cases defining a high-volume thyroid surgeon is important because it has implications for quality improvement, identification of criteria for referral and payers’ reimbursement, and surgical education.

**Metastatic Lymph Node Ratio in Papillary Thyroid Cancer Does Not Affect Survival**

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**INTRODUCTION:** The presence of lymph node (LN) metastases in papillary thyroid cancer (PTC) is associated with tumor upstaging and increased risk of recurrence. Metastatic lymph node ratio (MLNR) has been proposed as a better prognosticator for cancer staging. We present a retrospective analysis of MLNR in PTC from the National Cancer Data Base (NCDB).

**METHODS:** The NCDB was queried from 1998 to 2006 to include patients with T1-4M0 PTC undergoing near, sub, or total thyroidectomy, who had a minimum of 5 cervical LN concomitantly removed. MLNR was calculated by dividing the number of positive LN by the total number of LN removed. Patient survival was analyzed using Kaplan-Meier method. The impact of MLNR on overall survival (OS) was analyzed using a multivariate Cox regression analysis adjusted for relevant covariates.

**RESULTS:** There were 14,395 patients with T1-4M0 PTC who met inclusion criteria. The majority were female (72.1%). The mean age at diagnosis was 42.2 ± 14.3 years (mean ± SD). Mean number of lymph nodes removed was 16.1 ± 14 and mean positive LN was 5.2 ± 6.2. Increasing number of positive LN significantly decreased OS. On multivariate analysis, a positive MLNR was associated with a decrease in OS for all patients but an increasing MLNR did not impact OS. In patients with LN metastasis, a MLNR cutoff of 0.5 did not affect OS (hazard ratio, 1.13, 95% CI, 0.97-1.32, p = 0.123).

**CONCLUSIONS:** In PTC, positive cervical LN metastasis and an increasing number of positive LN significantly decrease survival, but MLNR does not provide added prognostic survival information.

**Targeting the Small Ubiquitin-Like Modifier Pathway as a Novel Treatment of Anaplastic Thyroid Cancer**

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**INTRODUCTION:** Anaplastic thyroid cancer cell lines 8505C, SW-1736, KAT-18, and Uhth74-c17 and a panel of primary ATCs were evaluated. Gene knockdowns were achieved through siRNA transfection. Expression was characterized by qRT-PCR, Western blot, immunohistochemistry, and flow cytometry. Tumorigenesis in xenograft mouse models was evaluated by log rank.

**RESULTS:** TFAP2A was expressed in 4 of 11 primary ATC tissue specimens surveyed. Of the cell lines, 8505C and SW-1736 expressed high TFAP2A levels, but only 8505C was also enriched for SUMO-conjugated TFAP2A. Knockdown of the SUMO pathway enzyme PIA51 in 8505C significantly reduced CD44 mRNA and protein expression; however, this effect was lost with concurrent knockdown of TFAP2A. In vitro treatment of 8505C with SUMO inhibitors similarly produced reductions in CD44 expression, with a population shift toward CD44 negativity on flow cytometry. Additionally, administration of SUMO inhibitors statistically improved tumor-free survival of nude mice flank-inoculated with 8505C cells (p<0.01).

**CONCLUSIONS:** SUMO inhibition repressed CD44 expression in 8505C, indicating an effect on the CSC population. Small molecule inhibitors repressed outgrowth of ATC tumor xenografts, further providing pre-clinical evidence for SUMO inhibitors as a novel treatment strategy. Repression of CD44 depends on expression of SUMO-conjugated TFAP2A, which may serve as a molecular marker for therapeutic effects of SUMO inhibitors.

**Urinary Metabolomics Analyses Identify Novel Markers of Malignant Adrenocortical Neoplasms**

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**INTRODUCTION:** Adrenal incidentalomas are common and must be differentiated from adrenocortical cancer (ACC). Currently, size, growth, and imaging are used to differentiate malignancy but are imperfect. The objective was to determine whether urinary small molecules (<1000 Da) could diagnose ACC compared with pathologically confirmed benign adrenal tumors.

**METHODS:** Preoperative urine specimens prospectively collected from patients with ACC (n=19), and benign adrenal tumors (n=46) were analyzed by unbiased liquid chromatography/mass spectrometry to discover diagnostic metabolites. Creatinine-normalized features were analyzed by Transomics, SIMCA, and false discovery rate adjusted unpaired t-test, and screened for an area under the cure (AUC) > 0.8. Features were identified through fragmentation patterns and database searches, and were quantified on an independent platform. An independent set of urine
specimens were collected prospectively from patients with ACC (n=12) and benign adrenal tumors (n=45) for validation.

**RESULTS:** Sixty-seven features discriminated ACC and benign adrenal tumors. Among the features, 4 metabolites were identified: creatine riboside (elevated 2.09-fold in ACC, p=0.0001), tryptophan (elevated 3.05-fold in benign adrenal tumors, p<0.0001), Nε,Nε,Nε-trimethyllysine (elevated 1.84-fold in benign adrenal tumors, p<0.0001), and 3-methylhistidine (elevated 3.01-fold in benign adrenal tumors, p=0.0003). Multivariate analysis showed the 4 metabolites combined with an AUC of 0.89, sensitivity of 94.7%, specificity of 82.6%, positive predictive value of 69.2%, and negative predictive value of 97.4%. Of the 4 metabolites, creatine riboside was validated in an independent cohort.

**CONCLUSIONS:** Urine specimens from patients with ACC have distinct metabolomes. Four metabolites—creatine riboside, Nε,Nε,Nε-trimethyllysine, 3-methylhistidine, and tryptophan—were identified as biomarkers. In an independent cohort, creatine riboside was verified.