molecular findings for between FTC and FA or AG.

Materials and methods: To indicate molecular differences between FTC and FA or AG, we analyzed the gene expression microarray data of 12 FTC, 38 FA and 58 AG.

Results: We identified 21 genes differentially expressed between FTC and FA or AG. A receiver operating characteristics (ROC) curve analysis for the 21 gene classifier was created in order to assess the diagnostic efficacy of the classifier. The area under the ROC curve (AUC) equals 0.9705. We obtained sensitivity of 91.7% and specificity of 97.9%.

Conclusion: Comprehensive gene expression profile was useful for diagnosis between FTC and FA or AG.

13. Quality of Life Outcomes after Thyroidectomy for Malignant and Benign Thyroid Disease

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Purpose: Recent data suggests quality of life (QoL) is reduced following thyroid cancer diagnosis, and is under-recognized by clinicians. Comparisons of QoL between patients with malignant and nonmalignant thyroid disease are lacking. We hypothesized that thyroid-specific QoL would be lower in thyroid cancer patients compared to patients following total thyroidectomy for benign disease.

Materials and methods: A pathology database identified patients with thyroid cancer ($n = 292$) or following benign thyroidectomy ($n = 425$) between 2000 and 2017. Patients were invited to complete a validated thyroid-specific QoL questionnaire (City of Hope), reporting scores 0–10, with higher scores indicating higher QoL. Scores were correlated with demographic and disease-specific variables.

Results: Completed surveys were received from 36% (malignant) and 24% (benign) of participants a median of 6.5 years following thyroidectomy. Most responders were female (71%), and underwent surgery at age 53 ± 14 years. The thyroid cancer cohort contained more men and had shorter time between thyroidectomy and questionnaire (6.7 vs 8.2 years, $p = 0.04$). Overall QoL scores were similar in the benign and malignant cohorts (6.8 vs 6.7, $p = 0.89$), with no differences observed in subdomains of physical, psychological, social or spiritual wellbeing ($p > 0.05$). However, distress at the time of diagnosis [(3.9 (cancer) vs 5.7 (benign), $p = 0.0001$)], and at initial surgery [(4.3 (cancer) vs 5.5, $p = 0.02$)] was higher in cancer patients.

Conclusion: Although an overall detriment in QoL in patients with thyroid cancer compared to benign thyroidectomy was not observed, increased cancer-specific distress was demonstrable at the time of diagnosis. Strategies to improve patient wellbeing should be targeted to the time of diagnosis and surgery.

14. Surgeon-performed Ultrasound in Assessing Thyroid Nodules using ACR-TIRADS and Total Malignancy Score: A Validation Cross-sectional Study

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Purpose: This study aims to compare the diagnostic reliability of total malignancy score (TMS) and the American College of Radiology Thyroid Imaging Report and Data System (ACR-TIRADS) in differentiating benign and malignant thyroid nodules.

Materials and methods: This cross-sectional study involved patients with thyroid nodules who presented to our institution between October 2017 and October 2019. The patients had ultrasound assessment performed by surgeons, followed by fine-needle aspiration or thyroidectomy. Ultrasound findings were scored according to ACR-TIRADS and TMS, and these were correlated with cytology or histopathology. The sensitivity, specificity, accuracy and area under the curve (AUC) of both scoring system were calculated for analysis.

Results: A total 150 patients with 223 thyroid nodules were examined. One hundred and eighty five nodules (83%) were benign and 38 malignant (17%). Based on cut-off score of ≥ 4 for malignancy, the ACR-TIRADS showed 97% sensitivity, 53% specificity, and 61% accuracy. For TMS, based on cut-off score of ≥ 3 for malignancy, it showed 84% sensitivity, 63% specificity, and 66% accuracy. Using continuous data, the area under the curve (AUC) for ACR-TIRADS and TMS were 82% ($p < 0.05$) and 85% ($p < 0.05$), respectively. The difference in accuracy and AUC between the two scoring systems were both not statistically significant ($p = 0.5$).

Conclusion: Both ultrasound scoring methods demonstrated good diagnostic accuracy in differentiating benign and malignant thyroid nodules. Total malignancy score was comparable and not inferior to ACR-TIRADS, however the latter is more practical for use as growth and Doppler characteristic are not included in the assessment.

15. Clinicopathological Evaluation of Papillary Thyroid Microcarcinomas

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Background and aims: Clinicians sometimes encounter papillary thyroid microcarcinomas (PMC) under 10 mm in diameter that is concomitant with lymph node metastases. In this study, we assessed PMC clinicopathologically to clarify the risk factors that worsen patient's prognosis.

Materials and methods: Fifty-one patients who underwent thyroid surgery at Aichi Medical University from September 2009 to October 2016 were enrolled. The patients were divided into two groups such as "pEX0" (28 patients) and "pEX-positive" (23 patients) according to pathological

findings of thyroïdal capsule invasion. We assessed the factors include patients' characteristics, pathological findings and serum thyroid hormonal level between the two groups followed by statistical analyzes.

Results: No statistical difference was showed between the two groups in the factor of gender distribution and the age at operation. Preoperative diagnoses of the cancer were done for the more cases of pEX-positive group than those of pEX0 group, 21 and 14 cases, respectively ($p = 0.004$). The pathological tumor diameter of pEX0 and pEX-positive were 5.42 ± 2.77 and 8.32 ± 1.61 (mean $\pm$ SD), respectively ($p < 0.001$). No significant difference of preoperative serum level of free T3, free T4, TSH and thyroglobulin was recognized between the two groups. The odds ratio of node positive for tumors invading thyroid capsule (pEX-positive group) compared to those with no capsule invasion (pEX0) is 13.20 with 95% confidence interval ranging from 3.45 to 50.42. Immunohistological staining of phosphatase and tensin homolog deleted from chromosome 10 (PTEN) and Akt was performed to detect the activated signaling pathway of these tumors. The activation of phosphoinositide 3-kinase-Akt (PI3K-Akt) cascade could not be found in any cases, however, PTEN was upregulated in all the tumors of the both groups. Immunohistochemical study showed the suppression of tumor growth by the overexpression of PTEN. Other factors such as vascular endothelial growth factor (VEGF), C-X-C chemokine receptor 4 (CXCR4) and so on correlated with metastases were also assessed immunohistologically. However, no significant marker was recognized.

