Abstracts

** Denotes Resident/Fellow Research Award Competition Paper*

NOTE: Author listed in **BOLD** *is the presenting author*

NOTES

Abstracts

***1.** ROUTINE PROPHYLACTIC CENTRAL LYMPH NODE DISSECTION FOR LOW-RISK PAPILLARY THYROID CANCER: A COST-EFFECTIVENESS ANALYSIS

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Background: Routine prophylactic central lymph node dissection (PCLND) following total thyroidectomy (TTX) for low-risk papillary thyroid cancer (PTC) offers the potential to decrease disease recurrence but may increase the rate of surgical complications. We hypothesized that routine PCLND is not cost-effective in low risk PTC.

Methods: A Markov transition-state decision model was used to compare the cost-effectiveness of TTX with and without PCLND from the societal perspective. Treatment outcome probabilities and their corresponding utilities were estimated based on literature review. Effectiveness was measured in quality-adjusted life years (QALYs). Costs were estimated using Medicare reimbursement data and the Nationwide Inpatient Sample. A 3% annual discount rate was applied to all future costs and QALYs. The threshold for cost-effectiveness was defined as an incremental cost-effectiveness ratio of less than $100,000/QALY. Sensitivity analysis and a 1,000 iteration Monte Carlo simulation were used to examine the uncertainty of cost, probability, and utility estimates in the model.

Results: The expected cost of the TTX with PCLND strategy was $10,291 with an effectiveness of 23.786 QALY. This strategy was more costly and less effective than TTX without PCLND, making TTX without PCLND the dominant strategy. PCLND became cost-effective during one-way sensitivity analysis when the lifetime probability of recurrence increased from 6% to 11.6% or the cost of reoperation for recurrence increased from $8,900 to $37,200. PCLND became cost-effective during two-way sensitivity analysis when the added probabilities of RLN injury and hypoparathyroidism due to PCLND were less than 0.04% and 0.05% respectively. The model was not sensitive to life expectancy, the quality adjustment utility factors for RLN injury or hypoparathyroidism, the additional cost of PCLND, or the relative risk reduction of PCLND on recurrence. During Monte Carlo simulation, TTX without PCLND was cost effective in 99.0% of the iterations and the dominant strategy in 83.4% of the iterations whereas TTX with PCLND was cost-effective in 1.0% of iterations and dominant in 0.1% of the iterations.

Conclusion: Routine PCLND for low risk PTC is not cost-effective unless the recurrence rate is greater than 11.6%. Selective application of PCLND should be individualized based on risk of recurrence, RLN injury, and hypoparathyroidism.

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***2.** A PROSPECTIVE EVALUATION OF SURGEON-PERFORMED TRANSCUTANEOUS LARYNGEAL ULTRASONOGRAPHY IN ASSESSING VOCAL CORD FUNCTION BEFORE AND AFTER THYROIDECTOMY

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Introduction: Although direct laryngoscopic examination of the vocal cords (VCs) is important before and after thyroidectomy, it generally causes patient discomfort and adds medical cost. Recent studies have suggested transcutaneous laryngeal ultrasound (TLUSG) could be an alternative to direct laryngoscopy (DL) in assessing preoperative and postoperative VC function. A prospective study was conducted to examine the accuracy of TLUSG in VC function before and after thyroidectomy and to evaluate the value of TLUSG as a screening tool for selective DL.

Methods: After appropriate consent, 204 consecutive patients underwent TLUSG the day before and a week after elective thyroidectomy. To reduce assessment bias, before examination, the surgeon performing the TLUSG was unaware of the patient's voice quality. During examination, passive and active movements of the true and false VC were recorded. All TLUSG was performed by one endocrine surgeon using standardized technique. Immediately afterwards, patients underwent DL by an independent endoscopist unaware of the TLUSG finding. Both TLUSG and DL findings were graded according to the extent of VC movement (Grade I = "both VCs with full or normal movement", Grade II = "at least 1 VC with reduced movement" and Grade III = "at least 1 VC with no movement"). Patients with grade II or III on DL were defined as having VC paresis or palsy (VCP). To calculate the accuracy of TLUSG, the TLUSG findings were correlated with DL findings.

Results: On DL, no patient had preoperative VCP while 17 patients had unilateral postoperative VCP. Altogether 331 nerves were at-risk and the overall postoperative VCP rate was 5.1%. TLUSG was unable to clearly visualize and assess VCs in 11 (5.4%) patients. Of these, 2 had VCP while 9 had no VCP on DL. Compared to DL, TLUSG had a test sensitivity, specificity, positive predictive value and negative predictive value of 14/15 (93.3%), 174/178 (97.8%), 14/18 (77.8%) and 174/175 (99.4%), respectively. Of the 175 patients with grade I on TLUSG, only 1(0.6%) patient turned out having a grade II VCP while the rest (99.4%) had grade I on DL.

Conclusion

TLUSG clearly assessed VC function in 193/204 (94.6%) patients undergoing thyroidectomy. Hypothetically, if we use TLUSG as a screening tool and select DL only for patients with grade II / III or unassessable VCs on TLUSG, the total number of perioperative DL could potentially be reduced by 85.8% with 1 (0.6%) asymptomatic / grade II VCP missed.

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***3.** OBSERVATION OF THE CLINICALLY NEGATIVE CENTRAL COMPARTMENT LYMPH NODES IN PAPILLARY THYROID CARCINOMA

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Introduction: The role of elective central neck dissection (CND) in the management of papillary thyroid cancer (PTC) is controversial. Proponents highlight high rates of occult nodal metastasis with implications for both post-surgical staging and adjuvant therapy. Our institutional approach has been to perform CND only when disease is suspected based on pre- or intra-operative evaluation of the central neck. The aim of this study is to report our experience of an observational approach to the clinically N0 neck in PTC.

Methods: Following IRB approval, the records of 1129 consecutive patients presenting with M0 PTC, who had total thyroidectomy for resectable disease between 1986-2005 were identified from our institutional database. The group was stratified by nodal status. 470 patients (42%) had pathological nodal metastases (pN1), 384 (34%) had nodes removed without metastases (pN0) and the remaining 275 patients (24%) had no nodal tissue removed (Nx). The Nx group formed our study cohort.
Patient, tumor and treatment characteristics were recorded and compared by Chi squared test. Local, regional or distant recurrences were counted if identified on clinical, ultrasonographic, radioiodine scan, or biochemical assay, with or without cytopathologic confirmation.

Results: With a median follow up of 70 months (range 1-275 months), the 10 year DSS in the Nx group was 100%, and no patients required further surgery on the central neck.

Four patients had suspicion of local recurrence on subsequent RAI scan. All were treated with RAI and are currently considered free of disease. Five patients were considered to have regional recurrence. Three had biopsy proven lateral neck disease and underwent neck dissection, one of who also recurred in the lung. Of the remaining 2 patients 1 had a low level detectable thyroglobulin and 1 had a sub-centimetre level VI neck node suspicious for recurrence which has been observed. Two further patients developed pulmonary metastases.

The 10 year local, regional and distant recurrence rates were 2%, 3% and 2% respectively.

Conclusion: Our results suggest that properly selected patients, without pre- or intra-operative evidence of nodal disease, who are observed, have low rates of recurrence and excellent survival. Despite the fact that these patients are likely to have a significant rate of occult micrometastasis, such patients can safely be managed with observation of the central neck rather than CND.

NOTES

***4.** IMPACT AND TIMING OF BILATERAL ADRENALECTOMY FOR UNCONTROLLABLE ACTH-DEPENDENT CUSHING'S SYNDROME

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Background: Reluctance to perform bilateral adrenalectomy(BA) for ACTH-dependent Cushing's syndrome(CS) from an untreatable primary source may result in worsening metabolic derangements and increased adverse events(AE). We hypothesized that post-BA patients(pts) would have better metabolic parameters and fewer deaths due to steroid excess than pts treated with steroidogenesis inhibition(SI) alone.

Methods: Data from pts with ACTH-dependent CS from an uncontrollable source treated between 1970-2012 were retrospectively reviewed by treatment group(SI or SI+BA). Validated severity scales were used to calculate a metabolic(M) score(hypokalemia, hyperglycemia, hypertension, proximal muscle weakness) and an AE score(thrombosis, fracture, infection, treatment-related AEs).

Results: 65 pts were included(16 pituitary, 49 ectopic); 21(32%) were treated with SI+BA and 44(68%) with SI alone. Presenting M scores and source of ACTH excess(ectopic vs. pituitary) were similar, but SI+BA pts had lower initial AE scores(p=0.04), likely due to selection bias. Both groups improved metabolically after treatment. However, post-SI+BA pts with resolution of CS had significantly lower M and AE scores than post-treatment scores in SI pts(p=0.02, p=0.01). SI+BA pts received SI pre-BA for a median of 7.8 mos(range 0.8-46.4). Of the SI+BA pts who had AE between presentation and BA, 39% occurred within 12 mos after presentation. 24(55%) of SI pts died with a median survival of 24.0 mos; steroid excess contributed to 71%. 6 deaths(29%) occurred in the SI+BA group; 3 of the 18 pts(17%) with sustained resolution of CS died of cancer-related causes(median 7.1 mos after BA). The others were alive at median follow up of 32.4 mos. Three pts had recurrent CS after BA(14%); all 3 died(2 related to steroid excess) at a median of 33.0 mos follow up. Minor perioperative complications occurred in 7 pts.

Conclusions: Post-treatment M and AE scores improved for SI, and to a greater extent, SI+BA pts. More than a third of AEs occurred in SI+BA pts preoperatively within 12 mos of presentation, emphasizing the importance of early surgical intervention. In addition, BA was associated with minimal complications. The majority of deaths in the SI group were related to steroid excess. Most SI+BA pts experienced sustained resolution of CS after BA; the few deaths in this group were related to primary disease. These data argue for the safety and efficacy of early BA in selected pts with uncontrollable CS.

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***5.** METABOLIC PHENOTYPING OF NEUROENDOCRINE TUMORS
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Background: Identification of novel tissue-based diagnostic biomarkers is one of the priorities for improving the management of neuroendocrine tumors (NET). We applied a personalised metabonomic phenotyping strategy as part of a pilot study to define metabonomic signatures that not only allow to discriminate malignant from non-malignant condition, but also to distinguish subgroups of NET.

Methods: Twenty six patients with NET (10 small bowel, 11 pancreas and 5 others) and 6 healthy individuals as controls were prospectively recruited (M:F = 19:7, mean age 52 years, range 27-80). Urine samples were subjected to 1H Nuclear Magnetic Resonance (NMR) profiling using a Bruker Avance 600MHz spectrometer (Bruker, Rheinstetten, Germany). Acquired spectral data were imported into SIMCA (v.13.0.1, Umetrics AB, Sweden) and MATLAB (v.7.12.0.635, MathWorks, USA) statistical software packages for supervised and unsupervised multivariate analysis using principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) respectively. Univariate analysis was performed by ANOVA.

