Introduction: The parathyroid carcinoma is the least common cancer type of endocrine origin, corresponding to less than 0.005% of human cancers. The differential histopathological diagnosis with other conditions as parathyroid adenoma and hyperplasia can be challenging. Thus, new strategies and tools to assist in differential diagnosis can have clinical relevance. This study aimed to identify differentially expressed immunohistochemical markers in patients with carcinoma, adenoma and parathyroid hyperplasia compared to normal parathyroid tissue, establishing markers which could be associated to the malignant phenotype.

Methods: The series consisted of seven patients with parathyroid carcinoma, 20 cases with a diagnosis of adenoma, two atypical adenomas and five hyperplastic parathyroid, plus two normal gland tissue. All patients underwent surgical treatment from January 2000 to December 2011. Immunohistochemical markers used were Ki-67, p27, galectin-3, p53, VEGF, Claudin 7, E-cadherin, metalloproteinase 2 and 9. Tumor tissue inappropriate and/or unavailable for conducting the proposed study and patients with multiple endocrine neoplasia were excluded. A critical review of all histological sections was performed by a single pathologist for diagnostic confirmation. The histopathological criteria have been used for the diagnosis of parathyroid carcinoma were: vascular, perineural, capsule or adjacent tissues invasion.

Results: The main clinical manifestation at diagnosis in patients with parathyroid carcinoma was nephrolithiasis. PTH and serum calcium at diagnosis were higher in carcinoma and atypical parathyroid adenoma. Tumor size was higher in parathyroid carcinomas with a mean size of 2.7cm. The initial option was surgical parathyroidectomy in one case, parathyroidectomy with partial thyroidectomy in five cases (three cases with ipsilateral neck dissection), and parathyroidectomy with total thyroidectomy and ipsilateral neck dissection in one case. Two patients underwent adjuvant radiotherapy.

The expression of Ki67, VEGF, Claudin 7, e-cadherin, metalloproteinase 2 and 9 did not differ between groups in our samples. The p53 protein was not expressed in any adenoma. The p27 protein expression was > 10% in 11 of 19 adenomas samples analyzed. The expression of galectin-3 was significantly higher in the group of carcinomas compared with other histologies (p=0.027).

Conclusion: Despite the small sample size, it was evidenced a differential expression of galectin-3 in patients with parathyroid carcinoma, which suggests that galectin-3 may be a useful marker in the diagnosis of this rare tumour.
PARATHYROIDECTOMY (PTX) IN PATIENTS WITH NEGATIVE OR INDETERMINATE PARATHYROID NUCLEAR IMAGING (PNI): WHEN AND HOW TO PROCEED?

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Background: Patients with primary hyperparathyroidism (pHPT) and negative PNI are often not referred for PTX and, when they are, such patients are known to be problematic for the surgeon in terms of increased failure rates for neck exploration (NE). Furthermore, there is no consensus on the extent of pre-operative work-up for this group of patients.

Methods: The records of 498 patents with pHPT undergoing PTX by a single surgeon over a 58 month period were reviewed. Patients with known Multiple Endocrine Neoplasia (MEN) syndromes and patients undergoing re-operative PTX were excluded. Prospectively gathered data on patient history, indications for surgery, physical exam, operative and pathologic information, surgical outcome and complications as well as imaging studies were evaluated. All patients in the study group underwent PNI. Based on pre-operative PNI reports, the patients were divided into one of 3 groups: Positive PNI (Group 1, n=374); Indeterminate PNI (Group 2, n=32); and, Negative PNI (Group 3, n=92). Group characteristics were compared using chi-square tests.

