

## Oral Presentation IV

### Changing Lymph Node Ratio, Recurrence, and Radioablation Trends in Papillary Thyroid Carcinoma

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#### BACKGROUND AND AIMS

Prophylactic central lymph node dissection with total thyroidectomy (TT) for the treatment of papillary thyroid cancer (PTC) is controversial because of the possibility of increased morbidity with uncertain benefit. We evaluated the changing trends of lymph node ratio (LNR), recurrence, and radioablation therapy. Also, we evaluated the safety of omitting radioablation after TT with PTC, especially on low PNR (positive node ratio) N1a patients compared with high PNR N1a patients.

#### METHODS

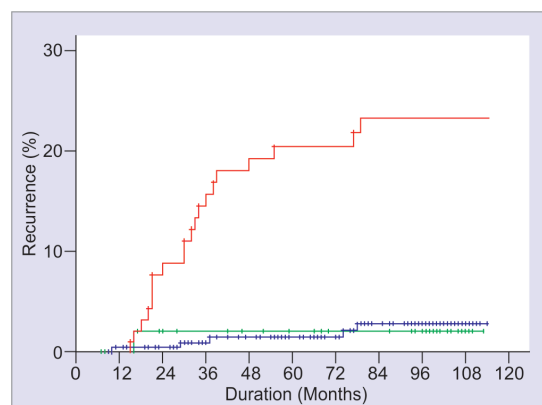
Consecutive 147 N1a and 216 N0 patients who underwent TT with central neck dissection were enrolled. We divided 147 N1a patients into two groups: 96 high-PNR vs 51 low-PNR group according to 50% of PNR, and compared three groups including N0 group.

#### RESULTS

There were 21/147 (14.3%) recurrences on N1a intermediate-risk patients and 5/216 (2.3%) on N0 low-risk patients. Of these 21 recurrences, 20 (95.2%) occurred in the high-PNR group and only 1 (4.8%) was in the low-PNR group. The recurrence in low-PNR group (Graph 1; green line) was significantly lower than in high-PNR group (red line; log-rank p value = 0.003), but significantly not different from the N0 group (blue line; log-rank p-value = 0.889). Although this study was a retrospective nonrandomized trial with less number of patients, the 10-year recurrence of omitting RAI in low-PNR intermediate-risk N1a patients with less than 50% of PNR was shown to be comparable with 216 N0 low-risk patients.

#### CONCLUSION

Prophylactic central neck dissection may lead to upstaging and low recurrence, but also to overuse of radioablation. Lymph node ratio could be a useful predictor of recurrence and useful guidance in radioablation therapy.



Graph 1: Recurrence analysis

### Long-term Prognosis of Advanced Papillary Thyroid Carcinoma with Extra-thyroidal Extension: Role of “Shaving-off” Resection

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#### BACKGROUND AND AIMS

Optimal management of advanced papillary thyroid carcinoma (PTC) remains controversial. In particular, the surgical strategy for extra-thyroidal extension to the adjacent nerves (Ex-N) or the trachea (Ex-T) poses a dilemma because functional preservation

of these structures often takes priority over curability. The aim of this study is to reveal the clinical course of advanced PTC with Ex-N and/or Ex-T after surgery.

## METHODS

Of the 1,640 patients who underwent initial surgery for PTC from 1981 to 2004, 155 (9.4%) had advanced disease with Ex-N and/or Ex-T without other invasion. Medical records were reviewed to collect following variables: demographic data, operative findings, surgical procedures including curability, pathological findings, adjuvant or additional therapies, and follow-up observations on relapse or progression of, as well as death from, the disease. Local recurrence-free survival (LRFS) and disease-specific survival (DSS) were estimated by the Kaplan–Meier method. The log-rank test was used for statistical comparisons. A  $p < 0.05$  was considered to represent statistical significance. Patients with distant metastasis were excluded.