Results: PLS-DA of small bowel NET demonstrated clear metabolic class separation from non-small bowel NET and from healthy controls (R2Y = 0.90, Q2Y = 0.58) with 100% sensitivity and specificity. Orthogonal PLS-DA of urine from small bowel NET and other NET also predicted class separation (R2Y = 0.92 , Q2Y = 0.15), with a high specificity (85.7%) and low sensitivity (20%). The gut microbial co-metabolite hipurate strongly correlated with the healthy control group (P<0.0001). Metabolites such as creatinine, methylhistidine and homocysteine and unknown metabolites (ppm 2.27 (m)) correlated with small bowel NET vs other NET.

Conclusions: Metabonomic analysis suggests that subgroups of NET may possess an individualised metabolic phenotype. Moreover, this approach represents a novel diagnostic strategy that may provide valuable insights into the aetiology and biological behaviour of NET. Our results suggest that metabonomic profiling could provide novel biomarkers for NET.

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***6.** PROSPECTIVE SCREENING AND WHOLE EXOME-SEQUENCING RESULTS IN FAMILIAL NON-MEDULLARY THYROID CANCER

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Background: Approximately 8% of non-medullary thyroid cancers are familial when two or more first-degree relatives are affected. It is unknown who and at what age individuals at risk of familial non-medullary thyroid cancer (FNMTC) should undergo screening. The aim of this study was to determine the first age of onset of thyroid cancer and nodule in at risk family members and to determine the inheritance pattern for FNMTC.

Method: Kindreds with FNMTC, defined as two or more first-degree relatives affected, were enrolled in a prospective study. Every family member at risk was screened by thyroid ultrasound and in two families whole-exome sequencing was performed. The whole-exome sequencing data was analyzed in affected parent-child pairs using the unaffected parent-child pairs to identify candidate susceptibility gene(s) and altered pathways.

Results: Thirteen kindreds with FNTMC underwent screening across three generations. The overall prevalence of a thyroid nodule(s) >5mm was 42% at screening; with nodules present in 31% of the second generation and in 75% of the anterior generation (anterior to index case generation). The youngest age a thyroid nodule was detected was 10 years old, and the youngest age at diagnosis of thyroid cancer was 18 years old. On screening ultrasound, presence of thyroid nodule microcalcification was associated with a significantly higher risk of cancer ($p<0.05$). Compared to index cases, subsequent family members diagnosed with thyroid cancer by ultrasound screening were diagnosed at a younger age (35 vs 47 years, $p<0.05$) and had lower rates of extrathyroidal invasion ($p<0.05$).

Whole exome sequencing of germline DNA in two families identified 31 nonsynonymous single-nucleotide polymorphisms (SNPs) in common in affected members and which could result in protein damage. Parent-offspring analysis of these SNPs showed alterations in genes involved in the p53 and bladder cancer pathway.

Conclusion: In FNMTC, at risk first-degree relatives should be screened with a thyroid ultrasound at the age of 10 years or older and this should include the anterior generation to the index case. The use of such a screening strategy may result in earlier diagnosis. Multiple SNPs in genes in carcinogenesis may be involved in FNMTC.

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***8.** CLINICAL UTILITY OF IMMUNOHISTOCHEMISTRY FOR THE DETECTION OF THE BRAF V600E MUTATION IN PAPILLARY THYROID CARCINOMA

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Background: BRAF V600E mutation is the most common genetic alteration in papillary thyroid cancer (PTC). This mutation is sometimes associated with an aggressive phenotype. We utilized a novel mutation-specific antibody for immunohistochemical (IHC) detection of the BRAF V600E mutation and correlated this with clinicopathological features. The study was designed to validate the accuracy of IHC detection of the BRAF V600E mutation and determine the clinical significance of the extent of staining.

Methods: A single-center prospective study analyzing 793 patients who underwent thyroid surgery for PTC from 2008-2011 was performed. 52 consecutive patients who underwent thyroid surgery for PTC were selected for DNA mutation testing for BRAF V600E. 40 were BRAF V600E positive and 12 were BRAF mutation negative. The same paraffin-embedded, formalin-fixed PTC samples were used to create tissue microarrays (TMA), with 3 cores from each sample. TMAs were analyzed using a novel BRAF V600E mutant-specific antibody for IHC. TMAs were scored on a standard intensity (0-3), proportion (0-100%) scale by a single pathologist who was blinded to the BRAF status of each sample. Tumors with intensity <1 and staining proportion <20% or non-specific staining were considered negative. Positively staining tumors (majority displayed >80% proportion) were then stratified into 3 intensity categories: <1, 1-2, >2. The 3 categories were assessed for clinicopathologic variables including age, extrathyroidal extension, lymphovascular invasion, and regional lymph node metastases.

Results: The BRAF V600E mutation-specific antibody showed a sensitivity of 90% and specificity of 100% for detecting the presence of the BRAF V600E mutation. With respect to the intensity of IHC staining, tumors with IHC intensity>2 were significantly more likely to have extrathyroidal extension ($p<0.05$). There was no difference in incidence for any of the other clinicopathologic variables.

Conclusions: IHC is a specific and sensitive method for the detection of the BRAF V600E mutation in thyroid cancer and may be an accurate, rapid, easily applicable and potentially cost effective alternative to standard molecular techniques. Furthermore, it may serve as a better predictor of tumor behavior. Findings from the current study support the potential use of IHC as a diagnostic and prognostic tool for thyroid cancer.

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***10.** GASTRIC INHIBITORY POLYPEPTIDE RECEPTOR: A FUTURE ALTERNATIVE TO SOMATOSTATIN TYPE 2 RECEPTOR IMAGING AND TREATMENT IN NEUROENDOCRINE TUMORS?

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Background: Somatostatin type 2 receptors (SSTR2) are expressed in 80-90% of neuroendocrine tumors (NETs). Ligands binding SSTR2 are effective for imaging, symptom control, and radioreceptor therapy of these tumors. However, SSTR-directed imaging is negative in 25% of cases, and not all patients respond to octreotide injections or radiotherapy. The aim of this study was to evaluate the expression of new NET target genes relative to SSTR2.

Method: RNA was extracted from primary tumors, matched normal tissue, and lymph node and liver metastases collected at surgery from NET patients at one center. Relative expression was assessed by quantitative PCR for SSTR2 and 12 genes previously found to be overexpressed in NETs (GIPR, BRS3, OPRK1, DRD1, GPR98, GRM1, SCTR, ADORA1, GPR113, OXTR, MUC13, MEP1B). Mean threshold cycles were normalized to GAPDH and POLR2A internal controls to determine expression levels (dCT). Results were compared by Welch two-sample t-test.

Results: Small bowel (SBNETs; 53 primaries, 30 liver, 43 nodal mets) and pancreas (PNETs; 38 primaries, 9 liver, 11 nodal mets) NETs were tested. Expression of SSTR2 in tumors was high (dCT=2.4, sd=2.2), and was 3-fold greater in tumor compared to normal tissue. Relative to normal tissue, tumor expression was increased for GIPR, BRS3, OPRK1, GRM1, GPR113, and OXTR by 14, 11, 21, 20, 5, and 44-fold, respectively. These fold-increases were significantly greater than those of SSTR2 ($p<0.01$). Yet compared to SSTR2, absolute expression in primaries was significantly lower for all of these genes except GIPR ($p<0.001$). GIPR expression was comparable to SSTR2 in tumors (dCT 3.1, sd=2.7 vs. 2.4, $p=0.2$), but had 8-fold lower expression in normal tissue than SSTR2 (dCT 7.2, sd=4.3 vs. 4.2, sd=1.9, $p<0.001$). Expression of SSTR2 and GIPR was similar in both PNET and SBNET primaries ($p=0.8$ and 0.6), and was not significantly higher in metastases than in primary tumors ($p=0.1$ and 0.5).

Conclusions: Compared to SSTR2, the genes BRS3, OPRK1, GRM1, GPR113, and OXTR show a greater difference in expression between normal and NET tissue, but have significantly lower absolute expression. GIPR, however, shows expression levels similar to SSTR2 in both primaries and metastases, with greater differential expression vs. normal tissue than SSTR2. Based on these favorable expression characteristics, we conclude that GIPR warrants study as an alternative or synergistic target for imaging and therapeutic strategies in NET patients.

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11. ADRENALECTOMY FOR SOLID TUMOR METASTASES: RESULTS OF A MULTI-CENTER EUROPEAN STUDY.

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Background: The adrenal glands are common sites of metastases and their removal may improve survival. However, most of the reported data are based on small and heterogeneous patient cohorts. We have evaluated the results of metastatic adrenalectomy based on a multi-center European survey.

Method: Multi-center retrospective study based on data from 30 European institutions. All consecutive patients registered at each participating institution were considered eligible provided the existence of pathological report confirming metastatic disease and the adrenal gland was completely removed.

Results: Data from 317 patients who underwent metastatic adrenalectomy since 1999 to 2011 were evaluated. The mean age was 58,9410.6 yr, and 223 (70.3%) were male. Primary tumor was lung (NSCLC) in 148, colorectal in 60, renal in 37, and Other in 72 patients. Adrenal metastases were synchronous (≤ 6 months) in 73 patients (23%), and isolated in 213 patients (67.2%). Laparoscopic resection was used in 161 patients (50.8%). Surgery was limited to adrenal gland in 231 cases (72.9%) and according to resection R0 was achieved in 274 (86.4%), R1 in 25 (7.9%) and R2 in 5.7%.

With a median follow-up of 20 months (0-190), 97 (30.6%) patients are alive w/o disease, 56 (17.7%) alive with disease and 164 (51,7%) have died.
The median DFI was 29 mo. (95%CI: 25-35), and for the whole cohort overall survival (OS) rates at 2, 5 and 10 years were 54.9 %, 35.4 % and 24.2% respectively. Patients with kidney primaries had a better OS (median 84 months, 95%CI: 32-136) as compared to those with NSCLC (median: 26 months, 95%CI: 22-30), colorectal tumors (median: 27 months, 95%CI:15-39) or other tumors (median: 24 months, 95%CI: 16-32) (p=0.015). OS was also improved for patients with metachronic disease (median: 30 months (95%CI: 19-41) compared to those with synchronic metastases (median: 23 months, 95%CI:15-31),(p=0.038). Patients with isolated metastases also had more prolonged survival compared to those with more disseminated disease, (p=0.030).

Conclusion: Surgical removal of adrenal metastases is associated to long-term survival in eligible patients. Patients with renal primary, metachronic disease and isolated adrenal metastases seems to have more favorable outcomes.
Based on these premises we believe adrenalectomy may be offered to all patients eligible in which a multidisciplinary intention-to-treat approach is possible.

