children admitted with DKA, those with pump failure were primarily older (60% above age 12), mostly white (63%), female (57%), from urban areas (78%), and almost 2/3rds had private insurance (60%). Adjusted analyses revealed that compared to DKA admissions without pump failure, pump failure was associated with older age, white race, residing in a rural area, private insurance, and higher income. Pump failure admissions were more likely in western and southern hospitals, otherwise there were no significant differences with respect to hospital characteristics. Compared to DKA admissions without pump failure, DKA admissions associated with pump failure had a longer mean length of stay (2.6 vs 1.5 days) and were more likely to have a higher severity of illness category. Conclusion: In this national sample, DKA with pump failure was more often observed among white, privately insured and high income children; these patient characteristics likely reflect the population of youth with diabetes who are more likely prescribed pumps in the US. Admissions for DKA concurrent with insulin pump failure accounted for a minority of pediatric DKA admissions but these admissions were associated with longer lengths of stay and severity of illness. Pump failure has important implications for care and management of children with diabetes.

**Thyroid**

**THYROID NEOPLASIA AND CANCER**

**Positive Predictive Value of TP53 Variants in Bethesda III/IV Thyroid Fine-Needle Aspirates**

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**MON-LB88**

**Introduction:** Somatic DNA variants in the tumor suppressor gene TP53 have been reported in papillary thyroid carcinoma (PTC), Hurthle cell carcinoma (HCC), poorly differentiated thyroid cancer (PDTC), and anaplastic thyroid carcinoma. However, TP53 variants are uncommon among cytologically indeterminate thyroid nodules, so their positive predictive value (PPV) for malignancy, when identified, is unknown. The original Afirma Xpression Atlas reported genomic variants from the mRNA of 511 genes, including TP53. Here we report the PPV of TP53 alterations among Afirma Genomic Sequencing Classifier (GSC) Suspicious Bethesda III/IV nodules in real-world clinical practice.

**Methods:** A consecutive cohort of Afirma GSC Suspicious Bethesda III/IV nodules submitted to Veracyte for molecular analysis and positive for only TP53 alterations by the Xpression Atlas was identified. Local surgical pathology diagnoses were sought with IRB approval. One nodule per patient was included.

**Results:** Thirty-eight TP53 variants were present among >13,000 Bethesda III/IV Afirma GSC Suspicious samples. Among the 22 with only a TP53 alteration, the first 16 consecutive nodules were included (7 nodules were Bethesda III and 9 nodules were Bethesda IV). Local surgical pathology diagnoses were available for 11 of these nodules. Seven nodules (64%) were malignant on surgical pathology: 3 cases of HCC, 1 PDTC, 1 follicular thyroid carcinoma (FTC), 1 follicular variant PTC, and 1 classical PTC. The mean size of malignant nodules was 3.6 cm (range 1.7-7.7 cm). The remaining four nodules (36%) were benign on surgical pathology, with a mean size of 2.6 cm (range 1.5-4.2 cm). Benign cases included 2 follicular adenomas (FA), 1 Hürthle cell adenoma (HCA), and 1 adenomatoid nodule (AN). Seven different TP53 variants were identified, and only one was observed at least 3 times (TP53: p.R248Q in 2 cases of HCC and 1 adenomatoid nodule). Given the small numbers, meaningful estimates of the variants’ individual PPVs could not be calculated.

**Conclusions:** TP53 variants among Afirma GSC Suspicious Bethesda III/IV nodules are very rare and associated with malignancy in 64% of nodules based on local pathology review. A broad range of both benign and malignant neoplasms, including HCC, PDTC, FTC, PTC, FA, HCA, and AN, were reported among nodules with TP53 alterations. The prognostic value of finding an isolated TP53 variant in Afirma Suspicious nodules remains unknown.

**Thyroid**

**THYROID NEOPLASIA AND CANCER**

**The Initial Dose of 131I as a Potential Independent Predictor for Residual/Relapsed Disease in Pediatric Differentiated Thyroid Cancer**

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**MON-LB83**

**Introduction:** In the guidelines for management of pediatric Differentiated Thyroid Cancer (DTC) 131I therapy is recommended for treatment of iodine-avid persistent locoregional disease that cannot be resected as well as iodine-avid distant metastases. To date, no consensus has been reached regarding the 131I dose for treatment of DTC in children. We report our institutional experience and highlight the initial dose of 131I as a potential independent predictor of residual/relapsed disease.

**Methods:** We performed a retrospective analysis of all pediatric patients diagnosed with DTC between 2010 and 2018. The cohort included all patients up to 21 years of age, with minimal length of follow-up of 24 months. The risk stratification was done following the American Thyroid Association guidelines for pediatric DTC. We defined residual/relapsed disease as detectable thyroglobulin and positive anatomical lesions in imaging studies during the follow-up period. The log-rank test was used to evaluate disease-free survival. The P value was set at < 0.05.

**Results:** Among 59 eligible patients, females were 69.5% (n=41) and males were 30.5% (n=18). The mean age at diagnosis was 16 years (9-21 years). All patients were alive at follow-up (median, 42 months; range 24 to 144 months).
Fifty-eight patients had classic papillary thyroid cancer (PTC) and only 1 patient had follicular thyroid cancer. Among the patient with PTC, 39.6% (23/58) had follicular variant PTC, 8.6% (5/52) had diffuse-sclerosing PTC and 17.2% (10/58) had other variants. Nineteen (32%), 30 (51%), and 10 (17%) had low-risk, intermediate-risk, and high-risk disease, respectively.

