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Sporadic and Familial Medullary Thyroid Carcinoma, State of the Art

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Medullary thyroid carcinoma (MTC) comprises 5-10% of all thyroid cancers. The majority of cases are sporadic (75%), however the proportion of MTC patients with a familial predisposition syndrome is the highest of any hereditary cancer syndrome (approximately 25%), and this possibility should be considered when evaluating any patient with MTC. The familial syndromes include: multiple endocrine neoplasia (MEN) 2A, MEN 2B, and familial non-MEN MTC (FMTC). Familial MTC syndromes affect about 1 in 30,000 individuals. MTC develops from the calcitonin producing parafollicular or C-cells. These cells are neuroectodermal in origin and thus belong to the amine precursor uptake decarboxylation (APUD) cell family. C-cells only make up about 1% of the thyroid cell mass and are primarily concentrated in the (1) posterior upper third of the gland. Histologically MTC is characterized by a solid mass of cells with uniform polygonal shapes and finely granular eosinophilic cytoplasm.(2) Pathologists have described the presence of amyloid deposition as being pathognomonic for MTC and are found in one third of MTC cases. It was recently reported that the sole constituent of these amyloid deposits is full-length calcitonin. (Khurana, Agarwal et al. 2004) C-cell hyperplasia may be a precursor to MTC, and is most commonly seen in familial forms of MTC.(3)

MEN2A is the most common subtype of familial MTC(80% of hereditary MTC cases). These patients develop multifocal, bilateral MTC (nearly 100% penetrance),

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pheochromocytoma (42% penetrance), and hyperparathyroidism (10-30% penetrance).(4) Features that occur more rarely in MEN2A are cutaneous lichen planus amyloidosis, and Hirschsprung's disease. MEN 2B patients develop MTC (very early onset, also with 100% penetrance), pheochromocytoma (40% penetrance) but do not have hyperparathyroidism. These patients also have multiple mucosal neuromas (often visible on the eyelids and lips), ganglioneuromatosis of the gastrointestinal tract, and megacolon (See Figure 1). FMTC represents a clinical variant of MEN2A in which MTC is the only clinical feature.(5) Controversy exists around what familial pattern of inheritance constitutes a patient as FMTC versus MEN2A. The strictest clinical criteria requires that the FMTC proband have more than 10 carriers of MTC in the kindred with multiple members greater than age 50 none of whom have been diagnosed with hyperparathyroidism or pheochromocytoma. (6) A less rigid definition characterizes FMTC as patients with at least 4 affected family members with MTC alone.(7) Caution should be exercised in any patient given the diagnosis of FMTC since misclassification of an MEN2A patient as FMTC may result in failure to screen for pheochromocytoma and hyperparathyroidism.

Clinical Presentation and Diagnosis

Presymptomatic preventative surgery for young patients with familial MTC syndromes will be discussed later in this chapter. In patients who did not undergo preventative surgery, familial MTC usually presents with multifocal, bilateral disease. Patients with sporadic MTC (sMTC) more commonly have unifocal tumors, later age of onset, and absence of C cell hyperplasia. Every patient presenting with newly diagnosed MTC should be counseled about the possibility of familial disease and offered genetic testing. MTC patients should have a full family history taken at the time of initial consultation, with attention given to thyroid and parathyroid disease, adrenal tumors, hypertension, Hirschsprung's disease, and sudden, unexplained deaths. Physical exam should take note of size of palpable neck nodules, fixation to surrounding structures, and the presence of cervical lymphadenopathy. Characteristic features of MEN2B phenotype, such as tongue nodules, should also be noted. Symptoms of extensive local disease include dysphagia, hoarseness, dyspnea, stridor and coughing. Direct examination of the vocal cords prior to surgical intervention may reveal vocal cord paralysis, indicating involvement of the recurrent laryngeal nerve. Patients presenting with elevated levels of calcitonin may exhibit diarrhea as the initial symptom of their disease

The dominant nodule should be evaluated first with fine needle aspiration (FNA) aided by immunocytochemical staining for calcitonin. In one study FNA was successful in diagnosing MTC in greater than 80% of patients. In the remaining patients the pathologic diagnosis was not apparent until the surgical specimen was evaluated histologically. (8)