NOTES

***12.** MIR-34A AND MIR-483-5P ARE CANDIDATE SERUM BIOMARKERS FOR ADRENOCORTICAL TUMORS

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Background: Adrenal incidentalomas are common and many patients with nonfunctioning tumors undergo an adrenalectomy to exclude an adrenocortical carcinoma (ACC) diagnosis. Recent molecular characterization studies have identified consistently altered microRNAs in ACC as compared to benign adrenocortical tumors but their applications to diagnose ACC is limited as most do not recommend that these tumors should be biopsied. Circulating microRNAs are emerging as novel and noninvasive biomarkers for a variety of human cancers. The objective of this study was to determine the feasibility and diagnostic accuracy of measuring serum circulating microRNAs dysregulated in ACC.

Method: Five microRNAs were selected from microRNA profiling studies in ACC (mir-let-7d, -34a, -195, -214, and 483-5p). A microRNA enriched column purification system was used to extract total microRNA from serum samples in patients with adrenal neoplasms. The levels of microRNAs in serum were measured by quantitative RT-PCR. A diagnosis of benign or malignant adrenocortical tumors was confirmed by pathology. A Mann-Whitney test ($p<0.05$) was used to compare microRNA expression level normalized to mir-16. The area under the ROC curve (AUC) was used to measure the diagnostic accuracy for the circulating microRNAs.

Results: Serum samples from 22 patients with cortical adenomas (n=22) and 17 patients with ACC (n=17) were analyzed. We found high mir-16 levels in all serum samples, a microRNA ubiquitously present in serum. All 5 microRNAs were also detected in all the serum samples. We found significantly higher levels of miR-34a ($p=0.001$) and miR-483-5p ($p=0.011$) in patients with ACC. The AUC for miR-34a was 0.81 and for miR-483-5p was 0.74.

Conclusion: For the first time, we show microRNAs which are altered in adrenocortical tumors are detectable in human serum samples from patients with adrenocortical tumors. Moreover, miR-34a and miR-483-5p are candidate serum biomarkers for distinguishing between benign and malignant adrenocortical tumors.

NOTES

***13.** THE INCIDENCE OF UNDIAGNOSED AND UNRECOGNIZED PRIMARY HYPERPARATHYROIDISM: A POPULATION BASED ANALYSIS FROM THE ELECTRONIC MEDICAL RECORD

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Background: When primary hyperparathyroidism (PHPT) is recognized, a review of the medical record typically reveals elevated calcium and/or parathyroid hormone (PTH) values have been present for long periods of time. The purpose of this study is to examine the electronic medical record (EMR) of a large health system to gain insight into the incidence of undiagnosed and unrecognized PHPT.

Methods: A health system EMR containing 6.5 million patients was queried. To exclude referral bias, only patients with a primary care physician in the hospital system were examined, reducing our population to 2.7 million patients. This group was queried for all patients with outpatient serum calcium values greater than 10.5 mg/dL. A 2 year sample was selected as a study group for further analysis.

Results: Of 2.7 million patients with primary care physicians located within the health system, 54,198 patients (2%) were found to have hypercalcemia (>10.5 mg/dL). In our 2 year sample of 7,269 hypercalcemic patients, only 1.3% had a recorded diagnosis of PHPT. Of the remaining patients, the EMR search revealed PTH was measured in 2,808 patients (39%), while PTH was not measured in 4,366 patients (60%). Of those patients with PTH measured, 1,786 patients (64%) had PHPT (PTH >30 pg/mL). For those patients without PTH obtained, a detailed chart review was done on 200 randomly selected patients to determine if hypercalcemia was most likely due to PHPT. Eighty-eight percent of these patients had calcium levels of 10.6-11 mg/dL, 9% had calcium levels of 11.1-11.5 mg/dL, and 2% had calcium levels of 11.6-12 mg/dL with 27-36% of each group estimated to have PHPT. Only 1% of patients had calcium greater than 12 mg/dL with just 11% estimated to have PHPT. The overall incidence of PHPT in the study population was 46%.

Conclusions: In our study population, the incidence of documented and estimated PHPT was higher than commonly reported (approximately 1%). In hypercalcemic patients, only 40% had PTH levels checked and 60% never had a PTH obtained, 26% of whom were likely to have PHPT. This study underscores the importance of evaluation of even mild hypercalcemia, as 1/3 of these patients have PHPT.

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***14.** CLINICAL AND THERAPEUTIC IMPLICATIONS OF SPROUTY2 FEEDBACK DYSREGULATION IN BRAF V600E PAPILLARY THYROID CANCER

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Background: BRAF V600E (BRAF+) is the most common genetic aberration in papillary thyroid cancer (PTC). This mutation activates the MAPK/ERK pathway and is thought to confer an aggressive phenotype. However, the clinical presentation of BRAF+ PTC varies from indolent to aggressive. Thus other phenotype determining factors are involved. We have shown that expression of Sprouty2 (SPRY2), a negative feedback regulator of the MAPK/ERK pathway, is increased in BRAF+ PTCs and that the feedback mechanism is intact. We also demonstrated that the expression of SPRY2 varies in BRAF+ PTCs. We hypothesize that the level of SPRY2 expression contributes to MAPK/ERK pathway output and accounts for the clinical heterogeneity in BRAF+ PTCs. The level of SPRY2 expression in the context of MAPK/ERK pathway output may be more predictive of the clinical behavior of BRAF+ PTC.

Methods: We developed a tissue microarray (TMA) with 30 BRAF+ PTCs with control thyroid tissue. The TMA was analyzed for SPRY2 expression and MAPK/ERK output (pMEK, pERK). These data were studied in the context of clinicopathologic factors (size, extrathyroidal extension, lymphovascular invasion etc.) to develop a risk stratification system more predictive of the biology of the tumor. To establish a functional role for SPRY2 we developed a stable recombinant lentiviral SPRY2-shRNA, silencing SPRY2 and increasing MAPK/ERK pathway output in BRAF+ PTC cells. We then treated these SPRY2 silenced cells with MAPK/ERK pathway inhibitors and assessed for growth effects.

Results: BRAF+ PTCs with intact feedback pathway, increased SPRY2 expression resulting in decreased MAPK/ERK output (n=4), do not exhibit lymph node metastases. Whereas, all BRAF+ PTCs with decreased SPRY2 expression and decreased MAPK/ERK output (n=8) have nodal metastasis. When SPRY2 is silenced the BRAF+ PTC cells are significantly more sensitive (10x) to MAPK/ERK inhibition. This provides a potential therapeutic and predictive role of SPRY2 in BRAF+ PTC.

Conclusions: Our model suggests that PTC behavior is dependent on both the driver of the MAPK/ERK pathway and its regulatory feedback. When the feedback pathway is intact the tumor phenotype seems to be less aggressive. This model offers novel explanations for the observed heterogeneity and has the potential to identify an unrecognized role of feedback regulation in PTC behavior and progression. This has a direct and important clinical implication and may alter our treatment strategies.

NOTES

***15.** PATIENTS WITH FOLLICULAR AND HURTHLE CELL MICROCARCINOMAS HAVE COMPROMISED SURVIVAL: A POPULATION LEVEL STUDY OF 22,738 PATIENTS

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Background: Patients with papillary thyroid microcarcinoma (mPTC, <1cm) usually have excellent outcomes. There is a scarcity of evidence outside of small single institution series regarding outcomes of patients with follicular thyroid microcarcinoma (mFTC) and Hurthle cell microcarcinoma (mHCC) (<1cm); optimal treatment for these tumors remains unclear.

Methods: Demographic, clinical and pathologic characteristics of patients with follicular and Hurthle cell microcarcinomas, together (mFHCC), were compared with mPTC in the SEER database, 1988-2009, using 2 tests and ANOVA. Disease-specific survival was calculated with the Kaplan Meier method, and its association with predictors using log-rank tests and Cox proportional hazards.

Results: 564 cases of mFHCC (371 mFTC and 193 mHCC) and 22,174 cases of mPTC were identified. The annual incidence rate of mFHCC increased from 4.0 per 10 million in 1988 to 7.5 per 10 million in 2009, representing an annual percentage change of +0.29% (Ptrend=0.289). mFHCC tumors were larger than mPTC on average (6.3 mm vs. 5.3 mm, P<0.001). They had lower rates of nodal metastases (9.6% vs. 33.4% mPTC, P<0.001), but mFHCC was more than eight times more likely to present with distant (extracervical) metastases than mPTC (4.1% vs. 0.5%, P<0.001). Disease-specific survival was decreased in mFHCC compared to mPTC (10-year survival 95.4% vs. 99.3%, respectively, P<0.001). There was no difference in survival for patients who underwent total thyroidectomy vs. thyroid lobectomy. After adjustment, follicular or Hurthle cell histology was independently associated with increased mortality (hazard ratio [HR] 5.3, P<0.001), as were age ≥ 65 years (HR 9.1, P=0.011), extrathyroidal extension (HR 9.5, P<0.001), and necessitating external beam radiation (HR 35.6, P<0.001). Five-year disease-specific survival in patients who have 0, 1, or 2 risk factors with mFHCC stratified by age ≥ 65 years and extrathyroidal extension was 99.2%, 95.1%, and 83.3%, respectively.

Conclusions: mFHCC is rare but presents more often with distant metastases, and patients have compromised survival compared to mPTC. This is most marked for older patients and those who have tumors with extrathyroidal extension. Patients with thyroid nodules ≤ 1cm in size and a cytologic diagnosis of follicular or Hurthle cell neoplasm should undergo thyroid lobectomy, which may be therapeutic if there are no other indications for total thyroidectomy.

NOTES

***16.** RASSF1A HYPERMETHYLATION AS A PUTATIVE MOLECULAR PROGNOSTIC MARKER IN PAPILLARY THYROID CARCINOMA

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Background: The role of epigenetic alterations in the genesis and prognosis of papillary thyroid carcinoma (PTC) is unclear and their potential to direct medical and surgical management remains unknown. Epigenetic silencing of the tumor suppressor RASSF1A via DNA methylation has previously been demonstrated in PTC. However, a quantitative assessment of RASSF1A promoter hypermethylation, the histopathologic implications of RASSF1A downregulation, and the utility of RASSF1A DNA methylation as a molecular prognostic predictor remain unexplored.

Methods: Analysis of RASSF1A gene expression in PTC (n=26) and normal (n=6) thyroid tissue was performed using quantitative PCR (qPCR) following methylation-dependent and –sensitive restriction enzyme digestion to generate a Hypermethylation Index (HMI). HMI was then evaluated for correlation with tumor histology, size, AJCC stage, focality, lymphovascular invasion, extracapsular extension, and lymph node metastases.

Results: RASSF1A promoter hypermethylation demonstrated an HMI 5.3x greater in PTC versus normal thyroid tissue (p=0.014). HMI was significantly higher in multifocal versus unifocal PTC (p=0.022). Furthermore, elevated HMI correlated with lymphovascular invasion and tumor size, especially in follicular variant PTC; however, these differences did not reach statistical significance (p=0.111 & p=0.166, respectively).

Conclusions: RASSF1A promoter hypermethylation is significantly elevated in PTC and seems to associate with multifocality, lymphovascular invasion, and larger tumor size. Thus, RASSF1A may serve as a prognostic marker of more aggressive PTC. The ease of evaluating single gene DNA methylation status with small amounts of DNA (i.e. – the amount obtained during routine fine-needle biopsy) suggests a potential role for RASSF1A as a future molecular prognostic marker in PTC.