Discussion: Generally, the prognosis of PMC patients is favorable. However, the theory does not apply to the cases that is associated with nodal metastasis or extra thyroïdal invasion. It is controversial whether the resective treatment is required for the proven PMCs or not. For the cases which are associated with extra thyroïdal invasion, the regional lymph nodal resection with lobectomy should be performed. The result of immunohistochemical evaluation might indicate that PMCs growth very slowly and its metastatic nature would be gained when the tumor invade the thyroïdal capsule.

16. How Big is Safe for Surveillance? The Impact of Tumor Size on Lymphovascular Invasion

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Introduction: Lymphovascular invasion (LVI) pose a significant impact on tumor recurrence and patient survival in differentiated thyroid cancer. However, LVI is not discernible before or during surgery. This study aimed to explore the potential predictors of LVI.

Materials and methods: We conducted a retrospective review of consecutive adult patients who had surgery for papillary thyroid cancer from January 2009 to December 2018. Logistic regression analysis was performed to identify preoperative factors associated with LVI. A generalized additive model (GAM) was used to examine the possible nonlinear relationship between tumor size and LVI.

Results: A total of 795 patients were included in the analysis. Patient age [odds ratio (OR) = 0.982], tumor size (OR = 1.466), clinical lymphadenopathy (OR = 6.975), and clinical extrathyroidal invasion (OR = 2.938) were independently associated with LVI. Among 198 patients with available genetic information, tumor size (OR = 1.599), clinical lymphadenopathy (OR = 3.657), and TERT promoter mutation (OR = 4.726) were predictors of LVI. For those who had no clinical lymphadenopathy or extrathyroidal invasion, GAM analysis suggested that tumor size >1.5 cm had an increased risk of LVI after covariate adjustment.

Conclusion: Tumor size is positively associated with the risk of LVI in papillary thyroid cancer. Tumor size of 1.5 cm may be considered as a safe limit for active surveillance.

17. Surgical Treatment of Functioning Pulmonary Metastases from Parathyroid Carcinoma

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Purpose: To reveal the effectiveness of surgical treatment of pulmonary metastases from parathyroid carcinoma.

Materials and methods: Patients who underwent surgery for pulmonary metastases causing severe hypercalcemia from parathyroid carcinoma between 2000 and 2019 were enrolled. The primary outcome was the effectiveness of surgery, defined as relief of hypercalcemia and associated symptoms. The role of preoperative estimation of total tumor volume (TTV) by CT scan was examined concerning the success of the surgery. The secondary outcomes included the incidence of renal impairment and survival time from initial thoracic surgery.

Results: Six patients underwent 15 operations for pulmonary metastases, including one staged bilateral thoracotomy and two operations with joint neck surgery for local recurrences. The initial thoracic surgery was successful in 5 (83%) patients, whereas it was not in one patient with numerous metastases. Among four patients with repeated thoracotomy, the second surgery was effective in one patient who received five further successive operations. Estimated TTV relative to parathyroid hormone (PTH) level was predictive of the success in some cases. Four patients developed renal impairment with eGFR <45. Three patients died from the disease, and the median survival time was 24 months (range: 4–203 months).

Conclusion: Surgery provides effective palliation for functioning pulmonary metastases from parathyroid carcinoma. Estimating TTV relative to PTH levels while watching renal function may be a valuable consideration to determine the timing of the intervention.

18. Maintaining TSH < 2.0 mU/L without Thyroxine is Difficult after Lobectomy for Low-risk Thyroid Cancer

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Purpose/Introduction: While current guidelines suggest the maintenance of TSH at 0.5–2.0 mU/L for low-risk differentiated thyroid cancer (DTC) patients after lobectomy, the proportion of patients who can achieve this target without thyroxine supplementation is unknown. This study aims to identify factors predicting failed maintenance of target TSH without thyroxine for low-risk DTC.

Materials and methods: This was a retrospective case-controlled study on consecutive patients who had undergone lobectomy for low-risk DTC. Patients having previous thyroidectomy, preoperative hypothyroidism or hyperthyroidism were excluded. Multivariate analysis was conducted to evaluate preoperative variables predicting failed maintenance of TSH ≤ 2.0 mU/L without thyroxine.

Results: Between 2010 and 2018, 130 patients (female 80.0%, mean age 49.6 ± 13.6 years) underwent lobectomy for low-risk DTC. The mean follow-up was 4.6 ± 2.9 years. Eighty-eight (67.7%) patients failed to maintain TSH ≤ 2 mU/L without thyroxine, with 25 (19.2%) and 11 (8.5%) of them having subclinical and genuine hypothyroidism, respectively. Their peak TSH level was 4.5 ± 2.9 mU/L. Thyroxine was prescribed in 42 (32.3%) patients at mean dose of 64.9 ± 25.7 µg. Higher preoperative TSH level was the only independent factor predicting failure to maintain TSH ≤ 2 mU/L without thyroxine (1.9 ± 1.0 vs 1.0 ± 0.5 mU/L) ($p < 0.001$, OR = 7.8, 95% CI 3.3–18.7). The proportion of patients having preoperative TSH > 2.0 mU/L was significantly higher in the failure group (40.9% vs 2.4%, $p < 0.001$). There was no significant association with age, gender, body-mass-index, preoperative T4 level, and lymphocytic thyroiditis on histopathology.

Conclusion: Over two-thirds of low-risk DTC patients failed to maintain postoperative TSH ≤ 2 mU/L without thyroxine following lobectomy. Postoperative regular TSH monitoring and liberal thyroxine supplementation are therefore recommended, especially for patients with preoperative TSH > 2.0 mU/L.

19. Photoacoustic Spectral Response for Thyroid Nodule Diagnosis: A Pilot Study

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Purpose: Thyroid nodules are a common problem, but only 5–15% is malignant. Fine needle aspiration cytology and ultrasound are the current standard diagnostic techniques but lack specificity for malignancy, thereby necessitating diagnostic hemi-thyroidectomy in many indeterminate nodules. Preoperative genetic assay and intraoperative frozen section histopathology have limited value. We studied the role of photoacoustic spectral response (PASR), a laser based noninvasive, mechano-biological technique.

Materials and methods: An experimental set-up was developed inside the operation theater. Immediately after the tissue specimen was excised, it was sliced open and placed in saline solution and experiments were performed to record PA signals. Each nodule or lobe was illuminated at 10 different locations and signals were recorded. Thus total of around 180 sample points were used for this entire study and multiple frequency domain techniques such as Fourier transform and empirical mode decomposition (EMD) were applied to the PASR signal to differentiate pathology and the results were compared with histopathologic results.