## RESULTS

A total of 56 patients underwent curative surgery (group C) while 10 patients ended up with non-curative operation (group NC). Extra-thyroidal extension was shaved off (group S) preserving invaded structures in 71 patients for Ex-N, 15 patients for Ex-T, and 3 patients for both Ex-N and Ex-T. The LRFS at 10 years were 89.8% for group C and 98.8% for group S. The DSS at 10 years were 94.7% for group C, 97.0% for group S, and 76.2% for group NC. The LRFS and DSS of group S were similar to those of group C ( $p = 0.09$  and  $p = 0.45$  respectively). The DSS of group NC was significantly lower than those of group C and S ( $p < 0.0001$  and  $p = 0.0004$  respectively).

## CONCLUSION

Surgery shaving-off extra-thyroidal extension without leaving any residual tumor can result in excellent in comparison with curative surgery.

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## Analyses of Small ( $\leq 5$ cm) and Large ( $> 5$ cm) Retrosternal Thyroid Extensions in Consecutive 492 Total Thyroidectomies

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## BACKGROUND AND AIMS

The majority of retrosternal goiters (RSG) can be delivered through the cervical approach, obviating the need for sternotomy. The size of retrosternal extension may have an impact on the surgical acumen and morbidity. We intend to analyze the impact of the size of retrosternal extension on various factors for safe thyroidectomy.

## METHODS

Data from 492 patients undergoing total thyroidectomy (TT) under a single endocrine surgeon were retrieved retrospectively from the prospectively maintained records over a period of 4 years (July 2011–May 2015) with a minimum follow-up of 6 months. A total of 59 patients (11.9%) had retrosternal extensions and all were removed by cervical approach. Based on the extent of retrosternal component, RSG were subdivided into small RSG ( $\leq 5$  cm) and large RSG ( $> 5$  cm). Various parameters were analyzed for small and large RSG.

## RESULTS

Of the 59 RSG (47 female and 12 male), 34 (57.6%) were small and 25 (42.4%) were large. Of these, 27 (45.8%) were positioned on the right side, 22 (37.3%) on the left, and 10 (16.9%) bilaterally. A total of 11.9% were reoperative. The majority were multinodular goiters (66.1%) with significant compressive features in 42.4%, while 35.6% were incidentally detected on imaging/intraoperatively. A significant proportion of these RSG were thyrothymic thyroid rests [TTR;  $n = 38$  (64.4%)] and 21 (35.6%) were true thyroid extensions. Malignancy was observed in 23.7% of the cases. When analyzing small and large RSG, as shown in Table 1, there was no statistical difference.

**Table 1:** Comparison of small and large RSG

<i>Parameters</i>	<i>Small RSG (<math>\leq 5</math> cm) n = 34</i>	<i>Large RSG (<math>&gt; 5</math> cm) n = 25</i>	<i>p-value</i>
Age in years	44.9 $\pm$ 13.4 (22–71)	40.8 $\pm$ 10.6 (25–58)	0.27
Size in cm	3.47 $\pm$ 0.9 (1.8–4.8)	6.86 $\pm$ 1.6 (5.2–11.4)	0.008
Bilaterality	5	5	1.00
Thyrothymic thyroid rests	58.8%	72%	0.22
Compressive features	35.3%	52%	0.35
Malignancy	17.6%	28%	0.33
Preservation of all four parathyroids	47.1%	40%	0.39
Parathyroid autotransplantation	38%	32%	0.41
Temporary hypocalcemia	58.8%	60%	0.57
Permanent hypocalcemia	0%	4%	0.42
Temporary RLN palsy	2.9%	4%	0.46
Permanent RLN palsy	0%	0%	NS

NS: Nonsignificant

## CONCLUSION

The majority of RSG are thyrothymic thyroid rests. With adequate surgical expertise, the size of retrosternal component has little impact on short- and long-term morbidity.

## Time Course and Pattern of Postoperative Recurrence of Papillary Thyroid Cancer

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## BACKGROUND AND AIMS

The recurrence of papillary thyroid cancer (PTC) is common, and a more rational and effective approach to the postoperative surveillance of PTC patients is needed. It requires a more complete understanding of the time course and patterns of recurrence. The objective of this study was to evaluate the time to recurrence and recurrence sites.

## METHODS

We retrospectively analyzed medical records of 134 PTC patients with the recurrence after initial treatment. To exclude the persistent disease, we defined recurrence as the development of new lesion 1 year after the initial operation. The time to recurrence was calculated when any initial recurrence occurred.