NOTES

***17.** HURTHLE CELL CARCINOMA: AN UPDATE ON SURVIVAL OVER THE LAST 35 YEARS

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Background: Hurthle Cell Carcinoma (HCC) of the thyroid is thought to be a variant of Follicular Thyroid Carcinoma (FTC). A low incidence and lack of long-term follow-up data have caused controversy regarding the survival characteristics of HCC. While some believe HCC has a worse prognosis than FTC, there are also data showing similar survival rates between the two cancers. In this study we aimed to clarify this controversy by analyzing HCC survival over a 35-year period using the Surveillance, Epidemiology, and End Results (SEER) database.

Method: We extracted 35 years of HCC and FTC cases from the SEER 9 database (from 1/1/75 to 12/31/09) and stratified the data by gender, age (≤45 and >45), stage, and race. We determined 5 and 10-year survival rates by constructing life tables using actuarial methods. Kaplan-Meier survival curves were compared with the log-rank test. We compared changes in survival over time by grouping cases into 5-year intervals. We used the Z-test to compare the equivalence of relative survival of these 5-year intervals.

Results: We identified 1416 cases of HCC and 4973 cases of FTC in the SEER 9 database. For cases diagnosed from 1975-1980, HCC showed a significantly worse survival profile compared to FTC [5-year: 75%(95%CI(60.2-85)) vs. 88.7%(95%CI(86-90.8)); 10-year: 66.7%(95%CI(51.5-78.1)) vs. 79.7%(95%CI(76.5-82.6))]. For cases diagnosed from 2004-2009 we found no difference in 5 or 10-year survival between HCC and FTC [5-year: 91.1%(95%CI(87.6-93.7)) vs. 89.1%(95%CI(86.5-91.2)); 10-year: 80.9%(95%CI(75.6-85.2)) vs. 83.9%(95%CI(80.8-86.6))]. Correspondingly, over the course of the entire 35-year period, HCC showed a steady improvement in survival [Change in 5-year survival: +16.1%; 10-year: +14.2%]. Conversely, FTC survival rates remained stable over the entire study period [Change in 5-year survival: +0.4%; 10-year: +4.2%]. The improvement in HCC survival was observed for both males and females, in age ≥45 years, for all stages, and among whites specifically.

Conclusion: We found that 35 years ago survival of HCC was worse than FTC survival. However, HCC survival has improved dramatically over time such that today HCC and FTC survival rates are now statistically the same. These findings explain how various studies over the last 4 decades have shown conflicting results regarding HCC survival but our data do not explain why HCC survival has improved so dramatically. This should be a topic of continued investigatio

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***18.** THE RELATIONSHIP BETWEEN CHRONIC LYMPHOCYTIC THYROIDITIS AND CENTRAL NECK LYMPH NODE METASTASIS IN PATIENTS WITH PAPILLARY THYROID CARCINOMA

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Background: Several studies have reported that concurrent chronic lymphocytic thyroiditis (CLT) and papillary thyroid carcinoma (PTC) is associated with improved prognosis, including decreased lymph node metastasis. In the largest cohort of patients reported to date, we sought to assess the relationship of CLT and central nodal metastasis (CNM).

Methods: We retrospectively studied 495 consecutive patients who underwent a thyroidectomy for PTC with at least one lymph node excised. Pathology reports designated the presence or absence of CLT. Lab, operative and cervical ultrasound reports were reviewed. Covariates from a multivariate regression were used to develop a model of predicted probabilities of CNM based on age, sex, tumor size, suspicious level VI nodes on ultrasound, and CLT.

Results: Of the 495 patients, 391 (79%) were female, 226 (45.7%) had concurrent CLT and 220 (44.4%) had CNM. The CLT group had more females (88% vs. 71.4%, P<0.001), a younger average age (43 years vs. 47 years, P=0.03), a lower incidence of CNM (35% vs. 52.4%, P<0.001), a lower incidence of lymphovascular invasion (21.0% vs. 29.7%, P=0.02), and a higher incidence of pT1a (40.3% vs. 25.3%, P<0.001) and pT1b (37.6% vs. 29.0%, P<0.001) tumors than the PTC only group. A larger proportion of patients with concurrent CLT used thyroid hormone supplementation prior to surgery compared to the PTC only group (32.7% vs. 5.4%, P<0.001). Thyroid hormone supplementation prior to surgery was found to have an 83.9% PPV for predicting CLT on final histopathology. Among patients with conventional PTCs, those with CLT exhibited a lower incidence of CNM than those without CLT (36.5% vs. 57.1%, P<0.001). For pT1a tumors, the incidence of CNM was significantly lower in the CLT group than in patients with PTC only (17.6% vs. 39.7%, P=0.002). Multivariate analysis showed that the presence of CLT was associated with a 55% decreased odds of CNM after adjusting for age, sex, tumor size, and suspicious level VI nodes on ultrasound (OR 0.45, 95% CI:0.22-0.91, P=0.03). Predicted probability modeling showed that all women with CLT and no suspicious level VI nodal ultrasound findings had a 9-11% risk of CNM with pT1a tumors and a 27-31% risk with pT1b tumors.

Conclusion: Female patients of all ages with CLT and T1a tumors have the lowest incidence of CNM of all patients with PTC. In this patient population, the practice of routine prophylactic central compartment neck dissection may have the least utility.

NOTES

***19.** A MULTI-INSTITUTIONAL INTERNATIONAL STUDY OF RISK FACTORS FOR HEMATOMA AFTER THYROIDECTOMY

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Background: Bleeding is the most dangerous complication following thyroidectomy, but its risk factors remain poorly understood. We conducted an international case-control study to determine the risk factors for hematoma.

Method: We identified 170 patients who developed a hematoma requiring return to the operating room following thyroidectomy from 11 institutions in 3 countries. Each patient was compared to 3 institution-matched controls over the same time period.

Results: The median time to identification of the hematoma was 6 hours. Eighty-three percent of hematoma patients returned to the operating room within 24 hours of their index operation. On univariate analysis, patients with a hematoma were older ($p=0.03$), had a larger thyroid by mass ($p=0.02$), more operative blood loss ($p<0.01$), higher postoperative blood pressures ($p<0.01$) and a lower body temperature ($p=0.02$) than controls. Additionally, they were more likely to have a bilateral thyroidectomy ($p=0.01$), preoperative anticoagulant use (<0.01), thyroiditis ($p<0.01$), COPD/asthma ($p=0.04$), use of hemostatic agents ($p<0.01$), smoking ($p=0.04$), and have a drain placed (0.03).

On multivariate analysis, the independently predictive variables were preoperative anticoagulation (OR=18.60), perioperative steroids (OR=5.12), thyroiditis (OR=3.27), smoking (OR=3.19), bilateral thyroidectomy (OR=2.12), elevated postoperative systolic blood pressure (OR=1.02) and higher operative blood loss (OR=1.01).

Conclusion: Several risk factors were independently predictive of postoperative hematoma. Most patients who developed a hematoma presented within 24 hours of thyroidectomy. Surgeons should consider close overnight observation for patients with an increased risk of this life-threatening complication.

NOTES

***20.** THE ROLE OF SURGERY FOR RECURRENT AND METASTATIC ADRENOCORTICAL CANCER

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Background: Adrenocortical cancer (ACC) often recurs locally and with distant metastases despite complete surgical resection. The efficacy of chemotherapy and adjuvant treatment are limited, and the role of surgery for recurrent disease is not well-established. We sought to demonstrate the survival and palliative benefit of surgery for recurrent ACC and identify predictive factors of successful surgery.

Methods: A review of all patients undergoing surgery for ACC from 1980-2010 at a single tertiary care center was performed. We compared surgery to other treatments including chemotherapy, radiation therapy, and interventional procedures.

Results: We identified 164 patients who had surgery for ACC, of whom, 125 patients had a complete resection (R0). Recurrence occured in 93 (74%) of these R0 patients at a median time of 15m (range = 1.5-150 m). Symptoms at recurrence were present in 71% (66/93) of patients including pain (34%) and hormone excess (43%). The sites of recurrence included locoregional (22), liver (26), lung (28), and other sites (29). There were 67 patients that underwent 115 surgical procedures while 26 patients had only non-operative therapy or no intervention for recurrence. Forty-eight of 67 patients had complete resection for recurrence. Patients undergoing surgery for recurrence had a longer overall survival compared to those undergoing non-surgical management or no therapy (65 m vs. 6 m, $p < 0.01$). Median survival for non-operatively managed patients (226d) and those undergoing no therapy (179d) was shorter than for patients undergoing debulking procedures (1272d) $p=0.002$. Complete resection of recurrence ($p=0.005$) and a disease free interval > 6 m (<0.001) were associated with survival after operative intervention while original size ($p=0.47$), grade ($p=0.8$), and stage ($p=0.23$) of tumor were not predictive. Symptoms of pain and those associated with hormone excess improved in 84.4% of patients undergoing surgery compared to 29% of non-surgically managed patients ($p=0.005$). Debulking had similar symptomatic improvement as R0 resection ($p=0.52$).

Conclusion: Patients with recurrent ACC can benefit from surgical intervention with improvement in survival and overall symptoms. Patients with a disease free interval of greater than 6 m and locoregional or oligometastatic recurrence are more likely to benefit from surgery, but the near universal improvement in symptoms may expand the criteria for surgery in patients with recurrent ACC.

NOTES

***21.** RECALCITRANT HYPOCALCEMIA AFTER THYROIDECTOMY IN PATIENTS WITH PREVIOUS ROUX-EN-Y GASTRIC BYPASS

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Background: Hypocalcemia is a known potential complication after thyroidectomy. Oral calcium supplementation may be inadequate in patients with malabsorptive enteric anatomy after roux-en-Y gastric bypass (RYGB). Such patients may develop symptomatic hypocalcemia requiring intravenous (IV) calcium and prolonged hospitalization after thyroidectomy. This complication is poorly described in the literature including only case reports and there is no current consensus on optimal post-thyroidectomy management in this unique population. The present study seeks to further describe this potential complication.

Methods: All patients from 2000-2012 undergoing thyroidectomy and having history of preceding RYGB were indentified retrospectively using a multi-institutional research patient data repository. Each of the 19 patients meeting inclusion criteria were matched 2:1 for age, gender, and BMI at initial operation. Cases were compared to controls with univariate analysis for the following outcomes: symptomatic post-operative hypocalcemia, requirement of IV calcium supplementation, and length of hospital stay (LOS).

Results: Average age, proportion of female patients, and BMI were equivalent between cases (n=19) and controls (n=38). Comparison of primary outcomes demonstrate the study group had a significant increase in incidence of symptomatic hypocalcemia (42% vs 0%, $p<0.001$), administration of IV calcium (21% vs 0%, $p<0.01$), and LOS (2.16 vs 1.23 days, $p=0.02$). Increase LOS in all cases within the study group was attributable to symptomatic hypocalcemia. One patient in the study cohort was readmitted with muscle spasm secondary to hypocalcemia.