Results: A total of 18 lobes were studied, 5 were malignant having papillary thyroid carcinoma (PTC), 3 were having follicular variant of papillary thyroid carcinoma (FV-PTC), 7 were benign hyperplasia and 3 were colloid cysts (Fig. 1). We obtained an efficiency of 100% to differentiate FV-PTC from other tissue variants and efficiency of 95% to distinguish PTC from benign tissue using EMD (Fig. 2).

Conclusion: This technique applied to thyroid nodules for the first time shows excellent promise as a diagnostic tool and needs further study to explore a role in preoperative clinical diagnosis with appropriate laser technology.

Fig. 1: Amplitude at different frequencies in the acoustic signal generates a unique spectral signature for FVPTC and appears related to mechano-biological properties

Fig. 2: Frequency spectra of intrinsic mode function 3 for malignant, colloid cyst and benign hyperplasia could be differentiated using empirical mode decomposition

20. A Retrospective Evaluation of the Timing of Distant Metastasis Occurrence in Papillary Thyroid Cancer

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Purpose/Introduction: The aim of this study is to retrospectively evaluate the timing of distant metastasis occurrence in papillary thyroid cancer (PTC) by the age of initial surgery, and to clarify changes of incidence rate during follow-up.

Materials and methods: From January 2007 to December 2016, 136 adult cases of initial radioiodine therapy for distant metastasis of PTC were performed. Metastases were discovered during follow-up in 83 cases. The timing of distant metastasis occurrence were evaluated in these cases by dividing into three groups by the age of 21–40, 41–60 and over 61 at the time of initial surgery. Also the follow-up was divided by 5 years in order to compare the incidence rates of metastases during follow-up.

Results: The average timing of distant metastasis occurrence were 17.4 years (209.4 months), 13.8 years (165.3 months) and 6.5 years (78.5 months) in each group. In the youngest age group, only 1 patient (4.0%) developed distant metastasis within 5 years. Eight patient (28.0%) developed distant metastasis in 6–10 years, 4 (16.0%) in 11–16 years and 13 (52.0%) over 16 years. The middle age group had 4 (13.8%) within 5 years, 5 (17.2%) in 6–10, 10 (34.5%) each in 11–15 and over 16 years. In the eldest group, 13 (44.8%) developed distant metastasis within 5 years, 11 (37.9%) in 6–10 years and 5 (17.2%) in 11–15 years.

Conclusion: In PTC, distant metastasis in elder patients, especially over 60, will develop much earlier than younger patients.

21. “Shaver Debulking” to Aid Thyroidectomy: Obviating the Need for Sternotomy in Retro-sternal Goiter

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Purpose/Introduction: Most retro-sternal goiters (RSG) can be removed by the transcervical route, but sometimes a sternotomy is thought to be required. I will present my series of 26 consecutive cases of RSG removed through the neck without sternotomy. The operation is a variation of one initially described by Lahey in 1945, of an intracapsular debulking technique, now assisted by a sinus or arthroscopic “shaver,” instruments which most hospitals already have. After being debulked, a typical extracapsular hemi- or total thyroidectomy is performed.

Materials and methods: This is a retrospective review of my experience with 26 cases over 10 years, with several case presentations, and an explanation with videos of the equipment and of the technique.

Results: All cases were performed without complications. The “debulking” is performed in a very controlled fashion, under visual and finger-palpation control, and is not difficult to do. Despite most surgeons’ expectations, the interior of a multinodular goiter is not very vascular, so bleeding was not a significant problem. Once debulked, the thyroid is easily delivered into the neck, and a typical extracapsular thyroidectomy proceeds.

Conclusion: The “shaver-debulking technique” for retrosternal goiter is safe and reliable, and easy to perform, and obviates the need for a sternotomy in most retrosternal goiters.

22. Mini-sternotomy for Thyroid Surgery

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Oral (Video) Presentation

Learning points: Mini-sternotomy for thyroid surgery is a useful approach for mediastinal and retrosternal goiters. The advantages, compared to a conventional sternotomy that continues from sternal notch to xiphoid process, include a smaller incision, decreased pain, faster recovery, shorter hospital stay and fewer complications.

Key steps: A mini-sternotomy involves a midline osteotomy from the sternal notch down the manubrium to the second intercostal space, where a second horizontal osteotomy is performed. A thyroidectomy is attempted first via a cervical approach, before a powered saw is used to make the osteotomies and a sternal retractor used to access the mediastinum and a total thyroidectomy then completed. The sternum is closed with wires as a drain is placed and the wound closed in layers.

23. Outcomes of Endoscopic Cauterization Treatments and Open Fistulectomy for Pyriform Sinus Fistula

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Introduction: Pyriform sinus fistula (PSF) is a rare congenital abnormality causing acute suppurative thyroiditis. We adopted an endoscopic chemo-cauterization treatment (ECCT) in 2007 and devised an endoscopic semiconductor laser-cauterization treatment (ESLCT) in 2015. If these endoscopic procedures were not possible, patients underwent open-surgical fistulectomy. We evaluated the outcomes of these three treatments.

Materials and methods: Eighty-three patients with PSF were treated between 2007 and 2018. Seventy-four patients underwent endoscopic cauterization procedures, 60 with ECCT and 14 with ESLCT, and the remaining 9 patients underwent fistulectomy. For the endoscopic procedures, patients were inserted suspension laryngoscopy under general anesthesia. The orifice of the PSF was identified. For ECCT, a small cotton ball soaked in trichloroacetic acid was put into the orifice for 1 minute repeated 3–6 times. For ESLCT, a metal-capped semiconductor glass-fiber was inserted into the PSF and was heated on active mode for 10 seconds repeated 3 times. We devised this procedure and Ethical Committee approved the trial. Barium swallow studies were performed to evaluate occlusion of the fistula after the treatments.

Results: Eighty-one patients had posttreatment barium swallow studies and 70 (86%) of them achieved closure of the fistula. Success rates were 8 of 9 patients (89%) for fistulectomy, 49 of 59 patients (83%) for ECCT, and 13 of 13 patients (100%) for ESLCT. Each procedure had some complications such as vocal cord paralysis and neck abscess.

Conclusion: Being less invasive and scarless, the endoscopic cauterization treatments especially with ESLCT should be a better alternative to the conventional fistulectomy.

24. Cryopreservation of Parathyroid Tissue: Why and How to Establish a Local Service

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Purpose: Iatrogenic hypoparathyroidism is a rare but life-altering complication of endocrine surgery, with an estimated incidence of 1% in high-volume centers, but is also influenced by the extent of surgery, previous therapy and number of glands removed. One of the primary tenets of endocrine surgery, is preservation of parathyroid function. For patients with thyroid disease, an inadvertently compromised parathyroid gland is routinely autotransplanted into the neck at the time of surgery. By contrast, for patients with parathyroid disease secondary to hyperplasia, the timing of autotransplantation needs to be further considered in order to balance the risks between persistent disease and permanent hypocalcemia. Cryopreservation preserves cellular function and permits the storage of parathyroid tissue for potential reimplantation at a later date in patients who develop hypoparathyroidism.