Results: Unilateral minimally invasive PTX was performed in 68.2, 46.9 and 31.5% of patients in Groups 1, 2 and 3 respectively (p<.001). Monitored local anesthesia was used in 54.6, 21.9 and 13.0% of operations in Groups 1, 2 and 3 (p<.001). Bilateral NE was carried out in 15.2, 37.5 and 42.4% of patients in Groups 1, 2 and 3 (p<.001) with single adenomas resected in 79.7, 65.6 and 64.1% of patients in Groups 1, 2 and 3 respectively (p=.003). Concomitant thyroidectomy was performed in 26.1% of patients in Group 3 compared with 15.8% of patients in Group 1 and 15.6% in Group 2 (p=.064). 38% of Group 3 patients had a history of pre-existing benign thyroid disease compared with 28.3% of Group 1 patients and 25.0% of Group 2 patients (p=.160). 9.8% of Group 3 patients were referred for surgical evaluation of the thyroid as well as for pHPT compared with 4.3% of Group 1 patients and 3.1% of Group 2 patients (p=.090). Intra-operative parathyroid hormone (ioPTH) criteria were met in all 498 patients with 2 early (<6 months) failures. Neck ultrasound (NU) was performed in 92.5, 90.6 and 100% of patients in Groups 1, 2 and 3 with true positive parathyroid localization results in 52.9, 34.5 and 21.7% of patients in Groups 1, 2 and 3 respectively (p<.001).

Conclusions: Head and neck surgeons should not be deterred from operating on patients with pHPT who have negative or indeterminate PNI. Patients with completely negative PNI are more likely to have potentially confounding benign thyroid disease. Pre-operative NU is of benefit and should be performed. Minimally invasive PTX can still be performed in patients with negative PNI provided ioPTH monitoring is used. While PTX in this setting is clearly more challenging, high surgical success rates equivalent to those patients with positive PNI can be achieved.
Objectives:

Hypocalcaemia is a common sequel after surgery for primary hyperparathyroidism. While in most cases it is transient and self-limiting, occasionally the hypocalcaemia can be severe and sustained and such patients may require closer monitoring and prolonged hospitalization. The purpose of this study is to determine if any preoperative parameters can predict the severity of hypocalcaemia following parathyroidectomy.

Methodology:

The case records of 70 patients who underwent parathyroidectomy for primary hyperparathyroidism from 2000-2013 was retrospectively studied. Their symptoms at presentation, preoperative biochemical parameters (serum calcium, PTH, ALP) and parathyroid size on ultrasound were compared with their serial post-operative serum calcium levels at 24, 48, 72 and 96 hours. For the purpose of analysis, patients were divided into 3 groups. Group 1 - Asymptomatic, biochemically normal (serum calcium always >= 8.5 mgs %); Group 2 - Asymptomatic, biochemically below normal (at least one reading < 8.5, but none < 8.0); Group 3 - Symptomatic (any one reading < 8.0).

Results:

A significant difference was found between Groups 1 and 2 when the pre-operative presenting symptoms were compared - mild (p=0.044) and severe (p=0.035). No correlation was found between pre-operative serum calcium levels or the parathyroid size with the post-operative calcium levels in the 3 groups. The medians of preoperative serum ALP were found to be 126.0, 192.0 & 358.0 IU/L in Groups 1, 2 & 3 respectively and although serum ALP levels appeared higher in Group 3, it was not statistically significant (p = 0.069). However, the medians of preoperative serum PTH levels of 278.0, 840.0 & 1519.0 pg/mL in Groups 1, 2 & 3 respectively, significantly correlated with post-operative serum calcium levels in all three groups (p = 0.006).

Conclusions:

Pre-operative serum PTH levels serve as a marker for predicting the severity of post-operative hypocalcaemia and higher values of PTH helps identify those patients that require close monitoring and longer hospitalization following parathyroidectomy.
LONG-TERM RESULTS OF PARATHYROID CRYOPRESERVATION. CLINICAL APPLICATION IN PARATHYROID AUTO TRANSPLANTATION.
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Objective:

1- To analyze the histological and in vitro functional status of 15 samples of cryopreserved parathyroid tissue, unfrozen after 3 to 11 years of cryopreservation. 2- To discuss the clinical results obtained in 4 patients affected by hypoparathyroidism after hyperparathyroidism (HPT) surgical treatment and auto transplanted with cryopreserved tissue.

