GENERAL SESSION I: MG AND PARNEOPLASTIC SYNDROMES
Friday, September 6, 2013 – 08:30 – 10:00

GS1.2: PARANEOPLASTIC SYNDROMES ASSOCIATED WITH THYMIC TUMORS

Eric Lancaster
University of Pennsylvania, Philadelphia/UNITED STATES OF AMERICA

Thymoma is associated with a diverse range of autoimmune neurological disorders. The most well-known and common manifestation involves antibodies to the nicotinic acetylcholine receptor in patients with myasthenia gravis. It is estimated that 20% of patients with myasthenia gravis have thymic tumors and 15-40% of patients with thymoma may have neurological syndromes. While the relationship between myasthenia and thymoma has been studied extensively, the other paraneoplastic disorders associated with thymoma have drawn less attention. The second most common autoimmune neurological disorder associated with thymoma (after myasthenia) is Isaacs' syndrome (acquired neuromyotonia), a syndrome of peripheral nerve hyperexcitability resulting in diffuse muscle fasciculations, hyperhidrosis, and muscle spasms. Encephalitis is somewhat less common and typically manifests as subacute memory impairment, seizures, confusion, and behavioral changes. Morvan's syndrome is also associated with thymoma and involves a combination of peripheral and central nervous system symptoms: fasciculations, hallucinations, cramps/muscle spasms, insomnia, and encephalitis. Patients with Isaacs' syndrome, Morvan's syndrome, or encephalitis may have antibodies to the voltage-gated potassium channel (VGKC) complex, but these antibodies rarely, if ever, actually target potassium channel subunits directly. Rather the main target antigens are two proteins associated with Kv1 potassium channels, LGI1 and Caspr2. (There may also be other, as yet unknown, proteins associated with the VGKC complex that are antigens in some cases). LGI1 is a secreted synaptic protein that organizes potassium channels and other proteins at CNS synapses. Patients with LGI1 antibodies have encephalitis, usually respond well to immunotherapy, and do not typically have associated tumors. Caspr2 is an axonal protein critical for organizing VGKCs into the correct subcellular domain, the juxtaparanodes, on myelinated axons of both the CNS and PNS. It is unsurprising therefore that patients with Caspr2 antibodies may have PNS (Isaacs' syndrome), CNS (encephalitis) or both CNS and PNS manifestations (e.g. Morvan's syndrome). Patients with Caspr2 antibodies may have PNS and CNS symptoms in either order, often months or years apart, or concurrently. Thymoma is particularly associated with Caspr2 antibodies and not LGI1 antibodies. In addition to VGKC complex antibodies, patients with thymoma may rarely develop encephalitis associated with paraneoplastic antibodies to Hu, CRMP-5, Ma, or other antigens. In these disorders the antibodies are probably not directly pathogenic and more likely represent a T-cell mediated response targeting neurons. The prognosis is correspondingly poor. Patients with thymoma may also present with autoimmune peripheral neuropathy, pain syndromes, and/or autonomic dysfunction (including Horner's syndrome). And some patients may have multiple autoimmune neurological syndromes. For example, patients with Morvan's syndrome due to Caspr2 antibodies may have co-existing myasthenia gravis with acetylcholine receptor antibodies. In these cases the combination of diffuse fasciculations from Morvan's syndrome and bulbar weakness from myasthenia may create a confusing clinical picture that could be mistaken for motor neuron disease (ALS). Polymyositis, autoimmune muscle inflammation, may occur in the setting of thymoma, and may be comorbid with myasthenia gravis. Stiff person syndrome, a disorder of hyperexcitability at the spinal cord level resulting in painful muscle spasms and debilitating increase in muscle tone, may also occur in the setting of thymoma. Stiff person syndrome is sometimes associated with antibodies to GAD65. Isaacs' syndrome is usually treated symptomatically with voltage-gated sodium channel antagonists such as phenytoin or carbamazepine. In severe cases immunotherapy with steroids, IVIg and other agents is required. For encephalitis or Morvan's syndrome associated with Caspr2 antibodies, treatment with steroids, IVIg and other immunotherapies should begin promptly. Most patients with Caspr2 antibodies respond to immunotherapy and recover to normal or to only mild disability over a period of weeks to months. However, relapses may occur with tapering of immunotherapy. Immunotherapy is also attempts for patients with classical paraneoplastic antigens (Hu, Ma, etc.) but is less likely to be effective. Tumor therapy is also any important consideration in all patients with thymoma and may help associated autoimmune disorders. The optimal treatments for all of these disorders have not been established. In summary, thymic tumors are associated with myasthenia gravis, encephalitis, Isaacs' syndrome, Morvan's syndrome, and other autoimmune neurological syndromes. Testing for antibodies to the nicotinic acetyl choline receptor, VGKC complex and other paraneoplastic antibodies may

assist with diagnosis. Due to these associations clinicians should be vigilant for signs of myasthenia gravis, Isaacs' syndrome, encephalitis and other neurological manifestations in patients with thymoma. These disorders may emerge at any point in the disease course and cause significant morbidity but often respond to immunotherapy. Conversely, the identification of myasthenia gravis or the other syndromes should prompt careful screening for thymoma and urgent treatment of any thymic tumor.

Keywords: thymoma, antibody, paraneoplastic, autoimmune

GENERAL SESSION I: MG AND PARNEOPLASTIC SYNDROMES

Friday, September 6, 2013 – 08:30 – 10:00

GS1.3: QUALITY OF LIFE MEASURES IN MYASTHENIA GRAVIS

Sami Khella

Neurology, University of Pennsylvania, Philadelphia/UNITED STATES OF AMERICA

Myasthenia gravis (MG) is a disease of immune mediated attack on the postsynaptic membrane of the neuromuscular junction causing weakness of skeletal muscles. This illness mostly occurs in adults and typically affects the eyes, oropharynx, respiratory, and axial muscles. The weakness is reversible with a variety of treatments. As treatment has evolved over the last 80 years, physicians have developed instruments to measure patient improvement. This discussion is a brief summary of the most salient measuring tools available.

Over 50 years ago, the World Health Organization defined quality of life, and more specifically, health related quality of life (HR-QoL) in its charter. The modern concept, a direct descendent of the original definition takes many forms, one of which is the perception of and satisfaction with the individual's current state of health with regards to physical, psychological and social well being regardless of the presence or absence of disease. An ideal HR-QoL instrument would capture these three domains and summarize them in a single metric. Using this definition, it is apparent that the first instruments in the published literature measuring treatment responses in patients with myasthenia gravis didn't include many of these domains. Instead, the concentration was on the physician's observations of the disease's response to treatment. The earliest and simplest category was achievement of remission. Later, categorization was based on various changes in muscle strength or eye-lid ptosis with cholinesterase inhibitors or immunosuppression. Probably the best-known iteration of these grading systems in the modern period is the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification.[1] To address functional status in clinical trials some investigators used non-MG specific scales, e.g. a modified Rankin score or the WHO Disability Assessment Schedule (WHO-DADS). With the advent in the 1980's of summative rating scales in MG, investigators noted the poor correlation with the grading and classification systems then available. The MGFA's Medical Scientific Advisory Board emphasized that the MGFA Clinical Classification should not be used to measure a change in severity because of the availability of ordinal severity rating scales. Some of these summative rating scales classify patients by physical examination findings, e.g. the Manual Muscle Test for MG or Mantegazza's et al. MG Score. While these instruments provide invaluable information regarding a patient's physical response to treatment, they do not address the critical domains of mental and social well being that may be equally, and in some cases more affected by MG. To that end, investigators developed scales to address impairment of the HR-QoL. Initially, non-MG specific scales were used, e.g. the Short Form (36) health survey (SF-36), a self-administered survey of emotional and physical factors. These proved insensitive to the focal weakness occurring in MG. For example, neither ocular nor bulbar weakness resulted in deterioration in HR-QoL when these scales were used in several studies.[2,3] Hence the development of the MG-specific questionnaire (MGQ), a self-administered, validated measure of functional status. Another is the MG Composite scale. This region specific targeted approach is theoretically attractive but has yielded mixed results. When patients were asked to choose 2 of the symptoms most bothersome to them out of the 10 listed on the MG Composite scale, they most frequently chose two of the following: ptosis, double vision and trouble swallowing. However, this "choose 2" paradigm didn't correlate well (lower sensitivity and specificity) with the clinical improvement detected by the total score of the MG Composite score.[4] While investigators have been advised not to use the "choose 2" paradigm, it is apparent that further clarification is needed as to why this tool is unhelpful. Perhaps, the scale is too insensitive to patients' needs or the therapy is inadequate. In further attempts at measuring HR-QoL, more multidimensional instruments are needed that measure tolerability of dysfunction – ptosis to a carpenter may affect her more than it does a neurologist. Such instruments should measure the impact of disease on the physical, psychological, social and occupational well being of an individual. One such tool is the

Individualized Neuromuscular QOL (INQoL), another is an MG-specific measure of QOL developed for a treatment trial. These questionnaires are 45 and 60 questions long respectively. The surveys assess domains of mobility, emotional well-being, general contentment, thinking, fatigue, and additional concerns. In one study, there was some correlation with some of the physical score instrument and a better performance than the SF-36. To simplify and allow use in daily clinical practice a 15 item MG-specific QOL (MG-QOL 15) tool drawn from the 60 question long MG QOLhas been developed. This tool correlated highly with the 60 item QOL for the physical domains, and it correlated well with the social domains of the SF-36.[5] It also correlated with MGQ, MG-MMT and MG-ADL. The MG-QOL 15 demonstrated high sensitivity and it has been validated in an 11-center prospective study of 175 patients with MG.[5] Much improvement has occurred in the last few decades in measuring treatment responses of the whole individual with myasthenia gravis. Much work remains to make these measuring instruments more refined, and simultaneously more comprehensive. They also have to be easy to complete, calculate and interpret.