Materials and methods: In this paper, we review the indications and procedural steps of cryopreservation, with particular emphasis on the regulatory issues involved in establishing a local service, tissue processing, billing and reimbursements, outcome (functionality), and complications.

Results: A detailed description of the technique as performed at our institution is described and illustrated. Despite clinical indications for its use, a universal protocol for cryopreservation does not exist and it remains unavailable to most endocrine surgeons in Australia.

Conclusion: Cryopreservation affords surgical insurance against the sequelae of permanent hypoparathyroidism. Our techniques are easy to adopt with only a modest initial investment of time and money, particularly for institutions that already cryopreserve other tissue types.

25. Laparoscopic vs Robotic Adrenalectomy: Clinical Series from a Single Center

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Introduction: Aim of this study was to compare the results of laparoscopic adrenalectomy (LA) vs robotic adrenalectomy (RA) performed in a single center.

Materials and methods: Patients who underwent laparoscopic and robotic adrenalectomy in a tertiary clinic between June 2012 and 2019 were reviewed retrospectively. Univariate analysis and propensity matching were performed to look for differences between the groups.

Results: A total of 158 patients were included; 85 patients underwent LA, 73 patients underwent RA. One hundred seven (68%) patients were woman. Mean age was 49.4 ± 12 years. Mean follow-up time was 55 months (4–93). The most common indication for surgery was pheochromocytoma (29%). In both groups, 5 patients underwent open surgery due to complications. Mean tumor diameter was 40 mm (4–120). Mean operation time in the RA group was 117 minutes (55–275 minutes), while 85 minutes (35–260 minutes) in the LA group ($p < 0.001$). Amount of bleeding was similar in both groups ($p = 0.540$). Six (8%) patients in the RA group and 2 (2%) patients in the LA group had intraoperative complications ($p = 0.145$). Each 1 mm increase in tumor diameter increased the risk of intraoperative complications by 1.05 times ($p < 0.001$). Six (10%) patients in the RA group and 3 (4%) patients in the LA group had postoperative complications like incisional hernia, adrenal insufficiency and surgical site infection ($p = 0.189$).

Conclusion: Robotic surgery for adrenal tumors is as safe and effective as laparoscopic adrenalectomy that provides successful outcomes.

26. Microanatomic Classification of Arterial Branches of Superior Parathyroid Gland from Inferior Thyroidal Artery

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Purpose/Introduction: Preservation of the parathyroid gland is essential procedure during thyroidectomy. We classified the arterial branches of superior parathyroid gland from inferior thyroidal artery into three distinct subtypes.

Materials and methods: The microanatomic features of the superior parathyroid arterial branches (SPB) were studied in 201 lobectomies during BABA robotic thyroidectomy from May 2017 to August 2018 in Seoul National University Bundang Hospital, Korea.

Results: Three subtypes of the SPB were identified related to the course of recurrent laryngeal nerve; type I, the SPB crossed under the recurrent laryngeal nerve to supply the superior parathyroid gland, type II, the SPB crossed over the recurrent laryngeal nerve, and type III, the SPB directly supplied superior parathyroid gland from the root of the inferior thyroidal artery. Of 201 superior parathyroid gland, the incidence of type I, type II, and type III was 62.7% ($n = 126$), 12.4% ($n = 25$), and 4.9% ($n = 10$), respectively. The incidence of combination of type I + II, type II + III, and type I + III was 4.9% ($n = 10$), 3.0% ($n = 6$), and 7.46% ($n = 15$), respectively. In 9 cases (4.9%), the vascular structures were unknown mostly due to lack of blood supply or intrathyroidal location.

Conclusion: According to our study, the superior parathyroid gland had good blood supply from the inferior thyroidal artery. The sum of the incidence of type I, type I + II, and type I + III was 75.1%, which means the SPB crosses under the recurrent laryngeal nerve should be carefully preserved during thyroidectomy (Fig. 1).

Fig. 1: Classification of superior parathyroid branch from inferior thyroidal artery

27. Is Fukushima's Thyroid Cancer Occurred Due to the Radiation Effect or Screening Effect?

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Introduction: After the Fukushima Nuclear Power Plant accident that followed the Great East Japan Earthquake on March 11, 2011, a large-scale thyroid ultrasound examination (TUE) survey began for people aged 18 years or younger at the time of the disaster. We examined whether our operated thyroid cancer (TC) in Fukushima via 8 years after the accident is due to the radiation effect or mass screening effect by TUE.

Materials and methods: Until December 31, 2018, 180 TC were performed surgical treatments at our department. These cases were analyzed clinicopathological findings.

Results: Even though the tumor smaller than 10 mm, almost cases were invasive PTC. Postoperative lymph node metastasis, extra-thyroidal invasion, and pulmonary metastasis were positive in 72%, 47%, and 1.7%, respectively. Total thyroidectomy was performed in 16 cases (8.9%) and hemithyroidectomy was performed in the remaining cases (91.1%). Our operated cases were not included super low risk cases recommended active surveillance and also very few of high risk cases. Most cases were classical PTC unlike solid variant PTC. BRAF mutations were indicated in most cases unlike Chernobyl. There was no significant difference in TC occurrence among some areas with different radiation levels. Age distribution pattern of our TC is almost same until now and similar to the pattern of nonradiation induced cancer.

Conclusion: The increase in the incidence of TC in Fukushima after the accident seems to be due to a mass screening effect, and not over-diagnosis/treatment by the large-scale and highly sophisticated ultrasound examination, and not due to a radiation effect.

28. Does Thyroidectomy Positively Affect the Quality of Voice in the Absence of Nerve Injury?

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Introduction: Vocal dysfunction can occur in the presence of thyroid nodule in apparently asymptomatic patients. Although the mechanism of postthyroidectomy voice change in absence of nerve injury is not fully understood, it can be attributed to changes in air flow across glottis and alterations in extra-laryngeal framework.

Materials and methods: Forty patients undergoing hemi/total thyroidectomy underwent preoperative and postoperative (10th day and 6 weeks) direct laryngoscopy, acoustic analysis (mean fundamental frequency F0, jitter, shimmer, normalized noise energy), voice quality estimates (hoarse, harsh breathy) and spirometry [maximum phonation time (MPT) and vital capacity]. Intraoperative parameters—CL grade for intubation, thyroidectomy difficulty scale (TDS) (vasculature, friability, mobility, gland size), RLN and EBSLN characters, strap division and final histopathology were studied.