Serum calcitonin measurement is a sensitive marker for MTC. It is useful in screening at risk individuals as well as monitoring previously treated patients for disease recurrence. Cost analysis in Europe has suggested that routine calcitonin screening in patients undergoing evaluation for thyroid nodules is cost effective, however this practice has not gained widespread acceptance in the USA.(9) In a screening setting a basal serum calcitonin exceeding 20pg/ml warrants further investigation to rule out MTC. A mildly elevated serum

calcitonin level can occur in C cell hyperplasia, autoimmune thyroiditis, chronic renal failure, advanced age, and variation among commercial assays. Calcitonin may be measured either in a basal state, or after stimulation by the secretagogues calcium and pentagastrin. Pentagastrin is no longer available commercially and basal measurements are commonly followed, using highly sensitive commercial assays.

Preoperative evaluation of patients with known or suspected MTC should include serum calcitonin measurement, carcinogenic embryonic antigen (CEA), serum calcium, and RET protooncogene analysis. Biochemical screening for pheochromocytoma (plasma metanephrines or 24 hour urine catecholamines) should be conducted in any MTC patient more than 10 years of age. Preoperative imaging may include a neck ultrasound with lymph node mapping of the cervical nodal compartments (Figure 2). The sensitivity of intra-operative palpation by an experienced surgeon to detect lymph node metastases is only 64%. (10) In patients presenting with a palpable thyroid nodule cervical lymph node metastases are common (>75%), with 10-15% of these patients also having evidence of distant metastases. (10) MTC most commonly metastasizes to the bones, liver, and lungs. Detection of distant disease begins with computed tomography (CT) of neck, chest and abdomen. CT is the most sensitive test to detect lung and mediastinal lymph node metastases. (11) Contrast enhanced MRI is most sensitive for the detection of liver metastases and bone metastases are seen best on either axial MRI or bone scan. In one series, CT has been found to be superior to FDG PET for lung, liver, and bone metastases. (12) However, FDG PET was more sensitive than CT in detecting neck and mediastinal disease. Imaging to identify distant disease is not indicated in every MTC patient. Imaging is most likely to detect metastatic disease in patients with a basal serum calcitonin >400pg/mL. (13)

Surgical Approach to MTC: Clinically Evident, Familial, and Sporadic

Differences in survival exist between patients who achieve complete remission, those with biochemical persistent disease, and those with evidence of distant metastatic disease. (14). MTC patients who present with clinically apparent disease (palpable mass) have a significant risk of having regional lymph node metastases. At our institution, over 75% of patients presenting with palpable MTC, hereditary or sporadic, have central cervical lymph node metastases (level 6 nodes), with a similar rate of spread to the ipsilateral lateral neck nodes (levels 2-4), and a 47% rate of involvement of contralateral level 2-4 nodes. (10) At a minimum, patients with palpable MTC should undergo total thyroidectomy with central lymph node dissection and unilateral dissection of level II-V nodes. Ultrasound evaluation of cervical nodes should be done prior to surgery and is useful in determining whether a contralateral level 2-4 dissection is necessary also. Ultrasound evaluation of central and low level 4 nodes may be limited in patients who have short necks or who are unable to extend the neck.

Preoperative calcitonin level should always be obtained. Asymptomatic adult or younger patients with positive *RET* mutation screening should have a central lymph node dissection (level 6) in addition to thyroidectomy if the preoperative calcitonin level is elevated (greater than 40pg/ml). Preoperative ultrasonographic evaluation of neck nodes should be done if calcitonin is elevated, and suspicious nodes should be marked and removed at operation.

Patients with codon 634 (level II) mutations have an increasing risk of lymph node metastasis beginning in the mid-teens, with over 40% cumulative risk by age 20.(15) The surgical approach in older RET mutation carriers should be individualized based on calcitonin level, presence of palpable disease, imaging results, RET mutation, and family history.

The likelihood of ipsilateral lateral compartment lymph node involvement (levels 2-4) is related to the presence and extent of nodal disease in the central compartment. In one study, the presence of 0, 1-3, or 4 central lymph node metastases was correlated with 10.1%, 77%, and 98% risk of metastatic involvement of ipsilateral level 2-4 nodes respectively. For contralateral lateral compartment involvement the rates were 4.9%, 28%, and 77% with no central lymph node metastases, 1-9, and 10 respectively. (16) Thus, in patients with preoperative imaging suggesting central lymph node metastases serious consideration should therefore be given to doing at least an ipsilateral level 2-4 compartment lymph node dissection.