Material and Methods:

1- Starting on 2002, the parathyroid tissue obtained during surgical treatment of secondary hyperparathyroidism (HPT) or primary parathyroid hyperplasia on 216 patients has been stored, when possible, in a cryopreservation bank. The regular procedure included patient informed consent, transportation from OR to laboratory in Dulbecco's modified Eagle medium, fractionation into 1 to 2 mm3 pieces under sterile conditions, inclusion in D-MEM plus DMSO cryopreservation medium and controlled descend of temperature up to -90°C. The final storage of the vials was in liquid nitrogen at -170°C. In 2013 15 samples, that were selected because the donor would not need a transplant anymore, were unfrozen in saline solution at 37°C and washed with Hank's solution in order to remove the DMSO. For each of the 15 patients' samples the vitality test was the same: one fragment was included in paraffin and processed with H&E (histological analysis) and using the TUNEL technique for apoptosis evaluation (viability post cryopreservation). Four other fragments were used for: in vitro PTH secretion test (exposed to CaCl2 0.6 mM solution), Calcitriol receptors' test (exposed to CaCl2 1.2 mM and Calcitriol 10^-8 M solution), control group (exposed to CaCl2 0.6 mM solution) and one fragment for post culture viability study (using H&E and TUNEL technique).

2- Four patients (patient 1: 58 y.o. female, secondary HPT; patient 2: 38 y.o. female, secondary HPT; patient 3: 50 y.o. male, primary hyperplasia in MEN I; patient 4: 80 y.o. male, secondary HPT) were transplanted with own cryopreserved parathyroid tissue after severe post surgical hypoparathyroidism, using the usual technique.

Results:

1- Despite that some samples showed unexpected levels of secretion, most of the specimens were able to secret PTH and showed calcitonin receptors, even after long cryopreservation time. All samples were histologically preserved after cryopreservation.

2- 90% showed a low apoptosis rate.

3- 80% were vital after the culture.

4- Two of the four transplanted patients showed improvement on the PTH levels and restricted the amount of calcium required.
Discussion:

Based on this experience, the cost benefit and the rationale of a parathyroid cryopreservation institutional bank are discussed. The potential clinical and research possibilities are discussed as well.
S356  PARATHYROID PRESERVATION DURING TOTAL THYROIDECTOMY AND ITS OUTCOMES - STUDY OF 50 CASES IN MYMENSINGH MEDICAL COLLEGE HOSPITAL, BANGLADESH.
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Introduction: Parathyroid preservation during thyroidectomy is essential for the effective surgical management of diseases of the thyroid gland. Preservation of the parathyroid glands cause low morbidity in thyroid surgery. The study was done with the aim to see the outcomes of parathyroid preservation.

Methods: This observational cross sectional study was done in the Department of Otolaryngology and Head-Neck Surgery, Mymensingh Medical College Hospital, Bangladesh from July'2012 to June'2013. 50 patients who underwent total thyroidectomy with or without neck dissection were purposively selected. Patients were divided into two groups- group A- where parathyroid gland identification was done and group B- where parathyroid identification was not done. Data was collected from interview, examination and investigations.

Results: Out of 50 patients age ranged from 13 to 62 years, the mean age was 37.1 years with a male-female ratio 1:2.57. The most common indication for performing surgery (total thyroidectomy, completion thyroidectomy with or without neck dissection) was multinodular goiter in 29 (58%) cases, then papillary carcinoma in 19 (38%) cases, medullary carcinoma in 1 (2%) cases and graves disease in 1 (2%) cases. Most of hypocalcaemia developed in patients underwent thyroidectomy with neck dissection 7/12(58.33%); it was followed by completion thyroidectomy 2/5(40%), total thyroidectomy alone 6/33(18.18%). Hypocalcaemia developed in 9/21(42.85%) cases of malignant thyroid disease and in 6/29(20.68%) cases of benign thyroid disease. 10/42(23.80%) patient developed hypocalcaemia where parathyroid glands were identified (two or more glands) and 5/8(62.5%) patients developed hypocalcaemia where parathyroid gland was not identified. Maximum patients 10 (66.66%) developed hypocalcemic tetany in second postoperative day (n= 15). 3 (20%) cases developed hypocalcaemia in 3rd post operative day. The result in this series showed that temporary hypocalcaemia occurred in 12(24%) cases and permanent hypocalcaemia occurred in 3 (6%) cases. The difference in development of hypocalcaemia between benign thyroid disease and carcinoma of thyroid and between identification and not identification of parathyroid gland was statistically significant (p< 0.05).