Results: F0, jitter and shimmer did not show significant change at 6 weeks (231.4 vs 237.36 Hz, 0.45 vs 0.46%, 1.9% vs 1.23%). Maximum phonation time showed significant improvement at 6 weeks when compared with preoperative value (POV) (14.83 vs 16.3 $p = 0.03$). The estimated mean flow rate [calculated as $EMFR = 77 + 0.236 (VC/MPT)$] significantly improved at 6 weeks when compared to POV (107.1 vs 109.8, $p < 0.05$). Two of the three voice quality estimates (hoarse and breathy) graded on scale (normal, mild, moderate, severe) showed significant improvement at 6 weeks when compared to POV ($p = 0.001$, <0.001 , respectively). Among intraoperative factors, CL grade (≥ 3) and TDS (≥ 10) were associated with inferior voice quality as compared to POV at 10 days but not at 6 weeks.

Conclusion: Thyroidectomy can have a positive impact on the airflow across glottis (MPT, EMFR) along with improvement in the harsh and breathy quality of voice.

29. The Timing and Location of Recurrence in Patients with Reoperation for the Neck Node Recurrence of Papillary Thyroid Carcinoma

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Purpose/Introduction: Despite the slow progression character of PTC, recurrent surgery occurs early period. The aim of this study was to determine the timing and location of recurrence in patients that underwent reoperative surgery due to neck node recurrence by reviewing the retrospective CT scan imaging of the recurrence of the thyroid papillary cancer.

Materials and methods: We reviewed the medical records from January 2002 to January 2018. All patients that had reoperative surgery due to neck node recurrence and CT scan results of preoperative evaluation and postoperative follow-up. Over this period, our cohort included 110 patients underwent reoperation due to neck node recurrence with CT scan result undergoing a total of 220 reoperations.

Results: We examined time from initial operation to first reoperation in 110 patients. The median time to reoperation was 28 months, with a range of 4 months to 186 months. Most reoperations (82.7%) occurred within the first 5 years, 43.6% were in the first two years from initial surgery (Table 1). The result of the retrospective CT review has newly developed cases (21, 19.1%), missed diagnosis cases (42, 38.2%), real recur cases after surgery (33, 30.0%), remnant LNs cases (14, 12.7%). We sub-analyzed remnant LNs 14 cases (Table 2). Reasons for remnant LNs included insufficient operation ($n = 5$) and difficult to approach ($n = 9$) (Table 3).

Conclusion: Many reoperations included missed diagnosis and surgeon's factor. This finding suggests strongly that meticulous preoperative evaluation, understanding about the extent of disease and quality of initial operation are important to improve the care of PTC patients with neck node recurrence.

Table 1: The timing to reoperation due to neck node recurrence

<i>Duration (year)</i>	<i><1</i>	<i>1–2</i>	<i>2–5</i>	<i>5–10</i>	<i>>10</i>
<i>n (%)</i>	20 (18.1)	28 (25.4)	43 (39.1)	17 (15.5)	2 (1.8)
<i>Accumulate n (%)</i>	20 (18.1)	48 (43.6)	91 (82.7)	108 (98.2)	110 (100)
<i>Time to reoperation, median (m) min.–max. (m)</i>				28 (4–186)	
<i>Duration of f/u, median (m) min.–max. (m)</i>				68 (8–198)	

Table 2: Retrospective CT review of reoperation patients due to neck node recurrence

	<i>Initial CT scan</i>		<i>Follow-up CT scan</i>	<i>n (%)</i>
	<i>Initial finding</i>	<i>Review finding</i>		
Newly developed lymph nodes	(–)	(–)	(+)	21 (19.1)
Missed diagnosis; false-negative	(–)	(+)	(+)	42 (38.2)
Recur after operation	(+)	(+)	(+)	33 (30.0)
Remnant lymph node after operation	(+)	(+)	(+)	14 (12.7)

Table 3: The details of cases in incomplete operation in patients with neck node recurrence ($n = 14$)

<i>No.</i>	<i>Sex</i>	<i>Age</i>	<i>Initial surgery</i>	<i>Recurrence site</i>	<i>RFS</i>	<i>ATA risk stratification</i>	<i>Serum TG status*</i>	<i>Postoperative RAI Tx (mCi)</i>	<i>Response to therapy</i>	<i>Reason</i>
1	F	45	Total thyroidectomy with CCND	Rt. level 4	61	Intermediate risk	Continuous elevation	200/250/300/300	Excellent response	Insufficient operation
2	M	50	Total thyroidectomy with mRND, Lt.	Lt. level 3	25	Intermediate risk	No elevation	150	Excellent response	Insufficient operation
3	M	43	Total thyroidectomy with mRND, Rt.	Rt. Para-esophageal LNs.	12	Intermediate risk	Continuous elevation	150	Excellent response	Insufficient operation
4	M	41	Total thyroidectomy with mRND, Lt.	Lt. level 2	18	Intermediate risk	No elevation	150	Excellent response	Insufficient operation
5	F	63	Total thyroidectomy with mRND, both.	Lt. level 3	22	High risk	Continuous elevation	150	Excellent response	Insufficient operation
6	F	31	Total thyroidectomy	Rt. level 7	59	High risk	Continuous elevation	30	Excellent response	Difficult to approach
7	M	47	Total thyroidectomy with mRND, both.	Both supra-clavicular LNs	36	High risk	Continuous elevation	250/250/200	Structural incomplete	Difficult to approach
8	F	31	Total thyroidectomy with mRND, both.	Rt. level 7	17	Intermediate risk	Continuous elevation	150/150	Excellent response	Difficult to approach
9	F	32	Total thyroidectomy with mRND, both.	Lt. level 1	16	Intermediate risk	Continuous elevation	200/100	Excellent response	Difficult to approach
10	F	23	Total thyroidectomy with mRND, both.	Rt. supraclavicular LNs	5	Intermediate risk	Continuous elevation	200	Structural incomplete	Difficult to approach
11	F	31	Total thyroidectomy with mRND, both.	Rt. supraclavicular LNs	6	Intermediate risk	Continuous elevation	150	Biochemical incomplete	Difficult to approach
12	M	36	Total thyroidectomy with mRND, both.	Between CCA and IJV on level II	11	Intermediate risk	Continuous elevation	150	Excellent response	Difficult to approach
13	M	22	Total thyroidectomy with mRND, both.	Suprahyoid bone	12	High risk	Continuous elevation	100	Excellent response	Difficult to approach
14	M	47	Total thyroidectomy with mRND, Rt.	Between CCA and IJV on level II	20	Intermediate risk	No elevation	150	Excellent response	Difficult to approach

*Serum TG status at recurrence

30. Therapeutic Outcomes of Nerve Injury in Surgery for Papillary Thyroid Carcinoma

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Purpose: Recurrent laryngeal nerve paralysis (RLNP) is a frequent complication of surgery for thyroid cancers. This study investigates outcomes of voice and swallowing problems in patients with papillary thyroid cancer (PTC).