Preservation of parathyroid function in these operations should be a major concern of the surgeon, and expertise in identification and preservation of the glands is essential for optimal outcomes. If a central lymph node dissection is performed, the lower parathyroids must be removed and autotransplanted because they are intimately associated with level 6 nodes. It is often possible to preserve one or both upper glands on an intact vascular pedicle, but if it is not possible, they should be removed and transplanted also. Normal parathyroids should not be discarded with the specimen, and an effort should be made to leave all normal parathyroid tissue in the patient. MEN 2A patients with primary hyperparathyroidism should undergo either total parathyroidectomy with autotransplantation or subtotal parathyroidectomy, leaving enough viable parathyroid tissue *in situ* to prevent hypoparathyroidism. For MEN 2A patients, the forearm is an excellent autotransplantation site (because of the risk of later graft-dependant hyperparathyroidism), while the sternocleidomastoid muscle is usually used for MEN 2B and FMTC patients.

In patients with clinically apparent, palpable sporadic MTC, total thyroidectomy with compartment oriented neck dissection results in long-term local control in most patients, and biochemical cure of disease in about 50% of patients.(17)FIGURE 3 At present a rational approach to the surgical management of sMTC should take into account the clinical evidence, the serum calcitonin level and preoperative ultrasound evaluation for lymph node metastases. Two reports from a center in Japan described a unilateral approach in some patients with sMTC. In these reports, a small number of patients were treated with lobectomy and unilateral node dissection alone, with good reported biochemical cure rates and no recurrence in the remaining lobe. (18) Our group has found this approach to be useful in palliative situations (bulky unilateral neck disease with distant metastases).

Post-operative Surveillance

A pre-operative calcitonin level serves as a marker of disease burden, and post-surgical reduction of basal levels indicates the success in eradicating the tumor. Calcitonin levels usually stabilize by about 72 h after surgery, but may continue to fall thereafter. Post-

operative surveillance is necessary to monitor for persistent or recurrent disease. Patients with mildly elevated (<150pg/mL) but stable serum calcitonin levels following adequate primary surgery should be observed. New calcitonin elevation, rapid calcitonin doubling time, or onset of palpable disease should prompt a metastatic workup. Workup for detection of local disease should start with a neck ultrasound. FNA of any suspicious masses may confirm the diagnosis. Evaluation for distant disease should include CT of the neck, chest and abdomen. FDG-PET imaging may also be helpful in detecting recurrence. Many patients with persistently high levels of calcitonin following surgery will do well for years without radiographic or clinical evidence disease recurrence.

Management of Persistent or Recurrent Disease

Surgical Therapy

Reoperation is usually reserved for patients with elevated calcitonin levels in the setting of inadequate initial operation, imaging evidence of recurrent or persistent disease, and threat of compression or invasion of the trachea and major vessels. In experienced hands, reoperative surgery for locoregional disease can achieve long term biochemical cure in up to one third of patients.(19) Prior to proceeding with neck reoperation with curative intent, a metastatic work-up is necessary to evaluate the lungs, liver, and bones. Patients who have systemic symptoms of the metastatic tumor burden (i.e. pain, flushing and diarrhea) may benefit from a palliative tumor debulking procedure.

Re-exploration of the neck carries a higher risk of complications, including thoracic duct leak, injury to a recurrent laryngeal nerve, and hypoparathyroidism. Central neck reoperations in children are especially dangerous because of the small size of the parathyroids, and should be avoided unless absolutely necessary. Redo central neck dissection may be facilitated by a “back-door” or lateral approach, where the strap muscles are mobilized laterally off of the carotid, and the space between the carotid and the trachea is entered through a previously un-operated tissue plane.(20) The recurrent laryngeal nerve and parathyroids may then be identified and preserved. Lateral neck dissections (Levels II through V) are performed as necessary based on preoperative ultrasound and surgical palpation. FIGURE 4