Conclusions: This study demonstrates that patients with previous RYGB may be subject to symptomatic hypocalcemia after thyroidectomy and that this hypocalcemia may be recalcitrant to oral calcium supplementation, requiring supplemental intravenous calcium with prolonged hospitalization. The pathophysiology is likely multifactorial including relative hypoparathyroidism in the setting of malabsorptive enteric anatomy and metabolic bone disease. In this patient population, recalcitrant postoperative hypocalcemia should be anticipated, calcium levels should be closely monitored and early calcium and vitamin D supplementation should be preemptively initiated.

NOTES

***22.** COST-ANALYSIS OF THYROID LOBECTOMY AND INTRAOPERATIVE FROZEN SECTION VS. TOTAL THYROIDECTOMY IN PATIENTS WITH A CYTOLOGICAL DIAGNOSIS OF 'SUSPICIOUS FOR PAPILLARY THYROID CANCER'

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Background: The optimal initial surgical management of a patient with a single thyroid nodule diagnosed as 'suspicious for papillary thyroid cancer (PTC)' on fine-needle-aspiration biopsy (FNA) is unclear. The intent of this study was to determine the incremental cost-utility of thyroid lobectomy with intraoperative frozen section (FS) or total thyroidectomy at initial surgery.

Methods: Cost-utility analysis was performed for a hypothetical cohort of adult patients with a cytologic diagnosis of 'suspicious for PTC' on FNA. Patients in the decision tree model underwent either initial total thyroidectomy (TT), or thyroid lobectomy with intraoperative FS and, depending on these results, completion thyroidectomy at the initial procedure or at a later time (TL). Patients continued in the model for 12 months. The incremental cost-utility ratio (ICUR), measured in U.S. $/quality-adjusted-life-year (QALY), was determined from the societal perspective and was considered to be cost-effective at a $50,000/QALY threshold. Input data were obtained from the literature and Medicare. Sensitivity analyses were performed for all relevant clinical inputs.

Results: In the base-case, TT and TL cost $6,216 and $6,510, respectively, with comparable QALYs (0.979 vs. 0.982). The base-case ICUR of TL was $100,235/QALY, strongly favoring TT as a more cost-effective modality given the minimal difference in patient utility. Sensitivity analyses demonstrated that the model was most sensitive to the accuracy of FS and to the rate of recurrent laryngeal nerve (RLN) injury. TL becomes cost-effective only if both FS and final pathology are benign in ≥91% of patients with preoperative suspicion for PTC (ICUR $56,892/QALY at 91%; ICUR $7,537/QALY at 100%). With increasing rates of unilateral (>5%) or bilateral (>2%) RLN injury with TT, TL becomes more cost-effective ($55,536 and $53,594/QALY, respectively).

Conclusions: In our model, TT at the time of initial surgery was the most cost-effective treatment for patients with a single thyroid nodule suspicious for PTC on FNA. Cost-utilities were dependent on rates of RLN injury and accuracy of FS and final pathology. Our results strongly support TT as the treatment of choice in these patients; TL is preferred only when complications reach unacceptable levels. This finding will likely be reproduced in other areas of specialty cancer/endocrine surgery and is important in the current efforts to develop accountable care organizations.

NOTES

***23.** PROSPECTIVE ANALYSIS OF CORONARY CALCIUM IN PATIENTS ON DIALYSIS UNDERGOING A NEAR-TOTAL PARATHYROIDECTOMY .

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Background: Patients with secondary hyperparathyroidism (HPT) and on dialysis are more likely to die of cardiovascular disease than the general population; and we have reported that near-total parathyroidectomy (NTPTX) reduces that mortality rate. Patients on dialysis experience accelerated vascular calcification, particularly in their coronary arteries with an average of a 15% increase in coronary calcification yearly. Cardiac CT enables objective measuring of coronary calcium quickly with low radiation exposure. The purpose of our study was to determine the impact of NTPTX on coronary artery calcium score (CACS).

Method: Sequential chest computed tomography for CACS measurement was performed in patients with CKD-5D before and after NTPTX between 11/2001 to 3/2008. Demographics, morbidities, CACS, outcomes, surgical findings, intact parathyroid hormone (PTH) measurements preoperatively, intraoperatively, and postoperatively in follow-up (mean = 5.1 years, range 2.4-11 years) were maintained in an IRB approved prospective database. 19 of 31 (61.3%) patients returned for a follow-up coronary CT.

Results: Preoperative mean PTH level and CACS were 1794 4 943 pg/ml and 979 4 1079, respectively; and postoperatively PTH and CACS were 321 4 244 pg/ml ($p<0.001$) and 1285 4 1577 ($p=0.044$), respectively. CACS was stable or reduced (<10% per year) in 14 of 19 patients (73.7%) and 42% of patients (n=8) had nearly undetectable (<1% per year) change in CACS after NTPTX. Only 1 patient had >15% increase in CACS, but CACS increased >10% per year in 5 patients. In patients with stable CACS, mean post-op PTH was 251.3 vs. 516.2 pg/ml in patients with increasing CACS; $p=0.02$. In patients with recurrent HPT (PTH>400) as compared to patients with stable post-operative PTH, CACS increased by 804 4 1081.9 vs. 16.2 4 84.1; $p = 0.01$.

Conclusions: Successful NTPTX with durable post-op PTH levels is associated with stabilization of CACS in patients with severe secondary hyperparathyroidism undergoing hemodialysis. This stabilization of CACS could contribute towards the improved survival seen after NTPTX.

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***24.** ONCOLYTIC VESICULAR STOMATITIS VIRUS AS A TREATMENT FOR NEUROENDOCRINE TUMORS

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Background: Therapeutic goals for neuroendocrine tumors (NETs) not amenable to surgical cure are limited to relieving symptoms and slowing disease progression. However, many cancer cells acquire defects in antiviral responses as homeostatic mechanisms are shifted away from antiviral signaling toward growth and proliferation. These changes make a variety of tumors attractive targets for oncolytic viral therapy. Therefore, we explored the ability of recombinant wild-type vesicular stomatitis virus (rwt-VSV) and its attenuated M protein mutant (M51R-VSV) to exploit defective antiviral pathways in NETs and subsequently result in cell death.

Methods: Viral infectivity of H727, UMC-11, and CNDT2.5 human NET cell lines was evaluated using green fluorescent protein (GFP) encoded M51R-VSV and flow cytometry. We tested the lethality of rwt-VSV and M51R-VSV with MTS assays at different times following inoculation with various multiplicities of infection (MOIs). We evaluated -interferon (-IFN) pathways in our panel of NETs by testing IFN production and defining the impact of exogenous IFN on viral susceptibility. Murine xenografts of human NETs were treated with a single intratumoral injection of M51R-VSV to study viral efficacy in vivo.

Results: Flow cytometry revealed viral GFP activity in >99% of tumor cells within 24 hours of M51R-VSV inoculation, thereby indicating that cell lines supported both viral infection and protein synthesis. Moreover rwt-VSV and M51R-VSV were able to kill >95% of cells within 3 days of inoculation, even at MOIs less than 1 pfu/cell. Thus NET cells succumbed to the oncolytic effects of VSV and released active viral progeny upon death. NET cells did not produce significant amounts of -IFN in response to infection, but pretreatment with exogenous -IFN protected cells from viral oncolysis in a dose dependent manner. Treatment with M51R-VSV resulted in significant tumor shrinkage compared with tumor growth in mock-infected xenografts after 10 days for H727 tumors (-27416% vs 144421%, $p<0.001$) and UMC-11 tumors (-5748% vs 33418%, $p<0.001$). Mice displayed no evidence of toxicity following injection with M51R-VSV.

Conclusions: VSV infects and kills human NETs by exploiting an inability to produce a type I antiviral response. M51R-VSV is safe and effective in vivo, and is therefore an excellent candidate for the treatment of advanced NETs. Furthermore, the work described herein provides a fundamental framework for future clinical trials.

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***25.** MINORITY RULES: 10% TALL CELLS CONFER THE AGGRESSIVE FEATURES OF THE TALL CELL VARIANT OF PAPILLARY THYROID CARCINOMA

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Background: The tall cell variant of papillary thyroid carcinoma (PTC) is generally recognized as being more aggressive than classical PTC. However, the percentage of tall cells necessary to make the diagnosis has been debated, with current values ranging from 30-70% of the tumor and lower percentages being classified as only having tall cell features. We hypothesize that the presence of tall cells, independent of percentage, confers a more aggressive histopathology.

Methods: A prospectively maintained database at a single tertiary referral center was reviewed to identify all cases from January 1998 through May 2011 that had a diagnosis of the tall cell variant of PTC or PTC with tall cell features. Tumor characteristics and recurrence were compared to a control group of classic PTCs. An endocrine pathologist who was blinded to the final diagnosis reviewed all cases to determine the percentage of tall cells in each tumor.

Results: One hundred fifteen cases of PTC were reviewed including 44 cases that had previously been diagnosed as having tall cell features or being the tall cell variant of PTC, and 71 cases of classic PTC. Eighty-seven cases (76%) had at least 10% tall cells in the tumor, and 28 cases (24%) had no tall cells. Sixty one percent of the cases previously defined as classic PTC were reclassified as they had some tall cells present, but would not have met criteria for diagnosis of tall cell variant. There were no differences in age, sex, and size between tumors with any tall cells and those with no tall cells. Tumors with greater than or equal to 10% tall cells had significantly more extrathyroidal extension (48.4% vs. 25.0%, $p = 0.041$), angiolymphatic invasion (16.1% vs. 0%, $p = 0.030$), and lymph node involvement (67.7% vs. 32.1%, $p = 0.003$) than tumors with no tall cells. There were more recurrences (9.7% vs. 3.6%, $p = 0.43$) in patients with greater than or equal to 10% tall cells compared to classic PTC, but this was not significant. These findings are maintained with increasing percentages of tall cells in the tumor.

Conclusion: There are no differences between PTC with tall cell features versus the tall cell variant; however, there are significant differences between tumors with tall cells and those that are classic PTC. Papillary thyroid carcinomas with as little as 10% tall cells should be considered as aggressive as the tall cell variant.

NOTES

***26.** LOWERING DOSES OF RADIOIODINE FOR REMNANT ABLATION DOES NOT INCREASE STRUCTURAL RECURRENCE RATES IN PAPILLARY THYROID CARCINOMA

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Background: Recent studies suggest that equivalent rates of ablation can be achieved using low doses of radioiodine (RAI) after total thyroidectomy for the treatment of papillary thyroid carcinoma (PTC). However the effect of lower dose RAI on the rate of PTC recurrence remains unclear. The aim of this study was to compare the rate of structural recurrence between patients receiving low dose and high dose RAI.

