characterized by increased CD90 expression and ALDHA1 activity. We identify phenotypically distinct cellular subsets in well-differentiated PanNETs and provide evidence for the stem-like properties of the CD90hi cell fraction. All PanNETs analyzed express CD47, a "don't eat me" signal co-opted by cancers to evade innate immune surveillance. Furthermore, we demonstrate that blocking CD47 signaling promotes engulfment of tumor cells by macrophages in vitro and inhibits tumor growth and prevents metastases in vivo.

CONCLUSIONS: Our findings provide a foundation for developing therapeutic strategies that eliminate tumor initiating cells in PanNETs and show how deep examination of individual cases can lead to potential therapies.

Is Multifocality an Indicator of Aggressive Behavior in Small Bowel Neuroendocrine Tumors?

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INTRODUCTION: Simultaneous development of multiple small bowel neuroendocrine tumors (SBNETs) suggests either significant environmental exposure with field cancerization or genetic predisposition. Whether the biologic behavior of tumors developing in this context are more aggressive than those seen in patients with solitary SBNETs is unknown. The objective of this study was to determine the incidence of multifocal SBNETs, and compare clinicopathologic factors, survival, and somatostatin receptor (SSTR2) expression with these from patients with unifocal SBNETs.

METHODS: Clinicopathologic variables from 135 patients with SBNET who were managed surgically at 1 institution were collected. Statistical comparisons were made using Welch's *t*-test, Wilcoxon rank sum test, and chi-square. Survival was assessed using the Kaplan-Meier method. Expression of SSTR2 was analyzed in resected tumors by quantitative PCR.

RESULTS: Forty-four percent of SBNETs were multifocal. When tumors were multifocal, the median number of primaries was 6 (range 2−129). Demographic and disease factors such as sex, grade, TNM stage, presence of distant metastases, preoperative serotonin levels, and postoperative hormone response were not significantly different between groups. Progression-free (PFS) and overall survival (OS) were not influenced by multifocality (median PFS 2.5 years for multifocal, 2.8 years unifocal, $p = 0.79$; median OS not reached for multifocal, 10.5 years unifocal, $p = 0.36$). There was no difference in mean SSTR2 expression (Table).

CONCLUSIONS: Multifocal SBNETs are common, but their etiology is unknown. Patient and tumor factors were similar between those with multifocal and unifocal tumors, and multifocality does not predict more aggressive disease or portend diminished survival. Similarities in SSTR2 expression suggests equal efficacy of somatostatin analogues.

Table. Comparison of key Indicators in Multifocal vs Unifocal Primary SBNETs

Variable	Multifocal (n=59)	Unifocal (n=76)	p Value
Sex: F, n (%)	20/59 (34)	35/76 (46)	0.21
Median size of largest primary, cm	1.8	2	0.22
Grade: G1/G2, n (%)	44/44 (100)	54/55 (98)	1
Tumor stage T3/T4, n (%)	40/59 (68)	46/76 (61)	0.49
Nodal stage: N1, n (%)	55/59 (93)	67/76 (88)	0.49
Metastasis stage: M1, n (%)	47/59 (80)	65/76 (86)	0.50
Distant metastases (non-liver, non-LN) , n (%)	26/59 (44)	39/76 (51)	0.50
Elevated preoperative serotonin, n (%)	52/54 (96)	59/66 (89)	0.28
SSTR2 mean expression (ΔCT; n=58)	3.10	2.84	0.59

Is There a Minimum Case Volume of Thyroidectomies Associated with Superior Outcomes? An Analysis of 37,118 Cases in the US

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INTRODUCTION: The surgeon volume-outcome association has been established for many procedures, including thyroidectomy; however, a threshold number of cases defining a high-volume surgeon remains unclear. Our aim was to determine the minimum number of total thyroidectomies (TT) per surgeon/year that is associated with superior outcomes.

METHODS: Adult patients undergoing TT were identified from the Nationwide Inpatient Sample, 1998-2009. Multivariable modeling with restrictive cubic splines was used to examine the association between a minimum number of annual TT/surgeon and complications and costs.

RESULTS: Among 37,188 TT cases, 48% had thyroid cancer and 52% benign disease. 6% experienced complications. After adjustment for patient and disease characteristics, the likelihood of experiencing a complication decreased with increasing surgeon volume up to 32 cases/year ($p<0.01$), followed by no further improvement. Increasing surgeon volume was associated with decreasing inflation-adjusted costs up to 29 cases/year (-$344, $p<0.0001$). Eighty-six percent of patients had surgery by low-volume surgeons (<32 cases/year). Median annual surgeon volume was just 7 cases (range 1-157 cases). There were no differences in patient demographic, clinical, and pathologic characteristics between those who had surgery by low- vs high-volume surgeons; patients undergoing surgery by low-volume surgeons were more likely to experience complications (6% vs 4%, $p<0.0001$).

CONCLUSIONS: This is the first study to identify a surgeon volume threshold (32 thyroidectomies/year) that is associated with improved patient outcomes. Identifying a threshold number of

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: CD44 is enriched in anaplastic thyroid cancer (ATC) and is a marker for thyroid cancer stem cells (CSCs). Recent studies in basal breast cancer demonstrate that small ubiquitin-like modifier (SUMO)-conjugated TFAP2A maintains CD44 expression and that SUMO inhibition clears CSCs. We evaluated the effects of SUMO pathway inhibition in ATC.

METHODS: 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 PIAS1 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