Radiation Therapy

Radioactive iodine ablation has not been shown to be beneficial in MTC likely because the tumor cells do not take up iodine. A “bystander effect” has been suggested for radioactive iodine treatment of small intra-thyroidal tumors but this has only been reported anecdotally. Currently published studies investigating the role of external beam radiation therapy (EBRT) in MTC have been retrospective series utilizing small patient cohorts. The benefit of EBRT in MTC thus remains controversial. Based on these studies patients most likely to benefit from post-operative EBRT are those whose pathology demonstrates “high risk features” such as microscopic residual disease, extraglandular invasion, or lymph node involvement. In the study by Brierley et al forty-six of 73 patients underwent EBRT at a median dose of 40 Gy. Overall, there was no benefit shown for those receiving EBRT. (21) Subgroup analysis of 40 patients with “high-risk features”, however, showed a higher local/regional

relapse-free rate in radiated patients compared to non-radiated patients. Unlike the surgical series, however, none of these studies showed that EBRT reduced calcitonin levels in any MTC patient. The added disadvantage of EBRT is its effect on tissues (i.e. radiation induced scarring and fibrosis) which makes subsequent surgical intervention more difficult and risky.

Systemic Therapy

The use of immunotherapy antibody based treatments targeted at CEA in selected MTC patients showed limited promise in clinical trials. A single study using the humanized anti-CEA mono-clonal antibody labetuzumab showed significant inhibition of MTC tumor growth in vivo but in a phase I trial employing labetuzumab there was only limited benefit in patients with advanced MTC.(22) It was expressed by the authors that the lack of a significant treatment response could be related to the relationship between pharmacokinetics and tumor burden suggesting that the drug would likely be more successful in patients with early stage disease.

Previous clinical response rates for chemotherapy in patients with locally advanced or metastatic MTC have been disappointing. The understanding of MTC molecular oncogenesis, however, has resulted in identification of novel molecular targets for treatment. The majority of current targeted molecular therapies fall under the classification of tyrosine kinase inhibitors (TKI).(23) Vandetanib (ZD6474, Zactima) is a novel anilinoquinazoline compound engineered to selectively inhibit vascular endothelial growth factor receptor (VEGFR), endothelial growth factor receptor (EGFR), and RET tyrosine kinases.(24) Several multi-institutional phase II trials are ongoing for MTC patients with unresectable, measurable, and locally advanced MTC. Results have been encouraging, but have not been published as of this writing.

Sorafenib, (BAY 43-9006), is an orally formulated TKI that selectivity targets RET.(25, 26) The drug in the United States is currently approved by the Food and Drug Administration (FDA) for the treatment of advanced renal cell cancer and unresectable hepatocellular cancer. Its efficacy in MTC has only been tested in very small pilot studies. (27) The results are promising with 2 patients exhibiting a response one of whom had a complete response just after 6 months of treatment. A larger, phase II trial is currently underway.

In a phase II trial using sunitinib (SU11248) treatment was associated with disease stabilization in 5/6 MTC patients.(26) The chemotherapeutic agent 17-Allylaminogeldanamycin acts as both a heat shock protein and a tyrosine kinase inhibitor. In vivo it has been shown to have specific activity against RET protein and MTC Cell lines. (23) This drug is currently being tested in patients with advanced medullary and differentiated thyroid carcinomas. Many of these newer targeted therapies have a cytostatic effect on tumor progression, with no complete, durable responses as yet. In the future, new agents and combinatorial therapy will be evaluated.

Prognosis and Long Term Survival

The American Joint Committee on Cancer defines four stages of disease in MTC. The different stages take into account tumor size, evidence of regional lymph node or distant

metastases, and tumor invasion. In one study 10-year cause-specific survival was 71%. Of the 53 patients with MTC the mean age at diagnosis was 46 and distribution of familial and sporadic MTC was 17% and 83% respectively. Prognosis was most influenced by stage and postoperative basal calcitonin levels correlated most strongly with survival.(28) In a later review of 104 patients of which 44% had hereditary MTC cause-specific survival was 89%. By univariate analysis, age, stage, gender, distant metastases, extent of surgery were all significant prognostic factors. Only age and stage, however, were statistically significant by multivariate analysis.(29) This was confirmed in a more recent review by Rendel et al where again the most sensitive predictors of survival were age at diagnosis and tumor stage.(30) In this series, there was a difference in survival time based on whether patients achieved biochemical and radiographic remission. In those who did not, 10-year survival was slightly reduced to 73%. These observations demonstrate the indolent nature of the disease, the appropriateness of reoperative surgery when technically possible, and the potential usefulness of cytostatic agents that keep clinically occult disease under control.