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Keywords: myasthenia gravis, quality of life, outcome measures, MG QOL 15

GENERAL SESSION I: MG AND PARNEOPLASTIC SYNDROMES

Friday, September 6, 2013 – 08:30 – 10:00

GS1.4: DEVELOPMENT OF THE PATIENT-DRIVEN MYASTHENIA GRAVIS REGISTRY

Henry Kaminski
Department Of Neurology, George Washington University, Washington/UNITED STATES OF AMERICA

Patient registries are organized systems that use observational methods to collect uniform data and have proven to highly effective in establishing platforms for planning clinical trials, assessment of patient characteristics, performing economic analyses, and providing a conduit for patient education. After decades of patient requests, the MG Foundation of America sponsored the development of a registry based on patient based submission of data. Using as a model a highly successful of registry dedicated to multiple sclerosis, the organizing committee obtained commentary from physicians involved in clinical care and research, patients, nurses, the ITMG, and administration of the MG Foundation to finalize the registry questions. The 24 page questionnaire covering demographic, insurance, diagnostic, quality of life, and treatment issues will require web-based data entry, hosted by the University of Alabama at Birmingham. Investigators will be able to access de-identified data after Ethics or Internal Review Board approval. Individuals from across the world could submit information to the system, but at present the registry is highly biased towards US healthcare issues. The MG Patient Registry was activated in July of 2013. Initial response to the MG Registry will be presented. Yearly newsletters will be sent to participants that provide summaries of data acquisition as well as MG related educational information.

Keyword: myasthenia gravis, patient registry

GENERAL SESSION II: THYMUS AND THE IMMUNE SYSTEM
Friday, September 6, 2013 – 10:30 – 11:45

GS2.1: THYMOMA AND THE IMMUNE SYSTEM

Benny Weksler
Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh/PA/UNITED STATES OF AMERICA

Thymomas are rare neoplasms, with an incidence of 0.13 per 100.000. Thymomas are distiguished by their indolent and slow growing nature and by a relatively low rate of recurrence. Another distinguishing factor is the association of thymomas and autoimmune diseases. Between 30% and 50% of all patients with thymoma either will be diagnosed with an autoimmune syndrome, myasthenia gravis being the most common. Other less common autoimmune diseases include systemic lupus erythematosus, red cell aplasia, bullous pemphigus, and syndrome of inappropriate antidiuretic hormone secretion. Even more rarely, thymomas are associated with thyroiditis, polymyositis, rheumatoid arthritis, encephalitis, and ulcerative colitis. Less often recognized is the association of thymoma and immunodeficiency, often called Good's syndrome. Although lacking clear diagnostic criteria, Good's syndrome often presents with hypogammaglobulinemia, decreased number of circulating B and T cells, and abnormal CD4:CD8 ration. Patients with thymoma also have a higher incidence of extrathymic cancers. This is attributed to decreased or inappropriate immunosurveillance a T cell lymphocyte function. The most common extrathymic cancers are lymphomas, breast carcinomas, prostate cancer, and lung cancer. Interestingly, the incidence of extrathymic cancers is increased prior to the diagnosis of thymoma. Also autoimmune diseases and secondary neoplasms appear to be more common in World Health Organization (WHO) type B thymomas. The thymus is central to the development and selection of T cell lymphocytes (TCL) by releasing TCL attracting hormones. TCL's enter the cortical thymus where positive selection occurs. Only TCL's that bind to self Major Histocompatibility Complex (MHC) antigens are selected and allowed to proceed to the medulla. In the medulla, the important negative selection occurs and TCL reacting to self tissue specific antigens are deleted. The Autoimmune Regulator gene (AIRE) is thought to be crucial in the process of negative selection by controlling the expression of tissue specific antigens in the thymic medullary epithelial cells.

Although this is a simplistic explanation of the role of the thymus in TCL development, this model of clonal selection holds true and serves to illustrate some of the current theories on the association of thymomas and autoimmune disease and secondary neoplasms. It is important to note that patients with thymomas have immature TCL's in the periphery that are thought to originate from the tumor itself. Also, in over 90% of thymomas the neoplastic cells do not express AIRE. There are different theories on the etiology of the immune disturbances in patients with thymoma. The current theories are not mutually exclusive.

a. Immature T-cell theory Thymocytes derived from thymomas may be immature, which is supported by expression of antigens such as TdT+, T6+, T4+, and T8+, which are markers of TCL immaturity. Immature thymocytes lack the important negative clonal selection in the thymic medulla where self-tolerance is induced. Those immature TCL's are released to the periphery and become autoreactive. The higher incidence of immune disorders in patients with WHO type B thymoma that are thought to originate from the cortical thymic epithelial cells appear to partially support this theory.

b. Neoplastic-genetic theory Antigen specificity is acquired in the thymic cortex causing a rearrangement of T-cell receptor genes. In thymomas, the neoplastic cortical cells are rapidly dividing, increasing the chances of genetic mutations. Neoplastic thymic epithelial cells in thymomas are genetically different from normal thymic epithelial cells and often present with impaired expression of HLA-DR. This affects positive cortical selection and may be a factor in auto reactivity to HLA-B8 and HLA-A24, both significant predictive factors for myasthenia gravis.

c. Combined cellular and humoral theory This theory links the cellular and humoral arms of the immune system. The first step is the release of a large number of thymoma derived CD8 TCL's with impaired self-tolerance, initiating the autoimmune process. CD4 TCL's are then activated, which in turn activate B cells to produce autoimmune antibodies. The presence of autoantibodies in patients with thymoma and a range of autoimmune diseases support this theory. Also, this theory explains the immunodeficient syndromes in patients with thymoma, believed to be caused by autoantibodies directed towards cytokines such as interferon gamma, interferon alpha, IL-22, IL-17, and IL-12.

All three theories are attractive and it is quite possible that all three mechanisms interact in patients with thymoma.

However, all three theories are centered on the released of abnormal or immature TCL to the periphery by the thymoma. This may not explain our finding of increased incidence of extrathymic cancers prior to the diagnosis of thymoma. Some of the patients in our study had an extrathymic cancer diagnosed over 5 years prior to the diagnosis of thymoma, and the incidence of extrathymic cancers prior to the diagnosis of thymoma was 8 times that of the age matched general population. We have been working with an alternative theory that may explain the higher incidence of cancers prior to the diagnosis of thymoma. We hypothesize that the disturbance in TCL's "education" originates in the non-neoplastic thymic epithelial cells, which may explain the immune deficiency prior to the diagnosis of thymoma. We also hypothesize that the thymoma may be a marker of an already disturbed thymic epithelial cell. In summary, thymomas are closely linked to immune phenomena such as autoimmune diseases, immunodeficiency, and increased incidence of secondary cancers. It is hard to explain all syndromes with current theories and it is quite likely that more than one theory plays a role in each case. More studies are needed to properly clarify the role of the thymic epithelial cell and thymoma in the immune syndromes associated with thymoma.

GENERAL SESSION II: THYMUS AND THE IMMUNE SYSTEM
Friday, September 6, 2013 – 10:30 – 11:45

GS2.2: THYMOMA, ANTICYTOKINE AUTOANTIBODIES, AND IMMUNODEFICIENCY

Sarah Browne
Laboratory of Clinical Infectious Diseases NIAID, NIH, Bethesda/UNITED STATES OF AMERICA

The importance of anticytokine autoantibodies in disease pathogenesis is being increasingly appreciated with examples including pure red-cell aplasia due to anti-erythropoietin autoantibodies, pulmonary alveolar proteinosis due to anti-GM-CSF autoantibodies and adult onset immunodeficiency due to anti-interferon-gamma autoantibodies. Patients with thymic malignancy have high rates of autoimmunity leading to a variety of autoimmune diseases, most commonly myasthenia gravis caused by anti-acetylcholine receptor autoantibodies. High rates of autoantibodies to cytokines have also been described, particularly in the context of opportunistic infection, although their specific contribution to the development of autoimmunity or immunodeficiency remains to be quantified. Interestingly, many patients also show aberrancies in B and T cell subsets, further complicating whether the basis of their immunological dysfunction is humoral, cellular or both. Further investigation into the relationship between anticytokine autoantibodies and thymoma may shed light on the immunological complications seen frequently in thymoma as well as inform us about underlying mechanisms of autoimmunity and anticytokine autoantibody production in general.

Keywords: anticytokine autoantibodies, immunodeficiency

GENERAL SESSION II: THYMUS AND THE IMMUNE SYSTEM
Friday, September 6, 2013 – 10:30 – 11:45

GS2.3: CELLULAR CROSS-TALK IN THE DEVELOPMENT OF THE THYMIC ENVIRONMENT

Richard Hodes
NIH, Bethesda/UNITED STATES OF AMERICA

Cross-talk between mature single positive (SP) thymocytes and thymic medullary epithelial cells (mTEC) is critical for thymic development and maintenance of self tolerance. We have analyzed the role of CD28-CD80/86 and CD40-CD40L costimulatory interactions, which are mediators of negative selection and self tolerance, on mTEC development. We find that these costimulatory pathways are critical for medullary development and that their function involves regulation of LTa, LTb and RANK expression. To probe the mechanism underlying the requirement for SP thymocytes in medullary development, we assessed the effect of selective deletion in TEC of TRAF3, an inhibitor of non-classical NF-kB signaling. We find that TEC-specific deletion of Traf3 sustains RelB-dependent mTEC development in the absence of CD40 and LTbR, or in the complete absence of TCRab SP thymocytes. In contrast, deletion of TRAF3 failed to reverse mTEC deficiency in the absence of RANKL, consistent with a necessary role of RANKL expressed on cells other than SP thymocytes. These findings demonstrate a striking link between costimulatory requirements for negative selection of self-reactive T cells and the requirement of these same CD28 and CD40L costimulatory pathways for development of the medullary compartment in which negative selection occurs. We further find that signaling by costimulatory molecules expressed by SP T cells is needed to overcome TRAF3-imposed arrest in mTEC development mediated by inhibition of non-classical NF-kB. We conclude that TRAF3 imposes requirements for SP T cells and costimulation-mediated crosstalk in generation of the medullary

compartment in which costimulus-dependent tolerization occurs.