Methods: A retrospective cohort study of patients undergoing surgery and RAI for PTC was undertaken. The primary outcome measure was the rate of recurrence requiring re-operative surgery. Secondary outcome measures were the proportion of patients with stimulated thyroglobulin (Tg) < 2ng/ml and the use of recombinant TSH (rTSH). Two patient groups were compared; Group A which received low dose RAI at initial ablation and Group B treated with traditional high dose RAI (>3GBq).

Results: 1072 patients having total thyroidectomy with or without lymph node dissection for PTC in the period 1980-2012 were followed for a mean of 60 months. The mean age was 46yr and tumor diameter was 19mm. Group A comprised 156 (15%) patients treated with low dose RAI at initial ablation. In Group A 150 (97%) of patients had pT1-pT3 tumors. Group B comprised 790 (74%) patients treated with high dose RAI. 126 patients received no RAI. The mean cumulative dose of RAI was 2.4GBq for Group A and 6.6GBq for group B ($p<0.001$). The overall rate of recurrence requiring re-operative surgery was 3.7%. Structural recurrence rates for Group A and B were 2% and 4% respectively and not significantly different ($p=0.16$). Disease free survival stratified on tumor size at 5yr was 100% for Group A and 97% for Group B and equivalent ($p=0.2$). The commonest site of local recurrence was in the lateral neck compartment (62%), followed by nodal recurrence in the central compartment (28%). On multivariate analysis extrathyroidal extension of the primary tumor was the major factor predicting local recurrence, hazard ratio 3.1 ($p=0.007$). The risk of structural recurrence was not increased by the use of low dose RAI ($p=0.26$), or rTSH ($p=0.85$). The proportion of patients with Tg<2ng/ml at final follow up was equivalent between Group A and B adjusted for tumor size.

Conclusion: In patients with pT1-pT3 PTC, low doses of RAI at initial ablation do not increase the risk of structural recurrence requiring re-operation.

NOTES

***27.** THE IMPACT OF SURGICAL VOLUME ON OUTCOMES OF PATIENTS UNDERGOING THYROID SURGERY FOR BENIGN AND MALIGNANT CONDITIONS

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Background: Total thyroidectomy (TT) is perceived to have a low complication rate with excellent outcomes. We aimed to evaluate the association between the indications for surgery on patients' outcomes after TT, and examine the impact of surgical volume on these findings.

Methods: The nationwide inpatient sample (NIS) was used to identify all patients who underwent TT from 2000-2009, using ICD-9 procedure codes. Patients who underwent additional neck dissection were excluded. Indications for surgery, clinical and demographic characteristics, co-morbidities and postoperative complications were collected along with surgeon volume and hospital characteristics to predict patient outcomes. Surgeries were stratified into four groups according to surgeon volume, unknown, low (<10 surgeries), intermediate (10-99) and high (>100). Univariate and multivariate analysis were used to examine the effect of Graves' disease on outcomes after Surgery.

Results: 46,261 patients were included in this analysis. The majority of procedures, 23,027 (50%), were performed for benign thyroid disease. TT was performed for thyroid malignancy in 20,371 (44%) patients and 2,863 (6.3%) for Graves' disease. Patients with Graves' disease had the highest postoperative complications (17.5%) compared to patients undergoing TT for benign (13.9%) and malignant (13.2%) thyroid disease, who had an equivalent rate of complications (p=0.001). After stratification by surgeon volume, Graves' disease was a significant predictor of postoperative complications among surgeries performed by low and intermediate volume surgeons ($p<0.05$). However, Graves' disease was not a significant predictor for postoperative complications when performed by high volume surgeons (p=0.81).

Conclusion: Surgery for Graves' disease is associated with a higher risk of complications when it is performed by less experienced surgeons. This finding should prompt recommendations for increasing surgical specialization and referrals to high volume surgeons in the management of Graves' disease.

NOTES

***28.** EFFECT OF RE-OPERATION ON OUTCOMES IN PAPILLARY THYROID CANCER
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Background: The influence of lymph node recurrences of papillary thyroid carcinoma (PTC) on overall prognosis is uncertain. We performed a population-based longitudinal analysis of the association between re-operation and mortality.

Methods: Patients with a diagnosis of PTC were abstracted from the California Cancer Registry database (1999-2008). These patients also had an initial surgery for PTC abstracted from the Office of Statewide Health Planning and Development database (inpatient records 1999-2008, outpatient records 2005-2008). Re-operation was defined as any lymph node dissection (LND) following initial thyroidectomy. Multivariate logistic regression was applied to assess the association of re-operation with all-cause mortality and disease-specific mortality.

Results: Initial surgery for PTC was performed on 12,078 patients during the study period. Re-operations were performed in 231 patients (1.9%). The median time to re-operation was 266 days, with 58.4% and 84.0% of re-operations being performed within 1 and 2 years of initial surgery, respectively. The mortality rate from PTC was 2.2% (271 patients). Patients who died from PTC had a median survival time of 23 months. Adjuvant radioactive iodine therapy (RAI) was administered to 64% of patients and had no influence on the rate of re-operation. However, RAI was associated with reduced all-cause mortality (OR = 0.70; $p<0.0001$) and disease-specific mortality (OR = 0.55; $p<0.0001$). After adjusting for age, gender, tumor size, comorbidity, stage, and RAI, re-operation was associated with an increased rate of all-cause mortality (OR, 1.72; 95% CI, 1.11-2.69; $p<0.0163$) and disease-specific mortality (OR, 3.20; 95% CI, 1.90-5.39, $p<0.0001$).

Conclusion: Re-operation is independently associated with mortality in PTC. This raises the question of whether preventing lymph node recurrence by optimizing initial surgical management would improve outcomes.

NOTES

***29.** ATTRIBUTABLE COSTS OF DIFFERENTIATED THYROID CANCER IN THE ELDERLY MEDICARE POPULATION

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Background: Although long-term survival of patients with differentiated thyroid cancer (DTC) is common, little is known about the cost attributable to the disease and follow-up care. The objective of this study was to use data from the Surveillance Epidemiology and End Results (SEER) database to study costs attributed to the stage of disease, treatment options, and recurrence of DTC in the elderly, as well as the cumulative cost of the disease over five years.

Method: We identified non-HMO patients aged 66 years or older diagnosed with DTC between 1995-2005. The final sample included 2,761 with DTC and 422,259 non-HMO noncancer comparison group cases without thyroid cancer taken from the SEER 5% Medicare sample and matched by a propensity score calculated from age, gender, race/ethnicity, and comorbidities. Costs were payments made by Medicare for all-cause medical treatments. Using the Bang and Tsiatis method, cumulative costs were estimated at 1 and 5 years by estimating average costs for each patient in each month up to 60 months following diagnosis. Total costs were weighted sums of monthly costs, where weights were the inverse probability that the patient was not censored. Using the Lin method, multivariate analyses of costs were performed by fitting each of the 60 monthly costs to linear models that controlled for demographic characteristics and comorbidities. Marginal effects of covariates on 1- and 5-year costs were obtained by summing the coefficients for months 1-12 and months 1-60, respectively. Confidence intervals were obtained by bootstrapping.

Results: Cumulative total costs for DTC patients were $15,048 per patient in the first year following diagnosis and $41,373 per patient in the first 5 years following diagnosis. Disease stage was a significant determinant of costs. Patients with regional disease incurred higher costs at 1 year ($9,612, 95% CI: $6,703-12,725) and 5 years ($9,521, 95% CI: $3,670-$15,437). Patients with distant disease incurred costs of $28,059 (95% CI: $20,357-36,345) at 1 year and costs of $21,264 (95% CI: $9,615-32,130) at 5 years. Compared to surgery alone, patients undergoing both surgery and radiation incurred higher costs at 1 year ($13,380, 95% CI: $6,817-20,138) and 5 years $21,495 (95% CI: $10,359-33,886).

Conclusion: Well-differentiated thyroid cancer in the elderly is associated with significant economic burden that is largely attributable to patient demographics, stage of disease, and treatment modalities.

NOTES

31. A NOVEL OPTICAL APPROACH TO INTRAOPERATIVE DETECTION OF PARATHYROID GLANDS

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Background: Inadvertent or accidental removal of parathyroid glands is a recognized challenge in endocrine surgery. Existing methods for identifying parathyroid glands are limited in their applicability and sensitivity, rendering them inadequate for intra-operative guidance. Thus there is a critical need for a diagnostic tool that provides sensitive, real-time detection of parathyroid glands during thyroidectomies and parathyroidectomies. We have developed an intraoperative technique using near infrared (NIR) fluorescence to detect the parathyroid gland regardless of its pathologic state, in vivo, in real-time.

Methods: NIR fluorescence was measured intra-operatively from 59 patients undergoing parathyroidectomy and thyroidectomy with informed consent. Spectra were measured from the parathyroid, thyroid, fat, muscle, and lymph nodes during surgery using a portable, probe-based fluorescence system at 785 nm excitation. Six measurements were recorded at each tissue site with a 300 ms integration time and averaged. Accuracy of the technique was evaluated by comparison to histology when available or visual recognition by the surgeon.

Results: NIR fluorescence can discriminate between parathyroid and surrounding neck tissues in 100% of patients. Parathyroid fluorescence was significantly stronger (2 – 11 times) than that of the thyroid with peak fluorescence occurring at 820 nm. Fat, muscle, and lymph nodes showed no autofluorescence. Disease state did not affect the ability to discriminate parathyroid glands but may account for variability in signal intensity.

Conclusions: NIR fluorescence can intraoperatively distinguish the parathyroid gland from the thyroid regardless of tissue pathology. Our approach utilizes the auto-fluorescence of the parathyroid gland when excited with NIR light, which has not been previously reported by any other group. We hypothesize the basis of this signal to be due to calcium sensing receptors present in abundance in the parathyroid. The strength and consistency of the observed signal indicates the simplicity and effectiveness of the method as an intraoperative tool. Implementation of this technique could limit surgical time, cut costs associated with expensive machinery and assays, and improve surgical success rates during parathyroidectomy and thyroidectomy.

NOTES

32. DEVELOPMENT OF A CALCIUM-SENSING RECEPTOR MOLECULAR IMAGING AGENT

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Background: The calcium-sensing receptor (CaSR) is expressed primarily by parathyroid and kidney cells. A molecular imaging agent which localizes to the receptor could have a significant impact on parathyroid surgery. Thyroid C-cells also express the receptor to regulate calcitonin release. Medullary thyroid carcinoma (MTC) will release calcitonin in response to calcium stimulation. A CaSR imaging agent may have a role in the diagnosis and treatment of MTC as well. We have developed several compounds that can functionally regulate CaSR function. We labeled one of these compounds with I-125 which in nude mice localized to a human MTC xenograft (TT cells) which expresses CaSR endogenously. Because of the significant background of using an iodine labeled compound in the neck, we synthesized a novel analogue containing a flourine residue for potential labeling with F-18 or a flourescent agent. We then demonstrated function of this analogue.