Genetic Basis of Familial MTC and Phenotype Correlations

The predisposition gene for MEN 2A, 2B, and FMTC is the *RET* proto-oncogene, located on chromosome 10q11.2. This gene encodes a tyrosine kinase receptor protein involved in growth, differentiation, and migration of developing tissues. The full-length protein includes an extracellular cysteine-rich ligand-binding domain, a transmembrane domain, an intracellular juxtamembrane domain, and an intracellular tyrosine kinase domain. The mutations responsible for MTC are missense mutations, that result in amino acid changes that cause “gain-of-function” alterations in the protein.(31) These are inherited in an autosomal dominant fashion. Thus MEN2 carriers confer a 50% risk of genetic transmission to their offspring.

There are consistent associations between the specific *RET* mutation (genotype) and clinical phenotype of patients with familial forms of MTC (TABLE 1). This includes age of onset, aggressiveness of MTC, and presence or absence of other endocrine neoplasms. MEN2B patients expressing the M918T mutation have the most aggressive forms of MTC with evidence of disease often present in early infancy. MEN2A patients have a variable course of MTC disease presentation and progression, whereas FMTC patients demonstrate an indolent form that more often presents in the later decades of life. There is considerable overlap between the *RET* codons affected in FMTC and those in MEN2A, which supports the theory that FMTC is a variant of MEN2A and not a distinct clinical entity.

Pheochromocytoma is detected in about 50% of patients with 634 and 918 mutations but rarely is seen in mutations of exon 10 (codon 609, 611, 620). The specific amino acid change within the codon may also affect expression of features in MEN 2. In MEN2A patients with amino acid substitutions at codon 618, the penetrance of pheochromocytoma is variable, where C618R shows 41% penetrance, C618G 24%, and C618Y 0%.(32) Hyperparathyroidism in MEN2A is most commonly associated with the C634R mutation. (33)

These genotype-phenotype correlations have important implications for the management of MEN2 patients and their families. Knowing the specific *RET* codon mutation allows the clinician to stratify patients into specific risk groups that help predict the age of onset and aggressiveness of MTC, as well as the need for biochemical surveillance of the associated endocrine neoplasms. The original consensus guidelines written in 2001 identify three risk groups: low (Level I), high (Level II) and highest (Level III).(34)

Preventative Surgery in MEN 2 Predisposition Gene Carriers

The best chance for cure in familial MTC is provided by complete surgical resection prior to malignant transformation or before spread beyond the thyroid gland. Patients with specific germ-line *RET* mutations are stratified into specific risk groups based on reported age of onset and aggressiveness of the disease. Patients with the highest risk (Level III) are MEN2B and should undergo prophylactic total thyroidectomy as soon as possible within the first year of life. Individuals with MEN2A mutations (codons 611, 618, 620, and 634) are considered high risk and should undergo thyroidectomy around age 5.(35) In our experience and others the risk of nodal metastases in MEN2A or FMTC patients less than 8 years of age is extremely low, and has not been reported if the calcitonin level is less than 40 pg/ml.(35) Furthermore, there was a 6-8% incidence of hypoparathyroidism in children undergoing routine central neck dissection.(35) For these reasons we no longer routinely perform central neck dissections in these young patients, unless indicated by preoperatively elevated serum calcitonin levels (>40 pg/mL in a child > 6 month old), radiographic evidence of lymph node metastases, or nodules >5 mm in size at any age. In familial MTC patients with level I *RET* codon mutations the need for prophylactic thyroidectomy before age 5 is controversial. If patients are not undergoing surgery they should be followed closely with annual basal serum calcitonin levels and neck ultrasound.

More than 50% of sporadic MTCs (sMTC) harbor a *RET* mutation in the tumor cells only (somatic mutation).(36) The utility of identifying whether a *RET* mutation is present in the tumor cells in sporadic MTC has yet to be defined, but it has been suggested that sporadic MTCs with somatic *RET* mutations in codon 918 are more aggressive than tumors without the mutation.(37, 38)

In the absence of symptoms consistent with catecholamine excess or known adrenal mass, routine surveillance for pheochromocytoma is dictated by the familial subtype and the identified *RET* mutation. The incidence of pheochromocytoma before the age of ten in any form of familial MTC is exceptionally rare, although our group recently removed a 5 cm pheochromocytoma from an 8 year old girl with MEN 2A (codon 634 mutation). Plasma metanephrines, or 24 hour urine catecholamines should be checked annually in patients with MEN 2A and MEN 2B. In MEN2A patients surveillance for primary hyperparathyroidism by measurement of serum calcium levels should begin around age 10 in those carrying the *RET* 630 and 634 mutations, and at age 20 years of age for those carrying mutations in the other codons.