Materials and methods: From 2000 to 2017, 540 thyroidectomies were performed for PTC at our tertiary center. Demographics, clinicopathological details and outcomes of nerve palsy treatments were collected. Patients were divided into two groups: those that underwent RLN amputation ($n = 21$) and those that didn't ($n = 24$).

Results: A total of 1,077 nerves were at risk during these surgeries (bilateral risk in 537, unilateral in 3 patients). Recurrent laryngeal nerve paralysis was seen in 45 (32F:13M) patients, unilateral in 42 (7.7%) and bilateral in 2 (0.4%). The median age of patients sustaining a nerve injury was 55 (range 19–83). The RLN was sacrificed in 21/45 (47%) patients due to gross disease infiltration. One patient had inadvertent nerve damage. Only 2 patients had primary nerve anastomosis performed intraoperatively. In this group speech therapy (ST) ($n = 8$), injection thyroplasty (IT) ($n = 2$) was offered. Five patients had no voice recovery and 5 had severely impaired swallowing, requiring long-term NG feeding. In 24/45 (53%) patients there was no RLN amputation. In 13/24 (29%), the tumors were shaved off the nerve (nerve preserved). These patients had full voice recovery at 12 months with ST ($n = 2$), IT ($n = 2$) or no treatment ($n = 9$). In 11/24 (24%), there was no disease involvement of RLN but palsy was found postoperatively. Voice improved in all but 1 patient in 12 months with ST ($n = 4$) and IT ($n = 1$). Tracheostomy was required in 5 patients (2 with bilateral injury, 3 with unilateral injury and contralateral side paresis). Except in 1, the tracheostomy was weaned off after 3 months following ST and IT. Overall incidence of permanent RLNP following total thyroidectomy for PTC in our cohort was 1%. Swallowing problems were seen in 3% of patients with RLNP.

Conclusion: Most RLN palsies without nerve amputation recover spontaneously within 12 months of surgery. However, RLN palsies with nerve amputations frequently require voice therapy to improve voice and swallowing outcomes.

31. Bio 3D Tissue Printing of Parathyroid Glands: Survival Experiment in the Laboratory and after Animal Implantation

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Purpose/Introduction: Research using bio 3D-printing technology is being conducted in a variety of diseases and organs. However, no studies have yet been made to print parathyroid glands using this technique. We use bio 3D-printing technology to tissue print the parathyroid gland and validate survival in laboratory and animal experiments.

Materials and methods: Parathyroid glands of patients with secondary hyperparathyroidism were used. Bio-inks were prepared by mixing parathyroid tissue cut into 1×1 mm and fat that had undergone decellularization. In laboratory studies, tissue-printed parathyroid glands (printing group) and untreated parathyroid glands (naive group) observed survival for 7 days in keratinocytes medium. In animal studies, two groups were implanted into the subcutaneous fat layer of mice and observed for 4 weeks.

Results: In laboratory studies, both groups survived for 7 days. The parathyroid hormone observed on day 7 was not significantly different between 6 pg/mg in the printing group and 5 pg/mg in the naive group. In animal experiments, tissues implanted in mouse subcutaneous fat were taken pathologically and stained. The optical density score increased gradually in both groups, and the printing group score (7.04 ± 0.52) was higher than the naive group (2.77 ± 0.68).

Conclusion: We performed the first 3D-tissue printing using parathyroid glands. In our animal experiments, we confirmed that the bio 3D-tissue printed parathyroid survived well for 4 weeks (Fig. 1).

Fig. 1: In laboratory studies, both groups survived for 7 days. In animal experiments, the optical density score increased gradually in both groups, and the printing group score was higher than the naive group

32. “One Stop Thyroid Clinic”: A More Cost-effective and Faster Management for Singapore

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Purpose: Patients referred to specialist clinics for evaluation of nodular goiters often require multiple specialist reviews and interventions by different specialists. This led to increased patient costs, inconvenience, requirements for multiple medical leaves but also prolonged work-up. A one-stop thyroid clinic was started to evaluate cost efficacy and turn-around time.

Materials and methods: A prospective study beginning in 2013–2017 involving new patients referred to thyroid surgeon for evaluation of nodular goiters. All patients underwent a 4-step “quadruple assessment” involving (a) detailed history and clinical examination, (b) baseline thyroid function with autoantibodies in selected cases, (c) surgeon-performed bedside ultrasound thyroid and (d) ultrasound-guided aspiration of cysts or needle biopsy of solid nodules within the same day. The costs and time taken to review patients for results were calculated.

Results: Of a total 575 patients with nodular goiters, 320 new cases with no prior investigations were selected. The average turnaround time for biopsy report was 8.21 days (1–16 days) from the original duration of 6 weeks. The cost for work-up showed a significant reduction in both subsidized patients (from \$402 to \$192 and private patients (from \$1,018 to \$488). The number of medical leaves were reduced from 4 days to 2 days (Fig. 1).

Conclusion: One-stop thyroid clinic has definite advantages in terms of patient convenience, faster work-up and reduced patient costs and need for medical leaves (Table 1).

Fig. 1: Patient movement to and fro between different specialists (ping-pong effect)

Table 1: Cost-efficacy of one stop thyroid clinic (numbers in brackets—traditional costs)

<i>Key markers</i>		
Time to work-up and review biopsy (FNAC) result	Average 8.21 days	Range 1–16 days
Cost of quadruple-assessment in ONE-STOP clinic	Subsidized patient—\$192 (\$402)	Private patient—\$488 (\$1,018)
Bethesda 1 result (inadequate/insufficient FNAC)	5 out of 320 patients	1.56%
Clinico-pathological correction with Bethesda and TIRADS (2015–2018)	Concordance rate benign lesions (TIRADS 2) 100%	TIRADS 2 lesions not to be subjected to FNAC

33. Improving Results of Primary Hyperparathyroidism Treatment: Additional Localizing Studies vs Bilateral Neck Exploration

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Aim: To compare results of primary hyperparathyroidism (PHPT) treatment by use of certain number of localizing studies combined with selective parathyroidectomy (SPTE) or bilateral neck exploration (BNE).