Conclusion: Frequency of parathyroid failure is more after thyroid surgery for malignant thyroid disease and it depends on extension of disease. It is concluded that relationship between identification of parathyroid and development of hypocalcaemia is inversely proportional.
SELECTIVE TREATMENT FOR HYPOPARATHYROIDISM AFTER TOTAL THYROIDECTOMY BASED ON PTH LEVELS

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Background: Hypocalcemia is the most common complication after total thyroidectomy and the major determinant in delay of discharge. The symptoms usually occur 24-48 hours after total thyroidectomy, and has been described with an incidence ranging from 1.7-68% of transitory hypocalcemia. Some authors routinely use oral supplementation of oral calcium, while others postpone hospital discharge waiting of multiple calcium dosages, to avoid those symptoms.

Objectives: Selective oral calcium/calcitriol supplementation to avoid clinical manifestations of hypocalcemia based on parathyroid hormone levels after total thyroidectomy.

Methods: Prospective study with 31 patients undergoing total thyroidectomy or completion, with or without central neck dissection. Parathyroid hormone (PTH) was measured 1 hour postoperative period. Patients with PTH > 15 pg/ml were discharged one day after surgery without calcium or calcitriol supplementation. Selective supplementation was determined by serum PTH levels with oral calcium (PTH > 5 pg/ml and <=15 pg/ml) or oral calcium with calcitriol (PTH <= 5 pg/ml) and correlated with symptoms of hypocalcemia during 10 days postthyroidectomy.

Results: None of the patients (14/33) with PTH levels >15 pg/ml developed symptoms (p=0.012). In nineteen patients with PTH <= 15 pg/ml, 11 (57.89%) patients had adequate supplementation and remained asymptomatic. Four patients (21.05%), didn’t follow the prescription and developed clinical manifestations of hypocalcemia. Four patients received the correct supplementation and developed symptoms. (p=0.018)

Discussion: The use of PTH after total thyroidectomy has been described in the literature as a predictor of hypocalcemia. PTH levels can define 2 groups of patients: those who are likely to remain asymptomatic and are safe for discharge, and those who are high risk to develop hypocalcemia and treatment should be instituted as soon as possible to avoid symptoms. Our study showed that patients with PTH >15 pg/ml can be safely discharged without supplementation, and for patients with PTH levels <15 pg/ml the use of calcium and/or calcitriol can avoid symptoms of hypocalcemia.

Conclusions: The selective supplementation based on postthyroidectomy PTH levels can be used safely to avoid clinical manifestations of hypocalcemia.
PTH 1 Hour after thyroidectomy

- ≤ 5 pg/ml
  - Calcium 2g/day
  - Calcitriol 0.75µg/day

- >5 and ≤ 15 pg/ml
  - Calcium 2g/day

- > 15 pg/ml
  - Supplementation according to symptoms
EVALUATION OF UTILITY AND COST OF INTRAOPERATIVE FROZEN SECTION FOLLOWING FINE NEEDLE ASPIRATE BIOPSY FOR THYROID NODULES

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Background: Fine needle aspirate (FNA) biopsy is an established tool in the diagnosis of patients with thyroid lesions. However, there remains ambiguity in surgical management of certain Bethesda categories of thyroid nodules. The potential for avoiding staged completion thyroidectomy leads some surgeons to advocate for intraoperative frozen sections at the time of hemi thyroidectomy. We retrospectively reviewed the Weill Cornell Medical College experience related to pathology charges and utility of intraoperative frozen section in patients with pre-operative FNA revealing Bethesda II-V diagnoses.