Conclusions

Medullary thyroid cancer accounts for 5- 10% of all thyroid cancers. The high frequency of familial cases mandates screening and genetic testing. The aggressiveness and age of onset of familial MTC is different depending on the specific genetic mutation, and this should determine the timing and extent of surgery. Sporadic MTC can present at any age, and is usually associated with a palpable mass and the presence of nodal metastases. Surgery is standard treatment for any patient presenting with resectable MTC. Further studies are needed to investigate the role of radiation therapy in the palliation and local control of post-resection and advanced stage MTC. New systemic therapies for metastatic disease are being investigated. Targeted molecular therapies, based on knowledge of the pathways affected by RET mutations, are being tested in multiple clinical trials.

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Figure 1.

Features of MEN 2A and 2B syndromes. A. Bisected thyroidectomy specimen showing multifocal, bilateral MTC tumors. B. Adrenalectomy specimen showing pheochromocytoma. C. Megacolon in patient with MEN 2B. D. Tongue nodules in patient with MEN 2B. (Photograph A courtesy of Dr. S.A. Wells. Photographs B, C and D courtesy of Dr. R. Thompson) (reprinted with permission from Moley, JF, Medullary thyroid cancer, from Textbook of Endocrine Surgery, ed. Clark, OH, and Duh, Q-Y, WB Saunders Co, Philadelphia, 1997)

Figure 2.

Schematic representation of the anatomic landmarks and lymph node compartments in the neck and upper mediastinum encountered in surgical reinterventions in medullary thyroid carcinoma. The central compartment is delimited inferiorly by the innominate vein, superiorly by the hyoid bone, laterally by the carotid sheaths, and dorsally by the prevertebral fascia. It comprises lymphatic and soft tissues around the esophagus as well as pretracheal and paratracheal lymph nodes which drain the thyroid bed (level VI). The submandibular nodal group (level I) is subsumed in the central compartment by some classifications. The lateral compartments span the area between the carotid sheath, the sternocleidomastoid muscle and the trapezius muscle. The inferior border is defined by the subclavian vein, and the hypoglossal nerve determines the superior boundary. The lymph node chain adjacent to the jugular vein is divided cranially to caudally in superior jugular nodes (level II), midjugular nodes (level III), and inferior jugular nodes (level IV). Lymph nodes situated in the posterior triangle between the dorsolateral sternocleidomastoid muscle, the trapezius muscle and the subclavian vein are classified as level V nodes. Mediastinal lymphatic tissue is referred to as level VII lymph nodes (Reprinted with permission from Musholt TJ, Moley JF. *Prob Gen Surg* 14, 1997).

Figure 3.
Total thyroidectomy and central neck dissection in a MEN 2A patient with palpable MTC.
(Photos by author)

Figure 4.
Photograph of central neck compartment after redo central neck dissection for persistent medullary thyroid carcinoma. Thyroid and central neck lymph nodes have been removed, parathyroids were removed and autotransplanted. (Photo by author)

Table 1

Genotype-phenotype correlation in hereditary medullary thyroid carcinoma. Risk levels are based on 2001 consensus guidelines (). Asterix indicates mutations not reported at the time of consensus guidelines publication.

Codon	Risk Level	MEN 2B	MEN 2A			FMTC	HSCR
			MTC	Pheo	HPT		
533	I		X	X		X	
9-bp ins	I*					X	
606	I*		X				
609	II*		X	X	X	X	X
611	II		X	X	X	X	X
618	II		X	X	X	X	X
620	II		X	X		X	X
630	II*		X		X	X	
631	I*		X	X		X	
634	II		X	X	X	X	
768	I		X	X		X	
777	I*					X	
790	I		X	X		X	
791	I		X	X	X	X	
804	I		X	X	X	X	
804+806	III*	X					
883	III	X					
891	I		X			X	X
912	I*						
918	III	X					