## RESULTS

The mean age was 44.8 years (15–83) and follow-up duration was 96.1 months (13–345). The most frequent site of initial recurrence was lateral neck compartment (83.6%), and 10.4% patients developed recurrence on the central neck. Distant metastasis including lung and bone was developed in 6.7% patients as an initial recurrence. The mean number of recurrence was 1.3 (1–6).

The mean time to distant metastasis was 92.5 months (13–307). Lung is the most common metastatic site (9.0%). There were two cases each of bone and brain metastasis.

In 56.7% cases, recurrence occurred within the first 3 years, and in 73.9% cases, it occurred within the first 5 years after initial operation. In 19.4% cases, recurrence developed between 5 and 10 years. In 5.2% cases, recurrence was detected between 10 and 20 years and in 1.5% cases between 20 and 30 years. The mean time to recurrence was 48.2 months (12–313). There was no PTC-cause-related death during the follow-up period.

## CONCLUSION

The lateral neck compartment was the most common site of recurrence. Although most of the recurrence developed within 5 years, recurrent disease developed after 10 years. Long-term management for PTC patients is needed. The understanding of recurrence timing and pattern would provide a foundation for the design of more effective surveillance protocols for PTC patients.

# Cancer-specific Survival of Differentiated Thyroid Cancer presenting with Synchronous and Metachronous Distant Metastasis

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## BACKGROUND AND AIMS

Differentiated thyroid cancer (DTC) has a good prognosis. But DTC presenting with distant metastasis has a particularly poor prognosis. We aimed to evaluate the cancer-specific survival in DTC patients presenting with distant metastasis.

## METHODS

A retrospective medical record review was undertaken of patients with stage M1 DTC at presentation (n=93), referred from 1982 to 2013 at a single institution.

We compared cancer-specific survival for two groups: (1) 70 patients had metachronous distant metastasis. (2) 23 had synchronous distant metastasis.

## RESULTS

The median age was 50 (11–87), with 63% females. Histology: papillary, 76 (81.7%) and follicular 17 (18.3%). The initial site(s) of metastasis were lung only (64.5%), bone only (9.7%), lung and bone (19.4%), and other multiple sites (6.5%). All patients underwent a thyroidectomy. Additional treatment(s) included: Radioactive iodine (RAI; 95.37%), excision of metastasis (16.1%), radiotherapy (EBRT; 15.1%), and chemotherapy or anticancer drug (14%). With a median follow-up time of 114 months, 82 patients are alive (88.2%) and 11 died (11.8%); synchronous distant metastasis has 5-year survivals of 91.3% and 10-year survivals of 78.3%, and metachronous distant metastasis has 5-year survivals of 88.3% and 10-year survivals of 66.2% (p=0.995).

## CONCLUSION

Differentiated thyroid cancer patients with distant metastasis can have long periods of cancer-specific survival (10-year survival of 71.7%). There were no significant difference between synchronous and metachronous metastasis. Differentiated thyroid cancer patients with synchronous distant metastasis need to do more on active treatment.

# Risk Group Stratification for Distant Metastasis in Patients with Minimally Invasive Follicular Thyroid Carcinoma

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## BACKGROUND AND AIMS

Although patients with minimally invasive follicular thyroid carcinoma (MIFTC) generally have an excellent prognosis, distant metastasis occurs in some patients. This study evaluated the risk factors for distant metastasis and compared the outcome between the subgroups, which were divided by the number of risk factors.

## METHODS

A review of patient records identified 195 patients who underwent initial surgery at Asan Medical Center from 1996 to 2010 and were subsequently diagnosed with MIFTC. After evaluating the risk factors for distant metastasis, patients were subdivided into four groups based on the number of risk factors: group 0, with no risk factor; group 1, with any one risk factor; group 2, with any two risk factors; and group 3, with all risk factors.