Keywords: thymus, crosstalk, NFkB

GENERAL SESSION III: BASIC SCIENCE
Friday, September 6, 2013 – 13:15 – 15:00

GS3.1: PRECLINICAL MODELS FOR THYMIC TUMORS

Yesim Gökmen-Polar
Department Of Pathology & Laboratory Medicine, Indiana University School of Medicine, Indianapolis/UNITED STATES OF AMERICA

Preclinical models have been important tools to understand the molecular pathology of human cancers and to develop better therapeutics. Various human cancer cell lines isolated from patient tumors have provided extensive information for the cellular and molecular mechanisms of cancer biology. Additionally, recent improvements in genomic technologies are providing rational therapeutic strategies targeting distinct pathways. The successful translation of such targeted drugs to clinical application depends on effective *preclinical proof of concept models* in relevant cancers. Recapitulating the underlying genetics, these models may offer distinct advantages in the preclinical testing of potential therapies. However, this has not been the case for thymic malignancies. New treatments are based on the studies extrapolated from other epithelial tumors. Targeted therapeutic strategies are not available due to the rarity and complexity of the disease and lack of relevant *in vitro* and *in vivo* models. In this presentation, I will be discussing the established preclinical models involving current *in vivo* and *in vitro* models and their utility relevant to thymic malignancies. ***In vitro* models** Among the four human cell lines reported to date, three were isolated from thymic carcinoma patients (1-3), while one cell line was established from type B1 thymoma (3). We recently have established and characterized a novel thymoma cell line (IU-TAB-1), which was derived from a patient with the stage II thymoma (WHO-type AB tumor)(4). Histological and FACS analyses confirmed the thymic epithelial (TE) nature of this cell line by the presence of epithelial cell markers (pan-cytokeratin and EpCAM/CD326), the presence of cell surface markers of TE cells and nuclear p63 and by the absence of lymphoid and other leukocyte and T-cell markers. Unlike the indolent behavior of IU-TAB-1, the thymic carcinoma cell line established by Ehemann et al. was derived from a poorly differentiated thymic carcinoma (Stage III) and exhibits a high proliferation index. ***In vivo* models** We have further developed an *in viv*o model (IU-TAB-1/NOD/SCID xenograft model) forming ectopic tumors that reached a volume of 1000 mm^3 at around 130 days when in Matrigel-plugs, and around 148 days when implanted alone (4). Importantly, the kinetics of tumor development is consistent with the indolent nature of AB thymomas. We also determined the tumorigenicity of the thymic carcinoma cell line (kind gift of Dr. Rieker, Heidelberg, Germany) in NOD/SCID xenograft model and demonstrated that the thymic carcinoma cells form tumors that reached a volume of 1000 mm^3 at around 45 days when in Matrigel-plugs, confirming that they grow faster than IU-TAB-1 xenograft model. The use of these xenograft models will permit studies of target validation and pre-clinical assessment of targeted therapeutics in this cancer. Our group has also developed an animal model (Thymoma insertional mutation; Tim-1), which spontaneously develop thymomas at a very high penetrance due to the transgene insertional mutagenesis into F2-G region of mouse chromosome 2 (5). Tumor progression leads to obstruction of the great vessels and death from cardiac failure. Disease is more aggressive in females than in males (at 20 weeks, approx. 75% versus 42% mortality, respectively). Translocation at the syntenic region in humans has been associated with thymomas (6). Cell lines have also been derived from thymic epithelial tumors developed in Tim-1 mice, designated as TVT cell lines, and possess the morphology and properties of cancer epithelial cells. Since the development of tumors in Tim-1 mice is variable and the mice can die early due to cardiovascular complications, we are in the process to develop a Tim-1 mouse derived syngeneic mouse model that will be useful for future preclinical drug screening in thymomas. Development of patient-derived tumor xenografts (PDX) is the next logical step, since these can provide a better understanding of the disease's biology. **Utility of preclinical models relevant to thymic malignancies** These preclinical models can be utilized to validate the functional aspect of the novel molecular targets as well as to evaluate novel therapeutic agents in thymic malignancies. Development of knock-in and knock-down of the genes associated with metastatic gene signature of thymoma (7) and thymic carcinoma (8) will help to understand the unique biology of thymic tumors on their path of progression and metastasis. Interestingly, the IU-TAB-1 cells are not metastatic and exhibit very low expression levels of genes upregulated in gene signature that determines metastatic behavior of thymomas, while thymic carcinoma cell line expresses genes that are upregulated in metastatic phenotype. Besides genetic manipulations, these models are necessary to evaluate both *in vitro* and *in vivo* efficacy of therapeutic agents as well as understanding the molecular basis of these agents found to have some efficacy in patients with thymic tumors. For

example, octreotide, a somatostatin analogue, with known activity in thymomas, can now be compared with next generation analogues such as pasireotide. Our gene expression studies have suggested that PDGFR pathway is significantly associated with metastatic phenotype in both thymoma and thymic carcinoma. Our initial efforts focused on the *in vitro* efficacy of dovitinib alone, a tyrosine kinase inhibitor targeting PDGFR and FGFR, and in combinatorial setting with vorinostat (SAHA), a member of a larger class of compounds that inhibit histone deacetylases (HDAC). Using MTT assay, IC_{50} values of dovitinib, the concentrations that inhibit 50% of cell survival, were similar for IU-TAB-1 (12 μM) and thymic carcinoma cell line (11 μM). No additive effect of SAHA on dovitinib was observed in both cell lines. Further studies are ongoing. In conclusion, these preclinical models will provide excellent tools to study the relevance and functional role of novel therapeutic agents as well as the rationale for combination therapies, and provide insight for the future treatment strategies of patients with these rare malignancies.

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Keywords: Preclinical models, thymoma, thymic carcinoma, human epithelial cancer cell lines

GENERAL SESSION III: BASIC SCIENCE

Friday, September 6, 2013 – 13:15 – 15:00

GS3.2: DEVELOPMENT OF GENE SIGNATURES FOR THYMOMA AND THYMIC CARCINOMA

Sunil Badve

Pathology And Laboratory Medicine, Indiana University School of Medicine and Simon Cancer Center, Indianapolis/IN/UNITED STATES OF AMERICA

Epithelial tumors of the thymic gland are classified as thymomas and thymic carcinomas based on presence of cytologic atypia. Thymic carcinomas are aggressive neoplasms associated with early recurrence, metastasis and often death. In contrast, thymomas are indolent and are relatively infrequent associated with recurrences or metastases. However, recent data including ours suggest that all types of thymomas, albeit with different frequencies, can give rise to metastases. The rarity of the tumors and the indolent behavior of thymomas have led to significant poor understanding of biologic behavior of these tumors. The prognosis of thymomas is based on the following 3 factors: Histologic type, Tumor stage, and the presence of residual disease of the surgery. The histological classification has been controversial.In the WHO working schema, spindle cell thymomas were classified as type A with the additional designation of AB for tumors which are lymphocyte-rich. Tumor is composed of polyclonal cells were classified as of B type with further sub-classification B1 to B3 based on the amount of epithelial cellularity and lymphocyte content. The WHO classification clearly stated that types A, AB and B1 are benign. Recent undertaken by our group in addition to others as clearly demonstrated that thymomas of all histological types give rise to metastatic tumors. The classification can in practice be quite difficult to apply. A recent study analyzed the concordance of 17 thoracic pathologists for classifying 95 cases of thymomas[1]. The overall level of agreement was moderate (kappa 0.45) with significant improvement (kappa 0.63) when cases were classified in two groups (A+AB+B1 and B2+B3+C). Tumor stage is typically determined using the Masaoka staging system. Tumors that are localized with minimally invasion of the surrounding structures have a better prognosis than those associated with invasion of pleura, pericardium and or great vessels. Patients without residual disease have a worse prognosis than those without any residual disease. The utility is operator dependent and to significant extent dependent on grossly visible disease. In order to progress beyond subjective morphological classification or intraoperative assessment of extent of disease, it is necessary to develop an objective method of accessing the prognosis of thymomas. As a first step in this direction, we analyzed the gene expression in a series of 36 thymomas[2]. The analysis of the gene expression study showed that clustering based on gene expression analysis correlated to some extent with histologic classification (*P*=<0.05). However none of the molecular clusters were histologically pure as there was a crossover of different histologies within each cluster. There was no correlation of histology with stage and metastasis. We further analyzed the correlation of gene expression with tumor stage and development of metastasis. Predictive analysis of microarray (PAM) identified 9 genes-based algorithm was associated with tumor stage. Similarly, a combination of 10 genes could identify cases associated with metastasis with a high degree of certainty. In order to

validate this data on qRT-PCR platform validation was performed on 75 cases[3]. This data initially showed that all the 19 genes together could reliably predict the outcomes of thymomas. The signature was further refined to include only the 9 of the 10 metastasis associated genes. The signature was independent of traditional prognostic factors such as tumor size, stage, histology type and extent of residual disease. Further plans include an independent validation of the gene signature in other well annotated cohorts as well as prospective evaluation in clinical trial. It is also important to note that the genes constituting the genes signature are not related to proliferation but have distinct well described roles in other cancers. Identification for prognostic signature in thymomas raises two important questions. 1) Would the signature have utility in thymic carcinomas? and 2) Given the difficulties inconsistently classifying thymomas and distinguishing them from thymic carcinomas, could the signature reliably separate these two entities? The expression of all 19 genes was analyzed in a relatively large series of thymic carcinomas (n=38). This analysis showed two important findings 1) the 9-gene signature is specific for thymomas and loses its predictive abilities in patients with thymic carcinomas. 2) A subsequent analysis showed that the outcomes of patients with thymic carcinomas can be predicted using a subset of 10 genes (from the 19 genes). These genes are distinct from those in the thymoma signature consistent with the biologic difference between the two entities. Given to the relatively small number of cases, we consider this analysis “hypothesis generating” result that needs further confirmation in additional cohorts of patients with thymic carcinoma. The rarity of thymic carcinomas is making it difficult to identify cohorts with well annotated follow-up information. The histologic distinction between thymomas and thymic carcinomas can be on many occasions quite difficult. The presence or absence of cytologic atypia is a subjective distinction. More specifically, the distinction of B3 thymomas with focal atypia from thymic carcinomas can be quite difficult. In addition, cytological atypia has now been described even in spindle cell thymomas. In a recent paper, Nonaka and Rosai describe a series of cases of spindle cell thymomas with significant cytological atypia and mitotic activity[4]. In view of these difficulties, we explored the possibility of using gene expression to distinguish the two entities. The data from this study is being presented at the 2013 ITMIG meeting (Gökmen-Polar et al). In brief, a 12 gene signature can accurately distinguish thymomas from thymic carcinomas ($p<0.001$). In summary, gene expression analyses have identified clear distinction between thymomas and thymic carcinomas. Within thymomas, we have described and validated 9-gene signature for prognostication; the signature is an independent prognostic factor. In a more exploratory analysis, we have further identified a signature that distinguishes thymic carcinomas a poor prognosis from those with relatively good prognosis. It must be noted that the signature of thymic carcinomas requires further validation.