Methods: Starting from our parent compound, which we have previously demonstrated to have calcylitic properties, several modifications were performed to synthesize compound 42. Human embryonic kidney cells (HEK-293), which do not express CaSR, were transfected with a CaSR-GFP construct. The transfected cells were preincubated with compound 42 at concentrations of 0.1, 0.2, 0.5, 1 and 2 mM for 30 minutes. The cells were then exposed to 4 mM calcium for 10 minutes. Immunoblotting for p44/42 mitogen-activated protein kinase (MAPK) (ERK1/2)/phospho-p44/42 MAPK (phospho-ERK1/2) and GAPDH was performed.

Results: Synthesis of compound 42 was confirmed. When exposed to increasing concentrations of compound 42, there is an inhibition of the MAP kinase signaling pathway as seen by a dose dependant decrease in phosphorylated ERK1/2 while the levels of total ERK did not change.

Conclusion: We have developed a novel molecule which demonstrates functional inhibition of CaSR, and has a favorable structure for labeling. This could improve the surgical treatment of parathyroid disease and medullary thyroid carcinoma.

NOTES

33. EXPRESSION OF FUNCTIONAL FOLATE RECEPTORS BY HUMAN PARATHYROID TUMOR CELLS

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Background: There is a need for improved parathyroid tumor imaging and for effective therapy for human parathyroid carcinoma. We have reported that human parathyroid cells (normals, adenomas, hyperplasias, and carcinomas) express folate receptors (FRs), as shown by immunohistochemistry and Western blotting, while human thyroid cells do not (Mod. Pathol. 25; S2:148A, 2012). The goal of the present study was to characterize the functionality of FRs on human parathyroid tumors.

Methods: Portions of 33 resected PTH tumors and 6 samples of normal thyroid tissue were obtained with IRB approval. Expression of genes for FR alpha and FR beta was measured using Illumina Human HT-12 Expression Bead Chips. FR alpha and FR beta expression on human parathyroid tumor cells was verified by quantitative RT-PCR. Folate incorporation by parathyroid tumor cells versus normal human thyroid cells was determined by incubating single-cell suspensions with 99mTc(CO)3-folate. Parathyroid tumor cells were incubated with 99mTc-Etarfolatide or 3H-folic acid and uptake was determined by gamma counting. In all binding experiments, specific targeting of FRs on parathyroid cells was demonstrated by blocking with cold folic acid. Normal thyroid and A549 cells served as FR negative controls, and KB cells were FR positive controls.

Results: The FR alpha gene was expressed in all parathyroids analyzed, and the FR beta gene was expressed by most, as shown by whole genome expression array and quantitative RT-PCR. There was significantly increased uptake of 99m Tc(CO)3-folate in parathyroid cells compared to thyroid cells (6.9 4 1.5 vs 1.7 4 0.1, % dose/tissue prep, respectively, p= 0.028). A dose-dependent uptake of 99mTc-Etarfolatide was detected and was significantly inhibited by pre-incubation with cold folate (for example, 3.4 4 0.6 unblocked vs 1.9 4 0.2 blocked, % dose/tissue prep, $p<0.01$). Uptake of 3H-folic acid by parathyroid tumor cells was also blocked by cold folic acid (1313 cpm unblocked vs 372 blocked), confirming FR-mediated binding.

Conclusions: Human parathyroid tumor cells express functional FR alpha and FR beta. Since novel folate-targeted reagents are available and may be exploited to image and treat human PTH tumors, we believe that these findings may be clinically relevant.

NOTES

34. MYOCARDIAL AND ENDOTHELIAL DYSFUNCTION IN SYMPTOMATIC PRIMARY HYPERPARATHYROIDISM PATIENTS AND ITS REVERSAL FOLLOWING PARATHYROIDECTOMY: A PROSPECTIVE CASE-CONTROL STUDY

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Background: Cardiovascular (CV) mortality in PHPT patients (pts) is attributed to myocardial & endothelial dysfunction based on studies in asymptomatic Caucasian pts. This prospective, case-control study objectively assessed myocardial & flow-mediated vasodilatation (FMD) in symptomatic Indian PHPT pts and their reversal after parathyroidectomy (PTx).

Methods: Consecutive PHPT pts (n=50,mean age47y) underwent 2-D Echo, tissue Doppler, serum N-terminal pro-brain natriuretic peptide (s-NTpro-BNP) estimation, and endothelial (FMD) & smooth muscle (Nitroglycerine mediated, NMD) vasodilatation before, 3 & 6 months after PTx. Age & sex matched normocalcemic controls (n=20) were studied similarly.

Results: Myocardial/mitral annular calcifications were seen in 24% pts. Pts had significantly higher left ventricular mass (LVM, mean+SD 194.3+72.8gm vs.150+5.3;p=0.012), interventricular septal thickness (IVS, 10.8+2.4mm vs8.8+1.8;p=0.001) & posterior wall thickness (PWT, 10+2.1mm vs8.8+1.8;p=0.02). Trend of lower LV ejection fraction(LVEF), & higher end diastolic (LVEDD), end systolic (LVESD) dimensions, end systolic (ESV) & end diastolic volumes (EDV) were noted. Diastolic dysfunction (lower E/A trans-mitral flow velocity ratio-1.1+0.5vs1.5+0.4;p=0.001) was noted {grade 1(E/A<1) in 22,grade II(E/A>2) in 5}. Pts had higher s-NTpro-BNP (463.4+1178.4 vs 42.5+2;p=0.002); titers were>125pg/ml in 22 & >400 in 6. FMD(0.11+0.09vs0.13+0.56,p=0.035) & NMD(0.16+0.1vs0.19+0.7,p=0.04) were significantly lower in pts. At 3 & 6 months post-PTx, all pts were normocalcemic. Significant, sustained improvement in LVM (LVEDD,IVS,PWT) and LV function (LVEDV,LVESV,stroke volume,LVEF) were noted at 3 & 6 months post-PTx. S-NTproBNP levels mirrored Echo changes with significant sustained fall at 3 & 6 months post-PTx. Diastolic dysfunction (E/A ratio) significantly improved at 6 months post-PTx. FMD, NMD did not improve significantly in 6 months follow-up.

Conclusion: Symptomatic PHPT patients have significant myocardial dysfunction in form of high s-NTproBNP (sensitive marker of myocardial damage), high LVM, diastolic dysfunction, and trend towards lower LVEF. Most of these parameters improve within 3 to 6 months post-PTx. Endothelial & smooth muscle mediated vasodilatation are deranged in PHPT pts, and donot improve by 6 months post-PTx. Evaluation with 2D-Echo, tissue Doppler and s-NTpro-BNP may help objectively monitor CV derangements and improve CV outcomes in symptomatic PHPT pts.

NOTES

35. PTTG1 OVER-EXPRESSION IN ADRENOCORTICAL CANCER IS ASSOCIATED WITH POOR SURVIVAL AND REPRESENTS A POTENTIAL THERAPEUTIC TARGET

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Background: Adrenocortical carcinoma (ACC) is associated with poor survival rates due to generally aggressive biology and a lack of effective systemic therapy. Some patients may have an indolent course despite metastatic disease. Aberrant p53 pathway function has been implicated in the pathogenesis of ACC but only 20% of adult patient's tumors harbor a p53 mutation. The objective of the study was to analyze ACC gene expression profiling data for biochemical pathway enrichment, prognostic biomarkers and novel therapeutic targets.

Methods: RNA samples from 47 ACC tumors and 4 normal adrenal glands were profiled on Affymetrix U133 Plus 2 expression microarrays and Gene Set Enrichment Analysis performed. Kaplan-Meier plots were used to assess survival in the 23 patients for whom we had survival data. Protein levels were determined by western blot. Drug dose response curves were generated to assess drug efficacy against ACC cell lines. Previously published expression datasets including survival data were analyzed as validation data sets to confirm findings in our discovery set.

Results: GSEA identified marked dysregulation of the cell cycle control, focused on the regulation of cyclin-dependent kinases and mitosis. Over-expression of PTTG1, which encodes securin, a negative regulator of p53 and a protein involved in sister chromatid adhesion, was identified as a marker of poor survival. Median survival for patients with tumors expressing high PTTG1 levels (log2 ratio of PTTG1 to average beta-actin <-3.04) was 1.7 years compared to 9.8 years if tumors expressed lower levels of PTTG1 (P=0.002). These findings were confirmed as valid by our analysis of previously published clinically annotated gene expression data. Treatment of two ACC cell lines with the histone deacetylase inhibitor, vorinostat, decreased securin protein levels in two ACC cell lines and inhibited cell growth with IC50 values of 1.69 uM and 0.891 uM, for SW-13 and H295R, respectively.

Conclusion: Over-expression of PTTG1 is correlated with poor survival in ACC. Because it is a negative regulator of p53, over-expression of PTTG1 may have a role in the pathogenesis of ACC. Our study shows that PTTG1/securin is a prognostic biomarker and investigation of it as a potential therapeutic target is warranted.

NOTES

36. INCREASES IN THYROID NODULE FINE NEEDLE ASPIRATIONS, SURGERIES, AND DIAGNOSES OF THYROID CANCER IN THE UNITED STATES

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Background: To provide population-based estimates of trends in thyroid nodule fine needle aspirations (FNA) and surgery volumes, we employed multiple claims databases to quantify rates of these procedures and their potential association with rising thyroid cancer incidence from 30,180 cases in 2006 to 48,020 in 2011.

Methods: Utilization data from a proprietary insurance claims database and the Centers for Medicare & Medicaid Services Standard Analytic File were used to estimate procedure volumes from 2006-11. Rates of FNA with/out ultrasound guidance were defined by CPT4 codes with a corresponding diagnosis of nontoxic uni- or multinodular goiter. Rates of outpatient thyroidectomy and lobectomy were derived from CPT4 codes with ICD-9 codes for thyroid neoplasms. Inpatient thyroid surgery rates were obtained from the 2006-10 HCUP Nationwide Inpatient Sample using relevant ICD-9 codes, with 2011 based on the trend from 2006-10. Completion thyroidectomies were excluded to identify unique patients undergoing primary surgery.

Results: Use of thyroid FNA more than doubled over the 5-year study period (16% annual growth rate), from 254,000 to 526,700. The increase in the rate of FNAs performed with ultrasound guidance (21%) was nearly double that of biopsy without guidance (11%). Thyroid FNA also grew as a percentage of all FNAs performed, from 49% to 65%. The total number of thyroid surgeries performed for thyroid nodules increased by 31%, from 99,613 to 130,216. Total thyroidectomies increased by 8%/year, from 45,588 to 72,344, whereas the number of lobectomies increased only 1%/year, from 54,055 to 57,872. As a result, for the first time, total thyroidectomy accounts for more than half (54%) of the primary operations for thyroid neoplasm in the U.S. Increasingly, thyroid surgery is an outpatient procedure, with 55% performed in the ambulatory setting in 2006 and 62% in 2011.