## RESULTS

The median follow-up period was 99.5 months (13–244). A total of 15 patients (7.7%) had distant metastases. Age > 45 years [hazard ratio (HR) 95% confidence interval (CI) = 3.79 (1.79–11.13)]; p = 0.025, tumor size > 4 cm [HR (95% CI) = 2.27 (1.5–8.07), p = 0.041], and vascular invasion [HR (95% CI) = 4.32 (1.46–15.02), p = 0.01] were shown to be independent risk factors in multivariate analysis. Group 2 and 3 patients showed significantly lower distant metastasis-free survival (DMFS) rates as compared with group 0 patients (p = 0.005 and < 0.001 respectively). Group 1 patients tended to have poor outcome compared to group 0 patients, but there was no significant difference (p = 0.069).

## CONCLUSION

Minimally invasive follicular thyroid carcinoma patients with two or more risk factors for distant metastasis showed significantly worse DMFS rates rather than those having no or only one risk factor, while DMFS rates between patients with no and only

one risk factor did not show any significant difference. Minimally invasive follicular thyroid carcinoma patients with no or only one distant metastasis-related risk factor may become candidates for close observation without additional treatments after hemithyroidectomy.

## Clinical Behavior and Outcome of Papillary Thyroid Microcarcinoma according to the Tumor Size

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### BACKGROUND AND AIMS

The objective of this study was to define a cut-off size above which the papillary thyroid microcarcinomas (PTMCs) are more aggressive and to investigate the impact of multiple risk factors on PTMC's outcome. And we planned to find the clinical relevance in treatment recommendations of PTMC patients.

### METHODS

From January 1986 to December 2013, a total 6,115 patients with PTMC who were treated by bilateral total thyroidectomy at a single institution were enrolled. Patients were divided into eight groups based on the tumor size with 1 mm interval. Clinicopathological profiles and follow-up details were investigated by a retrospective chart review. The mean follow-up duration was 44 months.

### RESULTS

In the 6,115 patients, the average age was 48.6 years, and the mean tumor size was 0.66 cm. A total of 54.1% had extrathyroidal invasion, 42.2% had tumor multiplicity, 30.3% had bilaterality, 34.8% had central lymph node metastasis, and 9.9% had lateral lymph node metastasis. Recurrence rate was 0.9%. On a comparative analysis with tumor size group (1 mm), patients with larger sized tumor had more extrathyroidal, bilaterality, and nodal disease. In ROC and logistic regression analysis, the tumor size of 0.7 cm was found to distinguish significant cut-off values of risk factors (extrathyroidal invasion, multiplicity, node metastasis, and number of risk factors). Multivariate analysis about recurrence revealed the lymph node metastases and the presence of other risk factors were the significant. In the presence of three or more risk factor groups, lymph node metastases and tumor size were significant factors for disease-free survival.

### CONCLUSION

Among patients with PTMC, tumor size more than 7 mm was associated with more aggressive disease. And the presence of lymph node metastases and two or more risk factors is strongly associated with disease-free survival. Although PTMC is generally associated with an excellent prognosis, clinicians should consider a different strategy for therapy and plan for follow-up according to the tumor size and the number of risk factors in PTMC patients.

## Treatment Outcomes in Brain Metastasis from Papillary Thyroid Cancer

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### BACKGROUND AND AIMS

Brain metastasis (BM) is a rare form of distant metastasis with papillary thyroid cancer (PTC). Patients with BM of PTC carry a poor prognosis. The aim of this study was to contribute to the understanding of this disease by analyzing patients with BM of PTC.

### METHODS

Between March 2003 and December 2013, the patient database at the Thyroid Cancer Center, Gangnam Severance Hospital, Korea, was analyzed to identify thyroid cancer patients who were treated. The medical records of 14 patients with BM were retrospectively reviewed, focusing on the following: patient characteristics, synchronous or previous distant metastasis, treatments including whole brain radiotherapy (WBRT), stereotactic radiosurgery surgery (SRS), characteristics of radiologic findings, and the time interval between the first diagnosis of primary thyroid cancer and BM and the survival after BM.