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Keywords: gene signature, thymoma, thymic carcinoma

GENERAL SESSION III: BASIC SCIENCE

Friday, September 6, 2013 – 13:15 – 15:00

GS3.3: NEXT GENERATION SEQUENCING OF THYMIC TUMORS: PRELIMINARY RESULTS

Milan Radovich
Surgery, Indiana University School of Medicine, Indianapolis/IN/UNITED STATES OF AMERICA

Background: Thymomas are one of the most rarely diagnosed malignancies. The challenge of histological subtyping of these tumors along with an inadequate understanding of the transcriptional biology is a hindrance to the development of prescriptive targeted therapies. Next-generation RNA sequencing enables a comprehensive and quantitative measurement of the entire transcriptome. Taking advantage of this technology, we performed comprehensive next-generation RNA sequencing on a set of thymomas to examine the transcriptional landscape of this disease and to identify novel molecular hallmarks which can lead to more precise therapeutic interventions.

Methods: RNA was sequenced from 13 thymic malignancies and 3 normal tissues obtained from the Indiana University Simon Cancer Center using a Life Technologies SOLiD sequencer. The WHO subtypes of our samples were evaluated by a single pathologist blinded to the outcomes of the sequencing and include: (4) type A, (2) AB, (1) B2, (5) B3, (1) C, and (3) normal tissues. For gene expression, reads were mapped to the human genome (hg19) using the LifeScope software with outputs imported into Partek Genomics Suite for statistical analyses and subsequent pathway analyses was performed using IPA 9.0 (Ingenuity Systems). Validation of microRNA expression was performed

using an additional set of 35 thymomas and a custom TaqMan Low Density Array (Life Technologies). For protein measurements, we used pre-made enzyme-linked immunosorbent assays (ELISAs) for PTEN, phospho-AKT (Ser-473), and Beta-Actin (Cell Signaling Technology).For cell based studies, a thymoma cell line (IU-TAB1) was used and cells were treated with a panel of PI3K pathway inhibitors currently in clinical trial (BEZ235, BKM120, CAL-101, GDC-0980, GDC-0941, MK-2206, PF-04691502, XL-147). Cell viability was assessed using the Promega CellTiter-Flour assay, with statistical analysis using Prism Graphpad.

Results: Unsupervised hierarchical clustering of gene expression values revealed 100% concordance between gene expression clusters and WHO subtype. A subsequent unsupervised clustering of 705 precursor-microRNAs also showed substantial concordance between clusters and subtype. By analyzing the dendrograms, A & AB tumors were significantly different from other thymomas. Using differential expression analysis, a substantial differentiator was a large microRNA cluster on chr19q13.42 that is significantly over-expressed in all A & AB tumors and whose expression is virtually absent in the others thymomas. Over-expression of this microRNA cluster, which is normally silent in adult tissues, has been documented to result in hyperactivated PI3K/AKT Pathway by down-regulating PTEN. This was confirmed at the RNA level using pathway analysis revealing over-expression of PI3K-p110, PREX2, and down-regulation of FOXO in A & AB tumors. To confirm the activation of the PI3K/AKT pathway at the protein level, we used ELISAs on protein lysate from our validation cohort and observed significant down-regulation of PTEN, and up-regulation of phospho-AKT (Ser473) in the tissues that were positive for the chromosome 19 microRNA cluster. Lastly, treatment of IU-TAB1 thymoma cells with a panel of PI3K/AKT/mTOR inhibitors resulted in marked reduction of cell viability suggesting sensitivity to these agents.

Conclusions: Next-generation RNA sequencing showed concordance with the WHO thymoma histologic classification and support the notion that AB thymomas are a variant of type A thymomas. Furthermore, the expression of a large microRNA cluster on chr19q13.42 which affects the activity of PI3K pathway is over-expressed only in type A & AB thymomas, suggesting the possible exploration of PI3K inhibitors in patients with these subtypes of tumor.

Keywords: RNA-seq, microRNA, thymoma, Next-Generation Sequencing

GENERAL SESSION III: BASIC SCIENCE

Friday, September 6, 2013 – 13:15 – 15:00

GS3.4: CANCER CARE ENGINEERING PROJECT

Patrick Loehrer

Hematology/oncology, Indiana University School of Medicine and Simon Cancer Center, Indianapolis/IN/UNITED STATES OF AMERICA

The complexities of cancer research, especially in rare tumors are substantial. The normative format for most traditional clinical research is the conduct of prospective randomized trials which are not possible in a disease like thymic malignancies where fewer than 750 cases are diagnosed annually in the United States. The Cancer Care Engineering (CCE) project is a knowledge acquisition framework that integrates clinical observations, patient outcomes and translational research so as to improve treatment outcomes. CCE began with collaboration between a transdisciplinary team (basic scientists, engineers, physicians) from Purdue University and the IUSCC who focused on a common malignancy, colorectal cancer. The challenge was optimizing information management and exchange of clinical information with multi-laboratory analysis of serum and colonic tissue obtained from patient volunteers undergoing routine colonoscopy. The CCE Hub emerged as a unique tool to address these issues. The Hub data base technology provided an opportunity to expand its capability through efforts with the International Thymic Malignancies Interest Group (ITMIG). The challenge was how to perform a global data collection of information of a rare tumor. Together with an ITMIG Working Group, an “essential dataset” spreadsheet was developed. A sophisticated portal was implemented to 1) authenticate contributing hospitals, 2) audit spreadsheets for format & content inconsistencies in addition to other data cleaning, 3) update database with cleaned or augmented hospital data, and 4) generate patient de-identified versions of the data to be used for staging analysis by CRAB[1]. We designed and implemented online searchable “data views” (updated in real time) to explore, search, graph and download – both for restricted hospital viewing and for full database exploration by CRAB from the cceHUB ITMIG portal. Data contributions on a retrospective database began in October, 2012 and as of January, 2103 over 8000 cases have been entered through the cceHUB ITMIG portal. Data has been contributed by hospitals in Turkey, Korea, China, Japan, UK, Thailand, Italy, Germany, Belgium, Netherlands, Argentina, Spain, France, Romania, Denmark, Greece, and the USA. In January, 2013 a prospective database was launched that has dataview

technology, with a customized, event-based workflow to capture detailed, comprehensive patient data by episode for initial presentation, imaging, pathology, surgery, treatment, staging and follow-up. Ongoing collected data will be used for research projects approved by ITMIG.
(Special acknowledgements to Drs. Ann Christine Catlin and Joseph F. Pekny from Purdue University)

GS4.2: RADIATION TECHNIQUES AND TOXICITY IN THYMIC MALIGNANCIES

Andreas Rimner
Memorial Sloan-Kettering Cancer Center, New York/UNITED STATES OF AMERICA

The use of modern radiation techniques with the goal of avoiding toxicity is particularly important in patients who have high expected long-term survival rates such as patients with thymic malignancies. Radiation techniques have markedly evolved over the past 2 decades from two-dimensional treatments to three-dimensional conformal radiation therapy (3D-CRT) and even more conformal intensity-modulated radiation therapy (IMRT) techniques. Furthermore, proton therapy may provide further advantages in sparing normal tissue, and is currently under investigation for thoracic malignancies including thymomas. The availability of on-board image guidance that allows patient imaging on the treatment table has improved our ability to more closely guide and monitor the treatment. Some of these techniques, in particular IMRT, have expanded the technical capabilities of targeting complex shapes, e.g. pleural implants in stage IVA thymomas, while sparing adjacent lungs or heart tissue. The evolution of these radiation treatment techniques has allowed greater sparing of normal organs at risk and led to a decreased risk for short- and long-term toxicities, as illustrated in many organ sites. Accurate target delineation is increasingly critical when highly conformal radiation therapy techniques are used in order to avoid marginal recurrences. Target delineation based on a dedicated treatment-planning CT scan involves the delineation of the gross tumor volume (GTV) in unresectable thymomas or the clinical target volume (CTV) as a surrogate of microscopic residual disease in postoperative thymoma patients. More recently, 4D planning CT scans can be obtained at the time of treatment planning that allow assessment of target motion throughout the respiratory cycle. This leads to an expansion of the GTV/CTV to an internal target volume (ITV). Finally, the ITV is expanded to the planning target volume (PTV), which takes any patient positioning uncertainty and variability into account and represents the volume that the radiation treatment is prescribed to. Modern imaging techniques including PET-CT and MRI may aid in even more accurate target delineation in the future. Radiation oncologists are encouraged to follow the definitions and reporting guidelines for the design of radiation therapy fields, as published by ITMIG. The short- and long-term toxicities of radiation therapy are tightly correlated to the volume that was irradiated, the radiation dose per fraction, and the total radiation dose, as well as the age of the patient and the time interval from the end of radiation therapy. The increased conformality of modern radiation techniques allows unprecedented sparing of normal organs at risk, such as the lungs, the esophagus, the heart, the brachial plexus, and the spinal cord. There has been a noticeable decrease in acute side effects with decreased radiation doses to these normal tissues. Given the location of most thymic tumors in the anterior mediastinum, superior to the heart, as well as the use of typically moderate radiation doses in the range of 50-60 Gy, acute toxicities from irradiation of thymoma patients are generally mild. The long life expectancy of most patients with thymoma, however, puts them at risk for long-term toxicities, such as coronary artery disease, lung fibrosis, esophageal stenosis, and secondary malignancies. While reports on the toxicity from radiation therapy specifically for thymomas are largely anecdotal, it is reasonable to draw conclusions on normal tissue tolerances and long-term toxicities observed in patients who underwent radiation therapy for other indications, such as lymphoma, breast cancer, and pediatric cancers. Avoidance of additional risk factors for long-term toxicities are a critical component of the follow-up care of long-term survivors and should include smoking cessation, management of hypercholesterolemia and hypertension, and routine screening for early detection of secondary malignancies when indicated.