Within the Low-risk group, 68% (13/19) received 131I. The mean initial dose was 60.9 mCi [26-150 mCi]. Eighty four percent (11/13) received ≤100 mCi and 27% (3/11) had residual/relapsed disease. Fifteen percent (2/13) received >100 mCi and none had residual/relapsed disease. Sixteen percent (1/6) of patients without 131I therapy had residual/relapsed disease. (P=0.48)

Within the Intermediate-risk group, all 30 patients received 131I. The mean initial dose was 97.5 mCi [27.3-215 mCi]. Sixty percent (18/30) received ≤100 mCi and 38.8% (7/18) had residual/relapsed disease. Forty percent (12/30) received >100 mCi and 16.6 % (2/12) had residual/relapsed disease. (P=0.15)

Within the High-risk group all 10 patients received 131I. The mean initial dose was 159.9 mCi [129.3-384 mCi]. Fifty percent (5/10) received ≤150 mCi and 60% (3/5) had residual/relapsed disease. Fifty percent (5/5) received >150 mCi and 20% (1/5) had residual/relapsed disease. (P=0.2)

Conclusion: There are no statistical differences of disease-free rate between the initial dose of 131I among all risk categories. However, the use of more than 100 mCi in the intermediate-risk category and more than 150 mCi in the high-risk category may be recommended.

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Translational Feasibility of Steroidogenic Factor-1 Antagonists as a Novel Targeted Therapy for Adrenocortical Cancer
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SUN-LB23
Adrenocortical carcinoma (ACC) is an aggressive cancer with devastating outcomes. ACC is usually locally advanced or metastatic at diagnosis and, despite tumor resection plus chemotherapy, has a high rate of recurrence. The 5-year survival rate among metastatic ACC patients is less than 15%. ACC responds poorly to the single FDA-approved drug, mitotane, which is non-specifically adrenolytic and highly toxic. Other chemotherapy regimens tested have been unsuccessful in improving overall survival. Steroidogenic factor-1 (SF-1 or NR5A1) is an orphan nuclear receptor essential for growth and development of the adrenal gland and is the major, active transcription factor in ACC (1,2). To address the need for a targeted therapy in ACC, we have identified potent small molecule SF-1 antagonists that block SF-1 transcriptional activity through the ligand-binding domain (IC50 = 15-20 nM in a CHO cell reporter assay). In short-term dissociated cell cultures established from SJ-ACC3 (3), a pediatric ACC patient-derived tumor xenograft (PDX), the SF-1 antagonists OR-907S and OR-070 blocked DNA synthesis as measured by inhibition of EdU incorporation in SF-1+ cells (IC50 = 500-600 nM, >80% efficacy at 10 μM) whereas OR-907R, the 100-fold less potent enantiomer of OR-907S, is nearly inactive. Because the SF-1 antagonist sensitivity of the dissociated SJ-ACC3 cells declines markedly with repeated passage of the PDX in immunocompromised (C.B-17 SCID) mice, we have utilized an alternative model system for evaluating tumor target engagement and growth inhibition: the rat Leydig tumor cell line (R2C), which is growth-inhibited by the SF-1 antagonists OR-907S and OR-070 in vitro (IC50 = 60-100 nM) and as a xenograft in immunocompromised mice (CD-1 nude). The SF-1-responsive gene signature identified by RNaseq in R2C cell cultures by comparison of OR-907S and OR-07R was replicated by OR-070 and other orally-bioavailable lead antagonists in R2C xenografts following 3 days of dosing, indicating engagement of SF-1 by these compounds. Significantly, R2C tumors were growth-inhibited following daily oral dosing for 4 weeks with OR-070 (10-30 mg/kg). These findings suggest that SF-1 antagonists could be a targeted therapy for ACC. OR-070 has >30% oral bioavailability in rat and dog, indicating that this structural class of SF-1 antagonists has potential for clinical development.References: (1) Mohan, et al., Curr. Opin. Endocrinol. Metab. Res., 2019; 8:72; (2) Corces, et al., Science, 2018; 362:eaav1898; (3) Pinto, et al., Clin. Cancer Res., 2013; 19:1740.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY

Loss of GLP-2R Signaling Activates Hepatic Stellate Cells and Exacerbates Diet-Induced Steatohepatitis in Mice
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SAT-LB101
A GLP-2 analogue is used in individuals with intestinal failure at risk for liver disease, yet the hepatic actions of GLP-2 are not understood. Treatment of high fat diet (HFD)-fed mice with GLP-2 did not modify the development of hepatosteatosis or hepatic inflammation. In contrast, Glp2r−/− mice exhibited increased hepatic lipid accumulation, deterioration in glucose tolerance, and upregulation of biomarkers of hepatic inflammation. Both mouse and human liver expressed the canonical GLP-2R, and hepatic Glp2r expression was upregulated in mice with hepatosteatosis. Cell fractionation localized the Glp2r to hepatic stellate cells (HSC), and markers of HSC activation and fibrosis were increased in livers from Glp2r−/− mice. Moreover, GLP-2 directly modulated gene expression in isolated HSCs ex vivo. Taken together, these findings define an essential role for the GLP-2R in hepatic adaptation to nutrient excess and unveil a gut hormone-HSC axis, linking GLP-2R signaling to control of hepatic stellate cell activation.

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