Conclusion: Thyroid FNA procedures have rapidly increased in the U.S., with a downstream rise in the number of thyroid surgeries (and especially total thyroidectomies) and identification of more thyroid cancers. The relatively greater increase in total versus unilateral surgeries suggests that operated patients are perceived to have greater risk of thyroid cancer based on preoperative assessments. These trends have important policy implications for resource utilization for the diagnosis and treatment of thyroid nodules, as well as surgical training and access to quality care.

NOTES

37. FACTORS IN CONVERSION FROM MINIMALLY INVASIVE PARATHYROIDECOMY TO BILATERAL PARATHYROID EXPLORATION FOR PRIMARY HYPERPARATHYROIDISM

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Background: Ongoing experience has documented general equivalence of minimally invasive parathyroidectomy(MIP) and standard bilateral parathyroid exploration(BPE) for primary hyperparathyroidism in most patients. BPE either as a planned procedure or as an intraoperative conversion is required for some patients for multiple indications. This study analyzes the factors, cure rates and predictors in conversion of MIP in an unselected surgical practice.

Methods: A prospective, single institution database of 1002 patients undergoing initial parathyroidectomy for primary hyperparathyroidism from 2008-2011 was analyzed for rates of MIP, BPE and factors in conversion from MIP to BPE. Localization studies included surgeon performed ultrasound and/or sestamibi. Intraoperative PTH(IOPTH) monitoring was used in all cases and IOPTH criteria were a >50% drop from baseline and a value in the normal range (≤65pg/mL).

Results: Of 1002 parathyroidectomies, 647(65%) were successful MIP and 355(35%) required BPE. Of the BPEs 169(48%) were planned and 186(52%) were intraoperative conversions. Indications for planned BPE included: negative or equivocal localization 110(65%); concomitant thyroidectomy 46(27%); MEN-1 7(4%) and lithium exposure 6(4%). Indications for conversion included: IOPTH criteria not met 86(46%); localization incorrect 66(36%); concern for multigland hyperplasia 30(16%); parathyroid cancer 2(1%) and uninterpretable IOPTH data 2(1%). In the MIP conversion cases multiple glands were excised in 120(65%), a single adenoma was excised in 66(35%). Persistent or recurrent disease, as defined by calcium and PTH above the normal range, occurred in 6(0.9%) MIPs compared to 10(5.4%) converted MIPs ($p<0.001$). Of the 16 patients with persistent or recurrent disease 3 had met IOPTH criteria for cure and were therefore false positives. Preoperative PTH and serum calcium was not significantly different between converted and successful MIPs. Utilizing the CaPTHUS scoring model (Kebebew, Arch Surg 2006), converted MIPs had lower mean score (1.78 vs. 2.19; $p<0.001$) primarily due to more frequently negative sestamibi, however most patients had scores ≤2 (MIPs-60% and converted MIPs-78%).

Conclusions: Conversion of MIP to BPE is required in 19% of patients, is due to multigland disease in most, cannot be predicted by preoperative PTH or calcium, but do have more negative sestamibi scans. Converted MIP has a 5-times higher failure rate than MIP using strict IOPTH criteria.

NOTES

38. A 27 YEAR FOLLOW-UP OF PATIENTS WITH PAPILLARY THYROID CANCER: THE IMPORTANCE OF A LONG-TERM STUDY

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Background: Long-term study of patients with papillary thyroid cancer (PTC) is difficult, but essential, since both recurrences and death occur many years after initial diagnosis. We report the outcomes of patients with PTC treated between 1968-1988 at our institution with a median follow-up of 27 years. The cohort was originally published in 1990 with a median follow-up of 11 years.

Methods: Demographics, tumor pathology, treatments, recurrences, and deaths from PTC were ascertained. Multivariate Cox proportional hazard model was used to identify risk factors associated with recurrence and death. Risk factors were age at diagnosis, history of external low-dose radiation exposure, stage, tumor size, multifocality, capsular invasion, follicular variant of PTC, nodal status, distant metastatic disease, and radioactive iodine treatment. Twenty-six patients were excluded from the multivariate analysis due to incomplete staging. Risk factors with p-values ≤ 0.05 were considered significant. Kaplan-Meier curves were used to determine recurrence and death rates. The 7th edition of the AJCC TNM guidelines was used for staging.

Results: Of 269 patients, 180 (66%) were female, 196 (73%) were ≤ 45 years of age, and 99 (37%) reported a history of prior external radiation exposure. A total of 211 cases were stage 1 (78%), 12 were stage 2 (4%), 10 were stage 3 (4%), 17 were stage 4a (6%), 13 were stage 4c (5%), and 6 cases were unknown stage (2%). Risk factors for recurrence by multivariate analysis were older age at diagnosis (HR 1.5, CI 1.1-2.1), follicular variant of PTC (HR 1.9, CI 1.1-3.2), larger tumor size (HR 1.6, CI 1.4-2.0) and metastatic disease (HR 10.6, CI 5.1-22.1). Significant predictors of death from PTC were older age at diagnosis (HR 2.9, CI 2.0-4.3) and stage of disease (Stage 3: HR 5.2, CI 2.2-12.7; Stage 4a: HR 3.7, CI 1.8-7.8; Stage 4c: HR 20.0, CI 8.3-48.2). The mean time to recurrence was 8 years and to death was 10 years. However, there were 3 cases of recurrence and 2 deaths from PTC after 30 years. Overall 30-year recurrence and death rates from PTC were 30% and 9%, respectively. The additional follow-up from the original study identified 9% more recurrences (n=6) and 9% more deaths from PTC (n=2).

Conclusion: The 27 year median follow-up achieved in this study is among the longest in the literature for PTC. Long-term follow-up is essential if the true natural history and death rates are to be known.

NOTES

39. LONG-TERM OUTCOME OF ULTRASOUND-GUIDED PERCUTANEOUS ETHANOL ABLATION OF SELECTED "RECURRENT" NECK NODAL METASTASES IN 25 PATIENTS WITH TNM STAGES III OR IVA PAPILLARY THYROID CARCINOMA PREVIOUSLY TREATED BY SURGERY AND I-131 THERAPY

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Background: Ultrasound-guided percutaneous ethanol ablation (UPEA) of selected neck nodal metastases (NNM) in papillary thyroid carcinoma (PTC) patients has been described (JCEM 96: 2717-20, 2011) as an effective, safe, and cheaper alternative to re-exploratory neck surgery in TNM stage I PTC patients managed by thyroidectomy and remnant ablation. Presently, there are few reports describing the efficacy of UPEA in more advanced localized disease.

Methods: We treated with UPEA 25 patients who presented with either stage III or stage IVA disease, and had "recurrent" NNM discovered at a median of 4 postoperative years. Prior to UPEA, 5/8 stage III patients (62%) had a total of seven neck re-explorations. The eight stage III patients also received 13 doses of radioactive iodine (RAI) therapy (mean 238 mCi). 8/17 stage IVA patients (47%) had a total of 12 re-explorations; 28 RAI doses were delivered to the 17 stage IVA patients (mean 226 mCi). Each of 37 NNM (mean largest size 13mm, range 7-25mm), selected for UPEA, was biopsied under ultrasound-guidance. The 25 patients were aged 46-73 years (mean 58 years). UPEA was administered (AJR 178: 699, 2002) in two outpatient sessions on successive days. Patients were evaluated at 3-6 months after UPEA, and annually thereafter. At each visit, NNM size was measured and Doppler flow assessed.

Results: All 37 NNM decreased in size after UPEA. None had detectable Doppler flow; 15 (40%) disappeared on re-scanning. None of the UPEA-treated NNM, followed on average for 58 months (range 4-141), required further intervention. Only 1/8 stage III patients (12%) and 4/17 stage IVA patients (22%) subsequently developed "new" NNM at sites requiring more surgery and/or further UPEA. The majority (5/7, 71%) of these later "recurrent" episodes were managed successfully by UPEA, rather than by further surgery. After UPEA, none of the 25 patients developed permanent hoarseness.

Conclusions: UPEA of selected NNM in stage III and IVA PTC has proved effective and in these 25 patients prevented, to date, 30 expensive, potentially hazardous, neck re-explorations. Estimating an average cost-saving of about $38,400 per UPEA procedure, it is likely that these particular 25 patients, by avoiding further surgery, saved themselves approximately $1.152 million. We would conclude that UPEA, performed by dedicated sonographers, is, therefore, not only safe and effective, but also considerably cheaper than the traditional surgical alternative.

NOTES

40. POTENTIAL ROLE OF 5- AZA-2′-DEOXYCYTIDINE INDUCED MAGEA4 EXPRESSION IN IMMUNOTHERAPY FOR ANAPLASTIC THYROID CANCER.
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Background: MAGEA4, a member of the cancer testis antigen (CTA) family is expressed in various cancers including melanoma, bladder, head and neck, lung, and is a potential target for TCR based immunotherapy. BRAF inhibitors and histone demethylating agents have been shown to induce/enhance the expression of various CTAs and melanoma differentiating antigens (MDAs) in melanoma and other cancer cells. We hypothesized that treatment with BRAF inhibitors or demethylating agents may lead to similar increases in the expression of CTAs in thyroid cancer cells.

Method: Human thyroid cancer cells (8505c, HTh7, BCPAP and TPC-1) were grown in medium with either 10 ×M azacytidine (Aza) , 1.0×M 5-aza 2′deoxycytidine (5-Aza-dC) , 10×M PLX4720 (Plexxikon) or control for 72 hours and evaluated for the presence of various MAGE-A family as well as MART-1 and gp100 gene expression using Taqman gene expression assays. Later 8505c cells were treated with PLX4720 in the presence of 5-Aza-dC. Methylation status of the MAGEA4 promoter was determined using a Methycode bisulfite conversion kit.

Results: None of the cell lines expressed any MAGEA1, A3, A4, A6, MART-1 and gp100 at baseline. Only 8505c cells (BRAF V600E hemizygous) showed an increase in MAGEA4 mRNA and a moderate increase in MAGEA1 with both 5-Aza-dC and Aza (5-Aza-dC>Aza). PLX treatment had no effect on the expression of MAGEA4/A1. 8505c cells with lentiviral knockdown of BRAFV600E showed a dramatic dampening of this increased expression of MAGEA4 which had been seen with both Aza and 5-Aza-dC. In addition, treatment of 8505c cells with the BRAF inhibitor PLX4720 in the presence of either Aza or 5-aza-dC decreased the induced expression of MAGEA4 (~ 5 fold change) but not completely. None of the treatments showed any significant changes in MAGEA4 promoter methylation status.

Conclusion: Treatment with demethylating agents increases MAGEA4 expression on the surface of 8505c thyroid cancer cells. In contrast to melanoma where expression of cell surface MDAs appear to be increased in response to BRAF inhibition, the tested thyroid cancer cells do not show increased expression of similar cell surface markers with BRAF inhibition. However, treatment with BRAF inhibitors decreased the demethylating agent induced increased MAGEA4 expression implying a role for downstream BRAF signaling in the MAGEA4 expression. Expression of MAGEA4 may make immunotherapeutic intervention possible in selected thyroid cancer