Keywords: radiation therapy, thymoma, technique, toxicity

GS4.3: CONTROVERSIES IN THE POSTOPERATIVE TREATMENT OF LOCALLY ADVANCED THYMOMA, AND THE DEVELOPMENT OF A RANDOMIZED TRIAL

Daniel Gomez
Department Of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston/UNITED STATES OF AMERICA

The indications for postoperative radiation therapy in the setting of locally advanced thymic malignancies have not been well established. Due to the rarity of the disease, data is primarily limited to small retrospective studies, often from a single institution. As a result, outcomes have varied between

reports, with some analyses demonstrating control rates of greater than 90%, and others with higher rates of progression. In light of this conflicting data, as well as because no randomized prospective studies have been performed to answer this question, recommendations regarding the utility of postoperative radiation therapy in the context of resected stage II-III invasive thymoma or thymic carcinoma are mixed. To attempt to provide strong data on this topic, ITMIG has recently initiated the design of a prospective phase III randomized trial in which patients with completely resected locally advanced thymic malignancies are randomized to postoperative radiation therapy or observation, with the primary endpoint being overall survival. This presentation will focus on the conflicting data examining the efficacy of postoperative radiation in the setting of completely resected thymoma in terms of improving locoregional control and survival, as well as the rationale and design of ITMIG's proposed randomized phase III study, currently in development through the Eastern Cooperative Oncology Group (ECOG).

GENERAL SESSION IV: TREATMENT ISSUES

Saturday, September 7, 2013 – 13:30 – 15:00

GS4.4: MANAGEMENT OF THYMIC CARCINOMA (WITH POSSIBLY A DISCUSSION ON TARGETED AGENTS)

Ritsuko Komaki

Department Of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston/UNITED STATES OF AMERICA

Thymic epithelial neoplasms are divided into thymomas and thymic carcinomas. Thymomas are epithelial tumors that have retained the organo typical features (well-developed lobular architecture, presence of a dual cell population of neoplastic thymic epithelial cells and lymphocytes, dilated perivascular spaces, areas of medullary differentiation, lack of cytologic features of malignancy of neoplastic thymic epithelial cells) of the thymic gland. On the other hand, thymic carcinomas are overtly malignant epithelial tumors showing cytologic atypia, invasive margins, and loss of an organo-typical appearance. It is important to clarify that thymoma does not represent the "benign" counterpart of thymic carcinoma, but rather exhibits at least low-grade malignant behavior with the potential for invasion and metastasis. Thymic carcinoma represents a heterogeneous group of tumors with a wide morphologic spectrum. Only rarely have larger series of thymic carcinoma been reported in the literature, and these have often included material derived from small biopsy specimens. In addition, many of the studies included neuroendocrine carcinomas or salivary gland–type thymic tumors, which show different clinicopathologic features and outcome altogether Although the predominant approach in the treatment of thymoma and thymic carcinoma is surgery, radiation therapy also has an important role, either as postoperative therapy to reduce the risk of mediastinal recurrence or as part of definitive treatment for patients that who cannot undergo surgery. We present here a review of radiation therapy for thymic malignancies and briefly discuss the potential benefits from novel technologies for such treatment. Thymic carcinoma is a rare but more aggressive tumor which has a tendency to fail locally and distantly. Thymic carcinoma has more frequent EGFR and/or HER2 abnormalities compared to thymoma., and the outcome of thymic carcinoma is usually worse than invasive thymoma. **Induction Chemotherapy or Molecular Targeted Agents:** For thymic carcinoma and invasive thymoma, our traditional chemotherapy regimens are cyclophosphamide, adriamycin, cisplatin and prednisone x3 cycles followed by surgery. However more recently thymic carcinoma has been treated as lung cancer. We need to check histology squamous carcinoma, neuroendocrine carcinoma, small cell carcinoma or adenocarcinoma as well as EGFR mutation, K-ras, and ALK mutation. If the thymic carcinoma demonstrates targetable mutation, those patients need to be treated EGFR-TKI, crizotinib etc. **Postoperative Radiation Therapy: Indications R0 (Completely Resected) Thymic Malignancies** In general, radiation should be considered more strongly as the risk of recurrence increases. Therefore, for patients with the lowest likelihood of recurrence (i.e. completely resected Masaoka stage I thymoma), radiation can be safely omitted. For those at intermediate risk of local recurrence after complete resection, i.e. those with aggressive tumor histologies (such as thymic carcinoma) or Masaoka stage II and stage III disease, retrospective evidence exists both to support and contradict claims of benefit from adjuvant radiotherapy after complete resection. In general, our institutional practice includes postoperative radiation for completely resected Masaoka-Koga stage III thymoma and stage II or III thymic carcinoma. Risk assessment and stratification is usually done in a multidisciplinary setting and drives the choice of adjuvant treatment. The International Thymic Malignancy Interest Group (ITMIG) published a set of definitions and reporting guidelines for the use of radiation therapy for thymic malignancies in 2011. Pertinent recommendations for postoperative therapy are as follows. First, the term "postoperative" should be used for situations in which the tumor is resected and no residual disease is evident on

imaging. If gross disease is present on postoperative imaging, then the disease should be defined as “recurrent” and the intent as “radiation for postoperative disease.” Second, the minimum acceptable dose for postoperative R0 disease is 50 Gy in 5 weeks. Finally, radiation to elective nodal regions not recommended, and the extent of malignancy before surgery should be used as a guide for designing the treatment fields. **Microscopic Positive Margins (R1) and Gross Disease (R2)** Radiation for R1 or R2 thymic malignancies should be started within 3 months of surgical resection. Doses between 40 Gy and 64 Gy are most appropriate for microscopically positive margins, whereas doses of 54 Gy or higher should be used for gross disease; both given in standard fractions of 1.8- to 2.0-Gy. Patients with positive margins should be considered for concurrent chemotherapy and radiotherapy, especially among patients with thymic carcinoma. **Definitive Radiation Therapy** Definitive radiation therapy is generally used for patients who are not candidates for surgery because of either the extent of disease at diagnosis or medical comorbidities. Because chemotherapy is a known radiation sensitizer, the combination of chemotherapy and radiation is considered most likely to control disease in these circumstances. In this setting, which is analogous to recurrent disease after surgical resection, we recommend radiation doses of 60 Gy -66 Gy to encompass gross disease plus a margin for microscopic regions at risk. Thymic carcinoma behaves more like non-small cell lung cancer arising from the thymus. Therefore, unresectable thymic carcinoma needs to be treated based on the histology or molecular biomarkers of expression e.g. EGFR, HER2 c-KIT and BCL-2. Approximately 50% of thymic carcinoma has squamous histology which can be treated with cisplatin based chemotherapy and radiotherapy. If unresectable thymic carcinoma has atypical carcinoid histology or small cell carcinoma arising from the thymus, etoposide and cisplatin plus radiotherapy might be the best option. For recurrent thymic carcinoma, molecular targeted agents e.g EGFR-TKI, c-KIT inhibitors and VEGFR inhibitors can be delivered in the protocol setting with or without radiotherapy. **In conclusion,** thymic carcinoma needs to be treated almost as lung cancer arising from the thymus. We need to individualize induction chemotherapy for resectable thymic carcinoma based on histology or molecular targeted agents based on EGFR mutation, K-Ras, mutation or ALK mutation, HER2-neu positivity or amplification or c-KIT and BCL-2 mutation. For unresectable thymic carcinoma such as small cell carcinoma arising from the thymus needs appropriate radiosensitzing chemotherapy or molecular targetable agent and radiotherapy would be recommend. The use of advanced radiation therapy technologies to minimize the dose to mediastinal structures for patients with thymic carcinoma is critical to reduce cardiac or lung toxicity especially long term survivors.