Methods: We performed a retrospective assessment of patient, surgical, and pathologic data for patients undergoing planned thyroid lobectomy with possible total thyroidectomy depending on intraoperative frozen section at Weill Cornell Medical College (WCMC) between 2008-2013. There were 427 specimens identified for which FNA, frozen section, and final pathology were available in this setting. Of these patients, the FNA diagnoses were 147 (34%) Bethesda II, 170 (40%) Bethesda III, 90 (21%) Bethesda IV, and 19 (5%) Bethesda V. At WCMC, charges for intraoperative frozen section, including materials and professional fees, are $251 per specimen.

Results: There were 76 thyroid carcinomas on final pathology. Likelihood of final diagnosis of malignancy with respect to pre op FNA were 11/149 (7%) Bethesda II, 23/169 (14%) Bethesda III, 26/90 (29%) Bethesda IV, and 16/19 (84%) Bethesda V. Frozen section assessment of the nodule in question contributed to diagnosis of malignancy and altered surgical management in 14/427 (3%). There were no false positives on frozen section. The likelihood of detection of malignancy and altering management on frozen section per FNA were: 1/149 (0.6%) Bethesda II, 4/169 (2%) Bethesda III, 1/90 (1%) Bethesda IV, 8/19 (42%) Bethesda V. Using intraoperative frozen section, the additional pathology charge alone per positive diagnosis of malignancy was $37,399 Bethesda II, $10,604 Bethesda III, $22,590 Bethesda IV, and $596 Bethesda V.

Conclusion: With the exception of Bethesda V lesions, intraoperative frozen section appears to have a limited role in evaluation of thyroid nodules. In only 1.4% of Bethesda II, III, IV lesions was frozen section useful in diagnosing malignancy and altering treatment. However, depending on individual institutional costs as well as the quality of life impact of avoiding a second surgery, there may be utility in performing frozen sections in a variety of Bethesda groupings.
S359  INDIVIDUAL PARTICIPANT DATA META-ANALYSIS OF PRIMARY SQUAMOUS CELL CARCINOMAS IN THE THYROID GLAND - FOCUS ON CLINICAL CHARACTERISTICS AND PROGNOSIS

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Context: Primary squamous cell carcinomas in the thyroid gland (ThSCC) is extremely rare, but exhibits aggressive clinical behavior and poor treatment outcome. However, the clinical characteristics and optimal treatment strategy of ThSCC are poorly defined because of its rarity.

Objective: To understand the clinical characteristics and to identify the prognostic factors for better clinical outcome in ThSCC, using a systematic review and individual participant data meta-analysis of published cases.

Data Sources: A literature search was conducted within Medline, EMBASE, Cochrane library databases and KoreaMed using the following Medical Subject Headings keywords: ‘primary’, ‘squamous’, ‘carcinoma’, ‘cancer’ and ‘thyroid’. Data of 84 patients from 39 articles and data of 5 patients treated at our institute met the inclusion criteria (N=89).

Study Selection: Inclusion criteria were the cases reported as primary ThSCC. We excluded non-English articles and studies with insufficient clinical information.

Data Extraction: Each report for eligibility was reviewed by multiple reviewers. Patient and disease characteristics, and treatment modalities were extracted from each article and medical record.

Data Synthesis: The mean age of the 89 patients at diagnosis was 63.0 years (range, 24-90) with twice as many females as males. The most common complaint was the anterior neck mass, followed by dyspnea or dysphagia, and extension to the adjacent structure was found in 72% of patients. The median survival was 9.0 months (95% CI, 6.0-23.0) and 3-year survival rate was 37.6% by Kaplan-Meier method, but only 20.1% by a shared frailty model for adjusting heterogeneity of literatures. Complete resection of tumors was the only significant prognostic factor in multivariate analysis, and the benefit of adjuvant treatment was not proved.

Conclusions: The prognosis of patients with primary ThSCC is very poor, but complete resection of disease is correlated with improved survival. To achieve complete surgical eradication of tumors, early detection and accurate diagnosis should be emphasized.