Materials and methods: Retrospective evaluation of treatment results of 480 PHPT patients (females: 447, 93.2%; males: 33, 6.8%; mean age 57 ± 12.1 years). All patients had increased calcium and parathyroid hormone (PTH) levels before surgery. Patients had different number of localizing studies performed before surgery: ultrasound alone (59, 12.3%), MIBI alone (27, 5.6%), 4D-CT alone (24, 5%), ultrasound + MIBI (189, 39.4%), ultrasound + 4D-CT (73, 15.2%), MIBI + 4D-CT (20, 4.2%), ultrasound + MIBI + 4D-CT (88, 18.3%). Number of studies was increased in cases with negative initial study or discordance between studies. SPTE was performed in 354 (74%) of cases, BNE—in 126 (26%) of cases. Calcium and PTH levels were estimated in 1–4 hours after surgery and on the 1st postop day.

Results: Rate of PHPT persistence was 5.6% when ultrasound alone was used (SPTE—5.4%, BNE—6.6%), 1.8%—with concordant ultrasound + MIBI results (SPTE—2.3%, BNE—0%), 6.5%—when ultrasound and 4D-CT were used (SPTE—7.8%, BNE—0%), 8.7% in cases of discordant or negative ultrasound and MIBI results followed by 4D-CT use (SPTE—10.2%, BNE—0%).

Conclusion: Isolated use of ultrasound is not supported by our data due to high persistence rate. In cases of negative or discordant data additional localizing studies followed by SPTE provide worse results than BNE after ultrasound combined with MIBI or 4D-CT.

34. Active Surveillance for Low Risk PTMC—Characteristics of Chinese Patients

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Purpose: To investigate the outcome of active surveillance (AS) in low risk PTMC patients in China.

Materials and methods: The FNAC confirmed and ultrasound confirmed TIRADS 5 low risk PTMC patients were recruited to the current study since April 2018. Each patient was evaluated in the thyroid clinic by a experienced thyroid surgeon every 6 months by ultrasound in the first two years and once a year thereafter. Thyroidectomy is recommended if the PTMC grows and/or invades the thyroid capsule.

Results:

	<i>n</i>	<i>Age (year)</i>	<i>Size (mm)</i>	<i>w/thyroiditis (%)</i>	<i>F/U (m)</i>	<i>Surgery</i>
FNAC-confirmed	52	38 (24–61)	6.8	38	35	7 (13%)
TIRADS-5	73	41 (25–66)	5.1	16	29	0
Total	125	40	5.8	25	30	7 (5.6%)

Conclusion: This cohort of Chinese low-risk PTMC patients who choose active surveillance are younger than those in Japan and USA. And more of them transferred to surgery during the same period of AS.

35. Optimal Surgical Management of Renal Hyperparathyroidism

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Secondary and tertiary hyperparathyroidism are major complications of chronic renal failure, and can persist following renal transplantation. The optimal surgical treatment of renal hyperparathyroidism is uncertain. We examined our experience with an audit of consecutive cases at our center. In a single-center retrospective audit of a 10-year period, we compared outcomes between total parathyroidectomy with autograft and subtotal parathyroidectomy. The theater database ORMIS was utilized to capture all parathyroidectomies over the study period, with this list filtered for operations performed for renal hyperparathyroidism. Patient records were accessed to determine reason for referral (secondary or tertiary hyperparathyroidism), dialysis or transplant status, type of operation, weight of resected tissue, duration of postoperative calcium infusion, length of stay, calcium and parathyroid hormone (PTH) trends and complications. These data were compared between groups, with exclusion of MIP and re-exploration operations. Of all patients undergoing parathyroidectomy for renal hyperparathyroidism ($n = 83$), the majority were performed for tertiary hyperparathyroidism. Approximately half the patients had functioning transplants or required definitive management of hyperparathyroidism before being waitlisted for transplantation. Fifty five patients underwent subtotal parathyroidectomy and 23 had a total parathyroidectomy with autograft, with the remainder undergoing MIP or re-exploration. Length of stay was significantly less in the subtotal parathyroidectomy group, with a trend toward shorter duration of postoperative calcium infusion. There was no significant difference in the postoperative calcium and PTH levels over time. Subtotal parathyroidectomy is not inferior to total parathyroidectomy with autograft, and may result in shorter duration of postoperative calcium infusion and length of stay.

36. Improvement of the Eighth Edition of the Tumor-node-metastasis Classification by Subclassifications of Tumor Extension and Node Metastases in Papillary Thyroid Cancer

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We investigated how to improve the 8th edition of TNM classification (TNM-8th) to predict prognoses more accurately by enrolling 5,683 papillary carcinoma (PTC) patients, who underwent surgery between 1988 and 2005 (median follow-up period, 15 years). We subdivided tumor extension (T4a) into two categories: T4a1, extending to the tracheal adventitia and cartilage, esophageal muscle layer, recurrent laryngeal nerve, and cricothyroid and inferior constrictor muscles, and T4a2, extending to other organs such as the tracheal and esophageal mucosa, jugular and brachiocephalic veins. We subdivided N factor into two categories: N1, size ≤ 3 cm, and N2, size > 3 cm. The 20-year cause-specific survival (CSS) rates were 99.3, 93.4%, 82.6%, and 11.3% for patients with stages I, II, III, and IVB, respectively. In patients < 55 years, although M0, N2 and/or T4a2 patients had the similar CSS to stage II patients. Therefore, they were upstaged to revised stage (restage) II. In patients ≥ 55 years, since stage III patients with T4a1 showed the similar CSS to stage II patients, they were downstaged to restage II. In contrast, N2 patients ≥ 55 years were upstaged to restage III, because they had a similar CSS to T4a2 patients. The number of restage III patients decreased from 406 to 136 and 20-year CSS rate became poorer, at 69.5%. In contrast, the number of restage II patients increased from 403 to 798, but the 20-year CSS rate was similar, at 91.8%. These findings suggest that subdivision of tumor extension and node metastasis further improves the TNM-8th for PTC.