Keywords: thymic, indivisualized, management, Carcinoma

O1.1: MYASTHENIA GRAVIS ASSOCIATED WITH THYMIC EPITHELIAL TUMOR: RETROSPECTIVE CLINICOPATHOLOGICAL ANALYSIS OF JAPANESE DATABASE CASES

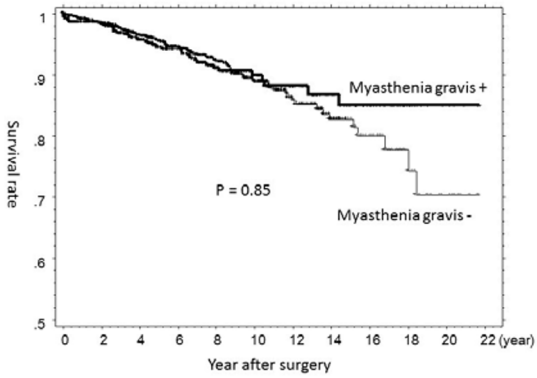
Jun Nakajima[1], Meinoshin Okumura[2], Kazuya Kondo[3], Ichiro Yoshino[4], Yoshitaka Fujii[5], Hisao Asamura[6], Kazuo Yoshida[7], Hiroshi Date[8], Kanji Nagai[9], Kohei Yokoi[10], Shinichiro Miyoshi[11]

[1]Department Of Thoracic Surgery, The University of Tokyo Graduate School of Medicine, Tokyo/JAPAN, [2], Osaka University, Osaka/JAPAN, [3], Tokushima University, Tokushima/JAPAN, [4], Chiba University, Chiba/JAPAN, [5], Nagoya City University, Nagoya/JAPAN, [6], National Cancer Center, Tokyo/JAPAN, [7], Shinshu University, Matsumoto/JAPAN, [8], Kyoto University, Kyoto/JAPAN, [9], National Cancer Center East, Kashiwa/JAPAN, [10], Nagoya University, Nagoya/JAPAN, [11], Okayama University, Okayama/JAPAN

Background: The relationship between thymoma and myasthenia gravis (MG) is well known. We investigated the detailed clinical characteristics of patients who had undergone resection of both thymoma and MG.

Methods: We registered patients with thymic epithelial tumor who had undergone resection between 1991 and 2010 at 29 institutes participating in Japanese Association for Research of Thymus (JART).

Results: The total number of registered cases was 3033. Of them, 3000 were eligible for the study. MG was found in 667 patients (22.3%) with stage I thymoma (n=262, 39.2%), 256 with Stage II (38.3%), 84 with Stage III (12.6%), 45 with Stage IVa (6.7%), and 18 with Stage IVb (2.7%). Earlier stage of the thymoma was more frequently observed in patients with MG than those without MG (p = 0.00036). Cases of MG were found in 12.5% of patients with type A thymoma, 14.9% with type AB, 23.8% with type B1, 40.3% with Type B2, 25.5% with Type B3, and 1.1% with thymic carcinoma, respectively. Patients with type B thymoma had more frequent involvement of MG (P<0.0001). The number of patients with MGFA class I, II, III, IV, and V was 191 (28.6%), 298 (44.6%), 98 (14.7%), 8 (1.2%), and 10 (1.4%), respectively. Average serum titer of anti-acetylcholine receptor antibody (AchRAb) of the patients with MGFA class I, II, III, IV, and V was 23.8, 58.4, 79.6, 46.8, and 43.1 nmol/L, respectively. Severity of MG correlated with MGFA classification in patients with thymoma. AchRAb was positive in 99.3% of patients with thymoma and MG. On the other hand, AchRAb was positive in 22.4% of patients with thymoma but without MG preoperatively. During the postoperative follow up, 60 patients with MG (9.0%) and 368 without MG (15.8%) experienced thymoma recurrence. Forty-three patients with both thymoma and MG died due to thymoma (n = 10), MG (n = 7), other malignancy (n = 9), or other disease (n = 17). The overall postoperative survival rate of patients with thymoma and MG was not significantly different from that of the patients without MG (figure).



Conclusion: Our database, with records of 3000 patients with thymic epithelial tumor, showed that a 22% of patients with thymic epithelial tumor were complicated by MG. Patients with WHO type B thymoma had more frequent involvement of MG. Almost all of the patients with both thymoma and MG had positive AchRAb, and 22.4% of thymoma patients without MG had positive AchRAb. In MG patients with thymoma, AchRAb correlated with MG severity. MG had no impact on the overall survival of patients with thymic epithelial tumor.

Keywords: thymoma, myasthenia gravis, anti-acetylcholine receptor antibody, multiinstitutional study

O1.2: THYMECTOMY IN MYASTHENIA GRAVIS: PROPOSAL FOR A PREDICTIVE SCORE OF POSTOPERATIVE MYASTHENIC CRISIS

Pierluigi Granone[1], Giacomo Cusumano[1], Giovanni Leuzzi[1], Elisa Meacci[1], Filippo Lococo[1], Marco Chiappetta[1], Valentina Dall'Armi[2], Dania Nachira[1], Monica Pastina[1], Stefano Margaritora[1]

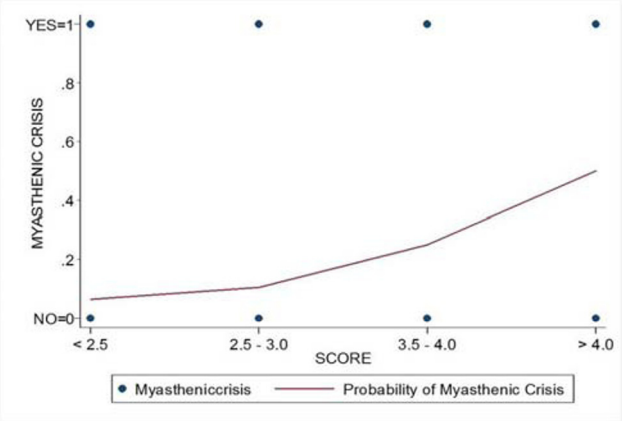
[1]Department Of Thoracic Surgery, Catholic University of Sacred Heart, Rome/ITALY, [2] IRCCS San Raffaele Pisana, Rome/ITALY

Background: Thymectomy plays an important role in patients with myasthenia gravis. This study aims to explore predictors of postoperative myasthenic crisis after thymectomy and to define a predictive score of respiratory failure.

Methods: From 01/1995 to 12/2011, the clinical data of 177 patients with myasthenia gravis who underwent thymectomy were retrospectively reviewed. The following factors were analyzed in relation to the occurrence of myasthenic crisis: gender, age, BMI, anti-AchR-antibody level, bulbar symptoms, comorbidities, duration of symptoms, Osserman-stage, MGFA, history of myasthenic crisis, use of immoglobulins or plasmapheresis, kind of medical therapy, spirometric and blood gas parameters, histolgy, kind of surgery, non-myasthenic complications, duration of intubation.

Results: Twenty-two patients experienced postoperative respiratory failure after thymectomy. Univariate analysis revealed a correlation with age higher than 60 years (p=0,040), Osserman-stage (2B, p=0,037; 3-4, p=0,015), bulbar symptoms (p=0,008), BMI higher than 28 (p=0,003), preoperative plasmapheresis (p=0,021), duration of symptoms higher than 2 years (p=0,036), invasive surgery (p=0,045), lung (p=0,008), pericardial (p=0,006) or pleural resection (p=0,012), VC% lower than 80% (p=0,025), PaCO2 higher than 40 mmHg (p=0,032). Multivariate logistic regression analysis showed that Osserman stage (2B, p=0,039; 3-4, p=0,013), BMI higher than 28 (p=0,035), history of myasthenic crisis (p=0,007), duration of symptoms higher than 2 years (p=0,036), lung resection (p=0,002) independently predict postoperative myasthenic crisis. Excluding history of preoperative myasthenic crisis (statistically associated to Osserman stage), we built a scoring system according to the odds ratio of Osserman stage (1-2A, 2B, 3-4), BMI (<28, ≥28), duration of symptoms (<1 year, 1-2 years, >2 years) and association with a pulmonary resection (fig. 1). This model helped in creating four classes (fig. 2) with increasing risk of respiratory failure (Group 1: 6%; Group 2: 10%; Group 3: 25%; Group 4: 50%; accuracy=85,5%; specificity=93,75%; sensibility=36,84 %).

Variables		Score [Range: 0 - 8.5]
OSSERMAN	Stage: 1 - 2A	0
	Stage: 2B	1
	Stage: 3 - 4	3
MG DURATION	< 1 year	0
	1 - 2 years	1
	> 2 years	2
LUNG RESECTION	No	0
	Yes	2.5
BMI	< 28	0
	≥ 28	1



Conclusion: Our model allowed in stratifying patients' risk and in predicting the occurrence of postoperative myasthenic crisis. Moreover, it could help anesthesiologist's decision on the duration of intubation. Further studies based on larger series are needed to confirm these preliminary data.

Keywords: myasthenia gravis, Thymectomy, myasthenic crisis

ORAL ABSTRACT SESSION I

Saturday, September 7, 2013 – 08:30 – 09:30

O1.3: PREDICTORS OF ONCOLOGICAL AND NEUROLOGICAL OUTCOMES AFTER SURGERY IN PATIENTS WITH THYMOMATOUS CLASS III MYASTHENIA GRAVIS

Vincenzo Ambrogi, Federico Tacconi, Francesco Sellitri, Tommaso C Mineo

Thoracic Surgery, Tor Vergata University, Rome/ITALY

Background: Thymomatous myasthenia gravis represents a peculiar and severe disease. This study is aimed at evaluating if features specifically related to the neoplasm (i.e. stage, histology, biology) may be significant predictors of neurological outcome after thymomectomy and viceversa neurological variables can affect the neoplasm evolution in a precise clinical class (Class III according to the Myasthenia Gravis Foundation of America) of myasthenia gravis.

Methods: We performed a retrospective analysis of 35 patients (16 male, 19 female) with thymoma and class III myasthenia gravis undergoing extended transternal thymectomy plus thymomectomy between 1985 and 2005. Class III was identified as a moderate weakness predominantly affecting limb or axial muscles (type a) or oropharyngeal muscles (type b). Patients operated before 2000 and therefore classified according to the Osserman's classification were retrospectively re-classified. Oncological endpoints was disease-free survivals. Neurolgical outcome was complete stable remission. As oncological predictors of poor outcome were considered age (>55), sex (male), Masaoka stage (II-III), histology according World Health Organization (B2-B3), incomplete resection and cell-cycle protein (p53 high-, p21 low-, p27 low) and glucose transporter-1 and vascular endothelial growth factor expressions. Neurological poor predictors were sex (male), symptom-duration (<12 months), quality of life levels (physical and mental component summaries SF-36 below median value), Myasthenia gravis score, steroid-use, oro-pharyngeal involvement, histology (B2-B3), hyperplastic residual thymus and evidence of ectopic thymic tissue.