### RESULTS

The mean age at initial diagnosis (ID) and BM were  $50.9 \pm 15.8$  and  $61.3 \pm 12.7$  years respectively. The mean duration between ID and BM was  $124.7 \pm 95.5$  months. All patients were treated with varied combinations of surgery, SRS, and WBRT except four

patients who had refused treatment. The median overall survival (OS) time after BM diagnosis was 10 months (1–19). Patients receiving treatment (WBRT and/or SRS) had a significant longer median OS of 16.5 months in comparison to 3.5 months for those treated without treatment statistically ( $p=0.005$ ).

## CONCLUSION

Patients who received aggressive treatment had a longer OS than those with only supportive care. Aggressive treatment, such as surgery, SRS, and WBRT should be considered in patients with BM.

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## Lenvatinib induces early Tumor Shrinkage in Patients with Thyroid Cancer

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## BACKGROUND AND AIMS

Traditionally, advanced thyroid cancer patients have limited therapeutic options. Recently, sorafenib and lenvatinib were introduced to patients with radioiodine refractory advanced thyroid cancer, and the treatment strategy changed much.

In the phase 3 study of lenvatinib (SELECT), the response rate of lenvatinib was 64.8%, and a median time to objective response of lenvatinib was 2 months (95% CI: 1.9–3.5). In the SELECT study protocol, tumor evaluation was performed every 8 weeks with CT or MRI imaging. Although lenvatinib was shown to have immediate effects on thyroid cancer, it is uncertain when lenvatinib starts showing its effect in shrinkage. In this study, we tried to evaluate tumor size by CT imaging frequently in 2 months.

## METHODS

Between May and December 2015, 16 patients diagnosed with thyroid cancer received lenvatinib therapy at our hospital. The subjects included 4 males and 12 females with median age of 69.5 (40–83).

Evaluation for the target lesion by CT scan was performed basically every 2 weeks in the 2 months after starting medication.

The reduction rate of tumor size was evaluated retrospectively according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, criteria. Positive tumor shrinkage was defined when tumor size decreased more than 10%.

## RESULTS

Tumors were shrunk more than 10% within 2 weeks in three patients (21%), within 4 weeks in six patients (42%), within 6 weeks in two patients (15%), within 8 weeks in two patients (15%), and after 8 weeks in two patients (15%). Tumor was not shrunk after 8 weeks in one patient (7%).

## CONCLUSION

Lenvatinib decreased the size of tumors more than 10% in 13 patients (81%) within 8 weeks.

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## Which Cytological Features suggested Malignancy in Thyroid Nodules with Intermediated Fine Needle Aspiration Cytology Results?

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## BACKGROUND AND AIMS

Five to fifteen percent of thyroid nodules with atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) category in fine needle aspiration cytology (FNAC) were estimated to be malignant. Though repeating FNAC was suggested, near one-tenth of patients would delay their treatment and undergo unnecessary re-FNAC. We aimed to investigate any cytological features predicting malignancy in thyroid nodules with AUS/FLUS results.

## METHODS

From January 2013 to December 2014, patients with FNAC result of AUS/FLUS undergoing thyroidectomy were retrieved from a prospectively collected database. Demographics, clinicopathological data, and cytological features were collected. Final pathology was correlated with different variables to find predictive factors.

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## RESULTS

Over 2 years, 112 out of 662 patients (16.9%) undergoing thyroidectomy had AUS/FLUS in their FNAC results. Majority of them were female (96/112, 85.7%) with a median age of 55 years (17–90). Twenty-four (21.4%) malignant lesions were found, and the commonest lesion was papillary thyroid carcinoma (n=23).

In nine cytopathological features assessed, the presence of intranuclear inclusion body (20.8 vs 2.3%,  $p=0.001$ ) and nuclear grooves (33.3 vs 12.5%,  $p=0.016$ ) was more likely to be malignant.

Fifteen out of 112 patients (13.4%) had repeated FNAC. The majority (47%) of the results was AUS/FLUS, followed by nondiagnostic (40%) and suspicious of malignancy (13%) respectively. None of the repeated FNAC showed benign lesion.

## CONCLUSION

Twenty-one percent patients with AUS/FLUS in FNAC were malignant. The presence of intranuclear inclusion body predicted malignant thyroid nodule. Repeating FNAC did not offer additional benefit in the decision of management in this group of patient.