37. Drug Repositioning in the Treatment of Anaplastic Carcinoma of the Thyroid

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Introduction: Anaplastic thyroid carcinoma (ATC) is an aggressive malignancy that is classified as stage IV when it is diagnosed regardless of the extent of disease. We have experienced complete remission in 6 out of 24 cases by applying unconventional combinations of preexisting drugs to its treatment. Oral valproic acid is an anticonvulsant which is also known to have HDAC inhibitor qualities. Bisphosphonates have an array of anticancer properties. The addition of these drugs may have helped improve the efficacy of chemotherapy and subsequent surgery.

Materials and methods: Twenty-four patients of ATC were treated with doxorubicin and cisplatin with oral valproic acid with the intention of combining surgery with 3 or more courses of chemotherapy. Some of the patients were also given alendronate in order to counteract the osteoporotic effects of steroids. The results were analyzed retrospectively.

Results: Ten patients completed three or more courses of chemotherapy out of which 8 patients received surgery. Six patients had complete resections of the tumor and entered sustained remission without recurrence or treatment for over a year. Three out of three stage IV-a, and three out of eight stage IV-b cases went into remission and have not recurred. The longest survivor lived over 11 years without recurrence.

Conclusion: Addition of valproic acid, and other drugs not conventionally classified as anticancer agents, may improve outcome for implacable diseases such as ATC.

Above October, 2007, below March, 2008

Total of 203.0 mg/m² of doxorubicin (DXR) and 394.7 mg/m² of cisplatin (CDDP) in 5 courses at 4 week intervals, average of 40.6 mg/m² of DXR and 78.9 mg/m² of CDDP per course, and 1,200 mg of oral valproic acid daily, 35 mg of oral alendronate weekly

38. Overview of Current Trends in Thyroid Surgery in Sri Lanka

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Introduction: Thyroid surgery has evolved globally over the last few decades. A questionnaire based study was done to assess the changing trends in thyroid surgery amongst Sri Lankan surgeons.

Materials and methods: A pretested questionnaire was sent to 106 surgeons and senior registrars. Decision making in the management of thyroid diseases and technical aspects of thyroidectomy were assessed. Results were compared with a study from 2008 ($n = 33$).

Results: Thirty two (30%) responses were collected. Experience ranged from 5 years to 25 years [mean = 9.18 years (19 years)]. Thyroidectomies per year ranged 30–200 [mean = 61 (53)]. Benign goiter was offered total thyroidectomy in 97% (35%). Differentiated and medullary cancer were offered total thyroidectomy $\pm$ lymphadenectomy over 90% in both studies. Graves (59–17%) and Hashimoto's thyroiditis (91%) were mainly managed nonsurgically. External branch of superior laryngeal nerve was identified by 31% (9% in past study). Recurrent laryngeal nerve was visually identified by all (100–92%). Nerve stimulation was not utilized. Parathyroids were identified by 81% (22%). Drain inserted by 56%.

Conclusion: Thyroidectomy is a common operation performed by most surgeons. There is change in the trends in thyroid surgery. Most surgeons perform total thyroidectomy for benign disease now. Routine identification of vital structures has improved in the last decade. Current trends in thyroid surgery in Sri Lanka appears to be in keeping with the global trends. Total thyroidectomy is the main operation for benign disease of the thyroid in this cohort.

39. Better Access to RAI and Advent of TKI Improved Outcome of Patients with Distant Metastasis from PTC

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Purpose/Introduction: Our previous report (Surgery 2008;143:35–42) could not verify the effectiveness of radioactive iodine (RAI) therapy on patients with distant metastasis (DM) from papillary thyroid carcinoma (PTC). The research included patients who underwent primary surgery between 1976 and 2002 and RAI therapy was applied for limited patients. After that period, accessibility to RAI therapy has been gradually improved

and tyrosine kinase inhibitors (TKIs) have been newly introduced in Japan. In the present study, we re-evaluated the treatment outcomes to clarify the efficacy of RAI and TKI therapies.

Materials and methods: Among 2,295 patients who underwent primary thyroidectomy from 1993 to 2018, 104 patients had DM at initial presentation and 107 patients developed DM during follow-up. Those 211 patients were retrospectively reviewed. The log-rank test was used to assess the differences in cause-specific survival (CSS).

Results: Among 129 patients who underwent RAI therapy, 37 (28.7%) showed uptake of RAI and 26 (20.2%) had objective responses. Until 2004, RAI therapy was conducted for 18 among 45 patients (40.0%) and it showed no significant effect on CSS ($p = 0.88$). After 2005, 111 of 166 patients (66.9%) had RAI therapy and they showed significantly better CSS than those without RAI (83.6% vs 65.8% at 5-year, $p = 0.0002$). Since 2012, 21 patients have been administered TKIs and they demonstrated significantly longer CSS than those who had progressive disease without TKIs (70.2% vs 45.4% at 5-year, $p = 0.0084$).

Conclusion: Proper use of RAI and TKIs could improve survival of patients with DM from PTC.

40. Predictive Factors of Recurrence for BMPTMC: A Single Center Study of 1,207 Chinese Patients

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Introduction: The American Thyroid Association (ATA) guidelines risk stratify BRAFV600E mutated multifocal papillary thyroid microcarcinoma (BMPTMC) into different recurrence risk groups by the extent of extrathyroidal extension (ETE). These findings need to be verified in additional studies.

Materials and methods: A retrospective cohort study was conducted in BMPTMC patients who underwent total thyroidectomy (TT) and central lymph node dissection (CLND) from 2008 to 2013. Overall, 1,207 patients were included.

Results: BMPTMC with ETE to capsule shows the same recurrence rate (3.8%) with intrathyroidal BMPTMC. Moreover, BMPTMC with ETE only to strap muscle, shows relatively lower recurrence rate (13.3%) compared with some intermediate risk categories such as cN1 and >5 pN1. Multivariate analysis using a Cox proportional hazards regression model shows that total tumor diameter (TTD) is associated with significantly higher recurrence for BMPTMC with or without other risk factors [hazard ratio (HRO) = 9.86 (95% CI 5.35–18.20), $p = 0.00$; HRO = 2.32 (95% CI 1.12–4.85), $p = 0.02$, respectively], while Hashimoto thyroiditis (HT) is found to be protective against the recurrence [HRO = 0.51 (95% CI 0.33–0.79), $p = 0.00$; HRO = 0.47 (95% CI 0.25–0.89), $p = 0.02$, respectively].

Conclusion: Taken together, capsular ETE and gross ETE to the strap muscles did not have the expected significant influence on recurrence for Chinese BMPTMC patients who underwent TT and CLND. Rather than the extent of ETE, TTD and the lack of HT were identified as predictors for recurrence among BMPTMC with or without other risk factors (vascular invasion, cN1, pN1 > 5, pN1 > 3 cm).