Results: There was no perioperative mortality. Disease-free survival rate were 67% at 5 and 56% at 10 years, respectively. At univariate analysis significant negative predictors were stage II-III (p=0.041), incomplete resection (p=0.019), B2-B3 histology (p=0.007) and cell-cycle protein expression (p=0.001), the latter resulting as the sole predictor at multivariate (p=0.003). Complete stable remission rate was 52% at 10 and 66% at 15 years, respectively. At univariate analysis significant negative predictors of complete stable remission were those related to the tumor and namely B2-B3 histology (p=0.021), incomplete resection (p=0.007) and cell-cycle protein expression (p=0.032). Traditional factors resulted marginal significant or non significant. No factor prevailed at multivariate analysis.

Conclusion: Incomplete resection of thymoma, B2-B3 histology and cell-cycle protein expression resulted the most significant predictors for both oncological and neurological poor outcome. Whereas traditional neurological factors resulted marginally or non significantly affecting the neurological outcome.These findings entails that thymomatous myasthenia should be considered a different neurological entity from the nonthymomatous one.

Keywords: myasthenia gravis, Thymomas, Thymectomy, Complete remission

ORAL ABSTRACT SESSION I

Saturday, September 7, 2013 – 08:30 – 09:30

O1.4: DETECTION OF HUMAN POLYOMAVIRUS 7 IN HUMAN THYMIC EPITHELIAL TUMORS

Marlies Keijzers[1], Dorit Rennspies[2], S Pujari[2], MA Abdul Hamid[2], Monique Hochstenbag[3], Anna Kurz[4], ErnstJan Speel[2], A Haugg[2], C Buck[5], Marc De Baets[6], Axel Zur Hausen[2]

[1]Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht/NETHERLANDS, [2]Pathology, Maastricht University Medical Center, Maastricht/NETHERLANDS, [3]Pulmonology, Maastricht University Medical Center, Maastricht/NETHERLANDS, [4]Department Of Internal Medicine Iv, University Hospital Aachen, Aachen/GERMANY, [5]Laboratory Of Cellular Oncology, National Cancer Institute, Bethesda/MD/UNITED STATES OF AMERICA, [6]Neuroscience, Maastricht University Medical Center, Maastricht/NETHERLANDS

Background: Although the molecular genetics possibly underlying thymoma pathogenesis have been extensively studied the etiology of human thymoma remains poorly understood. Based on its association with the autoimmune disease myasthenia gravis (MG) and the consistent finding that murine polyomavirus induces thymomas in mice we tested the presence of Human Polyomavirus 7 (HPyV7) in human thymic epithelial tumors.

Methods: We applied HPyV7 DNA Fluorescence in situ hybridization (FISH), DNA PCR and immunohistochemistry (IHC) in 37 thymomas (19 female, 18 male; mean age 58.3 years; range 34 – 82 years). Of these, 26 were previously diagnosed with MG. In addition, 2 thymic carcinomas and 20 fetal thymus tissues were tested for HPyV7.

Results: HPyV7 FISH revealed specific nuclear hybridization signals within the thymoma cells of 23 thymomas (62.2%). Fifteen thymomas revealed strong to very strong hybridization signals, whereas 8 revealed only weak positivity. With one exception the HPyV7 FISH data highly correlated with the HPyV7 DNA-PCR data. IHC showed the presence of HPyV7 on the translational level and immunohistochemical double stainings confirmed the presence of HPyV7 in the epithelial thymoma cellular compartment. One thymus carcinoma was HPyV7 positive the other negative. All fetal thymus tissues were tested HPyV7 negative.

Conclusion: We conclude that HPyV7 is frequently present in human thymic epithelial tumors and absent in fetal thymic tissues. No convincing association on HPyV7 and MG could be found. In as much HPyV7 is of relevance to human thymomagenesis remains to be established.

Keywords: thymoma, Human Polyomavirus 7

ORAL ABSTRACT SESSION II
Saturday, September 7, 2013 – 10:00 – 11:00

O2.1: TARGETED CANCER GENOME SEQUENCING IN THYMIC EPITHELIAL TUMORS

Andre Moreira[1], Robert Mcmillan[2], Helen Won[1], James Huang[2], Gregory Riely[3], Marc Ladanyi[1], Michael Berger[1]
[1]Pathology, Memorial Sloan Kettering Cancer Center, New York/UNITED STATES OF AMERICA, [2]Surgery, Memorial Sloan Kettering Cancer Center, New York/UNITED STATES OF AMERICA, [3]Medicine, Memorial Sloan Kettering Cancer Center, New York/UNITED STATES OF AMERICA

Background: Thymomas and thymic carcinomas (TCA) are rare tumors. There have been very few studies dedicated to the understanding of the biology of these tumors. An improved understanding of the molecular characteristics of thymoma and TCA may lead to a better comprehension of tumorigenesis, and more importantly lead to new therapeutic targets, thus opening new treatment options for these patients.

Methods: 13 pairs (tumor and normal tissue) of paraffin-embedded tissue from thymic carcinoma and 6 pairs of thymoma WHO type B3 were evaluated by exon capture of 275 cancer related genes (Agilent SureSelect Target Enrichment system), followed by next-generation sequencing (Illumina HiSeq). This approach identifies all sequence variants, small insertions and deletions, and copy number alterations involving the target genes.

Results: Mutations were identified in 11 of 13 (85%) TCA with median of 1 mutation per tumor (range 0-26).all TCA were classified as squamous cell carcinoma, one with 26 mutations was a CD5 positive poorly-differentiated carcinoma. The most mutated genes were TP53 (n=3), SMAD4 (n=2) and CYLD (n=2); and chromatin remodeling genes KDM6A (n=3), SETD (n=2), MLL3 (N=2), MLL2 (n=2). TP53 and KDMA6 were seen as a single mutation in one tumor each.. In this small sample, tumor with TP53 appear to have a more aggressive behavior. All 3 patients presented as Masaoka stage 4, received neoadjuvant therapy. 2 patients died of disease (mean survival 2.2years). In contrast 2 patients with stage 4 without TP53 mutations are alive with disease and 2 other died of unrelated cause. In contrast, in Thymoma B3, mutations were identified in 4 out of 6 tumors evaluated. 1 mutation was identified per tumor. Mutations in BCOR (BCL6 co-repressor) were seen in 3 thymomas and MLL3 (involved in histone methylation) in one tumor.

Conclusion: Genomic Exon sequencing of cancer target genes in thymic epithelial tumors shows a low frequency of mutation. However, there is a different pattern of molecular alterations between thymic carcinoma and B3 thymomas. Thymic carcinomas have more mutations in TP53 gene whereas B3 thymomas have a higher frequency of mutations in BCOR gene.

Keywords: genomic, thymoma, thymic carcinoma

O2.2: MICRORNAS IN THYMIC EPITHELIAL TUMORS: PRELIMINARY DATA

Mirella Marino[1], Federica Ganci[2], Carmen Vico[3], Andrea Sacconi[2], Etleva Korita[2], Enzo Gallo[1], Domenico Vitolo[4], Federico Venuta[5], Francesco Facciolo[6], Edoardo Pescarmona[1], Giovanni Blandino[2], Francesco Fazi[3]
[1]Pathology, Regina Elena National Cancer Institute, Rome/ITALY, [2]Translational Oncogenomics, Regina Elena National Cancer Institute, Rome/ITALY, [3]Medico-Surgical Sciences And Biotechnologies, University La Sapienza, Rome-Latina, Latina/ITALY, [4]Oncology, Hematology And Pathology, University La Sapienza, Rome/ITALY, [5]Thoracic Surgery, University La Sapienza, Rome/ITALY, [6]Thoracic Surgery, Regina Elena National Cancer Institute, Rome/ITALY

Background: Mature microRNAs (miRNAs), as new class of modulators, control gene expression and have been recently subjected to extensive characterization in several normal and tumor systems. These small single-stranded RNA molecules showed both diagnostic and prognostic values. Whereas mRNA transcript profiling is technically challenging, requiring snap-frozen fresh material, miRNAs, due to their small size and stability, can be studied in formalin-fixed paraffin embedded (FFPE) tissue. Since miRNAs frequently target hundreds of mRNAs, miRNA regulatory pathways and their deregulation are complex. Growing evidence indicates that targeting microRNAs biogenesis and pathways could allow the development of novel RNA-based drugs with anticancer activity.

Methods: FFPE tumor and normal tissues from the Regina Elena Cancer Institute and Policlinico Umberto I, Sapienza

University of Rome, were included in the study. Epithelial cell-rich areas from representative FFPE Thymic Epithelial Tumor samples belonging to different histological subtypes and matched normal peritumoral thymic tissues were considered. Patients who underwent any previous radiotherapy or chemotherapy treatment or with history of any other anticancer therapy were excluded. RNA from 54 tumor and 12 normal samples was extracted by miRneasy FFPE kit (Qiagen) and hybridized by the use of the Agilent Platform. The Human miRNA Microarray from Agilent contains probes for 906 human microRNAs from Sanger database Rel.16. After the statistic and bioinformatic analyses, signal processing and quality control, the different expression of the identified miRNAs was validated by quantitative RT-PCR (RT-qPCR) in additional tumor samples. The analysis included unsupervised and supervised methods.

Results: We found 9 upregulated and 5 downregulated miRNAs in TET ***vs*** normal thymic tissue. Data about the deregulation of miRs by RT-qPCR using a representative subgroup of samples are in agreement with results obtained from the array. In addition, preliminary results show the presence a group of miRNAs differentially expressed among TET subtypes (A, AB, B1 ***vs*** B2, B3 ***vs*** Carcinoma, according to the 2004 World Health Organization classification). Finally, by *in silico* analysis we identified putative target genes of the 14 deregulated miRs, some of them being important genes involved in cell proliferation and prognosis in different tumor systems.

Conclusion: In a well-characterized retrospective tumor series, we identified miRNAs able to differentiate TET ***vs*** normal thymic tissue and among prognostically-grouped TET histotypes that may be useful in the management of this disease. Moreover, we identified several putative target genes known to be involved in thymic carcinogenesis and in the maintenance and spreading of this tumor.

Keywords: bioinformatics, microRNA, Thymic Epithelial Tumors, miRNA Microarray

ORAL ABSTRACT SESSION II

Saturday, September 7, 2013 – 10:00 – 11:00

O2.3: IS SACRIFYING PHRENIC NERVE DURING THYMOMA RESECTION WORTHWHILE?

Olaf Mercier[1], Sarah Hamdi[1], Elie Fadel[1], Sacha Mussot[1], Dominique Fabre[1], Benjamin Besse[2], Thierry Le Chevalier[1], Philippe Dartevelle[1]

[1]Centre Chirurgical Marie Lannelongue, Le Plessis Robinson/FRANCE, [2]Department Of Cancer Medicine, Institut Gustave Roussy, Villejuif/FRANCE

Background: To determine whether involved phrenic nerve (PN) could be spared during thymoma resection.To determine whether involved phrenic nerve (PN) could be spared during thymoma resection.

Methods: A retrospective study was conducted on patients who underwent resection of thymoma adherent, on digital palpation, to at least one PN in our institution between 1998 - 2012. An en-bloc resection of the tumor and the invaded PN was performed unless both PN involved or compromised lung function leading to PN-sparing tumor removal, when feasible (PN adherent to the edge of the tumor without preoperative palsy). Postoperative radiation therapy was given to patients with spared PN or in Masaoka stage 3 and 4.

Results: There were 117 patients with a mean age of 57 years [range, 28-84]. PN was spared in 76 patients (65%) and removed in 41 (35%). Masaoka classification showed 68 stage-3 (58%) and 49 stage-4 (42%) and was similar between both groups. On permanent histology, 6 (14%) of the resected PN were not involved whereas a postoperative PN permanent palsy was found in 8 (11%) patients where the PN was spared. Postoperative mortality and morbidity were 0% and 6.6% in spared group and 2.4% and 4.9% in resected group, respectively without significant difference. Recurrence rate was significantly higher in spared group (39.5% vs 19.5%; p=0.02) but the 5-year disease-free survival rates (57% vs. 70%, p=0.08) and overall 5-year survival (74% vs. 88%, p=0.6) were not significantly different between spared and resected PN, respectively.

Conclusion: Sparing PN during thymoma resection achieved good long term and disease-free survivals in high-risk patients comparable to en-bloc PN resection. However, it carried a risk of higher risk of recurrence despite adjuvant radiation therapy. It should be reserved to patients with both PN involved or compromised lung function contraindicating any PN resection.

Keywords: Thymoma surgery, Phrenic nerve

O2.4: ANTITUMOR ACTIVITY IN ADVANCED CANCER PATIENTS WITH THYMIC MALIGNANCIES ENROLLED IN EARLY CLINICAL DRUG DEVELOPMENT PROGRAM (PHASE I TRIALS) AT INSTITUT GUSTAVE ROUSSY

Benjamin Besse[1], Myriam Kossai[1], Boris Duchemann[1], Celine Boutros[1], Caroline Caramella[2], Antoine Hollebecque[1], Eric Angevin[1], Anas Gazzah[1], Ratislav Bahleda[1], Christophe Massard[1], Philippe Vielh[3], Jean-Charles Soria[1]

[1]Department Of Cancer Medicine, Institut Gustave Roussy, Villejuif/FRANCE, [2]Radiology, Gustave Roussy, Villejjuif/FRANCE, [3]Pathology, Gustave Roussy, Villejuif/FRANCE

Background: Thymic epithelial neoplasms (TENs) represent a rare entity with poor prognosis and limited systemic treatment options, particularly in advanced stages and/or in thymic carcinomas (TC). The aim of this study was to assess the clinical benefit, the efficacy and toxicities of agents for patients (pts) with a refractory TEN enrolled in Phase I trials.

Methods: We reviewed retrospectively pts with advanced pretreated TEN enrolled in Phase I trials at the Institut Gustave Roussy (SITEP) between 1994 and 2012. Toxicities were reported and scored according to NCI CTCAE version 3.0. Efficacy was assessed using RECIST version 1.0.

Results: Twenty-two treated pts were enrolled (15 with TC, 7 with thymomas). The median number of prior systemic therapies was 2 (1-8). The median age was 50 years (range 23-72), and 4 females were treated. Treatment received were mTOR inhibitor (mTORi) in 4 of pts, antiangiogenic agents (AA) in 7 pts, and other targeted therapies in 8 pts. The median follow-up time was 22.1 months (range, 1.25-77.79 months). Autoimmune associated disease (AID) was reported in 6 pts. 36% had grade III/IV toxicity, 77% grade I/II toxicity and no toxic death was reported. AID exacerbated in one patient. One patient experienced a complete response (CR) and 3 a partial response (PR); 16 pts had stable disease (median 6.6 months) and 2 had a progressive disease. Objective response rate (ORR) was 18%, 29% for thymoma and 13% for TC. The median overall survival was 54.5 months (95% CI 25-75.50 months), 78 for thymoma and 46 for TC. The median progression free survival (PFS) was 6.6 months (95% CI 1.35-11.59 months), 6.3 for thymoma and 6.8 for TC. Median PFS was 11.6 months for mTORi, 6.9 for AA, and 6.6 for other targeted therapies.

Conclusion: Phase I trials appear as a sound therapeutic option in TENs pts progressing after standard treatments. Use of AA and mTORi seem to yield a good clinical response. Novel targeted therapies might be tested in Phase I trial setting in a biology-oriented approach rather than a stochastical one. We are currently offering a molecular profiling in our patients (MOSCATO trial) for a better selection of appropriate Phase I trial.

Keywords: mTOR inhibitors, phase I trials, thymic malignancies, antiangiogenic agents

O3.1: A MULTICENTER PROSPECTIVE STUDY OF CARBOPLATIN AND PACLITAXEL FOR ADVANCED THYMIC CARCINOMA : WEST JAPAN ONCOLOGY GROUP 4207L

Yoshihito Kogure[1], Fumihiko Hirai[2], Takeharu Yamanaka[3], Kenichi Taguchi[2], Koji Takeda[4], Haruko Daga[4], Tatsuo Kimura[5], Junichi Shimizu[6], Kaoru Tanaka[7], Yasuo Iwamoto[8], Akira Ono[9], Hidefumi Sasaki[10], Junya Fukuoka[11], Kenichi Nishiyama[12], Takashi Seto[2], Yukito Ichinose[2], Kazuhiko Nakagawa[7], Yoichi Nakanishi[12]
[1]Respiratory Medicine, Nagoya Medical Center, Nagoya/JAPAN, [2]National Kyushu Cancer Center, Fukuoka/JAPAN, [3]National Cancer Center Hospital East, Kashiwa/JAPAN, [4]Osaka City General Hospital, Osaka/JAPAN, [5]Osaka City University, Osaka/JAPAN, [6]Aichi Cancer Center Hospital, Nagoya/JAPAN, [7]Kinki University School of Medicine, Osaka/JAPAN, [8]Hiroshima City Hospital, Hiroshima/JAPAN, [9]Shizuoka Cancer Center, Nagaizumicho/JAPAN, [10]Nagoya City University Graduate School of Medicine, Nagoya/JAPAN, [11]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki/JAPAN, [12]Kyushu University Hospital, Fukuoka/JAPAN

Background: Thymic carcinoma (TC) is a rare malignant tumor originated within the thymus gland and is associated with a poor prognosis, differing from thymoma which is the most common type of thymic malignant neoplasm. No results of clinical trials focusing on TC have been reported. This single-arm study evaluated carboplatin and paclitaxel (CbP) in previously untreated patients (pts) with advanced TC.

Methods: Chemotherapy-naïve pts with Masaoka's stage III to IVb, ECOG PS 0 to 1, and more than 20 years old were eligible. The study treatment consisted of carboplatin (area under the curve 6) and paclitaxel (200 mg/m^2) every 3 weeks for a maximum of 6 cycles. The primary endpoint was objective response rate (ORR) by extramural assessment. Secondary endpoints included overall survival (OS), progression-free survival (PFS), and safety. All pts were followed-up until 24 months (mo) after last enrollment. Based on the SWOG 2-stage design, the planned sample size of 40 pts was determined to
reject the ORR of 20% under the expectation of 40% with a power of 0.85 and a type I error of 0.05.

Results: From May 2008 to November 2010, 40 pts were enrolled from 21 centers. Of 39 evaluable for analysis, the median age was 62 years (range, 36–84); 23/16 males/females; 3/10/26 with Masaoka's stage III/IVa/IVb; 9/11/19 with squamous cell carcinoma/poorly differentiated neuroendocrine carcinoma/other types. The median number of cycles was 6. There was 1/13 complete/partial responses with an ORR of 36% (95% CI, 21–53%; *P* = 0.031). The median PFS was 8.1 mo (5.4-13.1 mo) while OS did not reach the median value. The 1-year and 2-year survival rates were 85% (69–93%) and 71% (54–83%), respectively. Major adverse event was grade 3–4 neutropenia in 34 pts (87%). Two cases (5%) of grade 3 febrile neutropenia, neuropathy, and arthralgia were observed, respectively. There was no treatment-related death.

Conclusion: CbP showed higher efficacy in advanced TC as compared with anthracycline-based chemotherapy which is the current standard for the treatment of thymoma. Our results established that CbP, one of the standard treatments for non-small cell lung cancer, also serves as a key chemotherapy regimen for TC.

Keywords: thymic carcinoma, carboplatin, paclitaxel

O3.2: STAGE 1 RESULTS OF A 2-STAGE PHASE II TRIAL OF SINGLE AGENT AMRUBICIN IN PATIENTS WITH PREVIOUSLY TREATED THYMIC MALIGNANCIES

Heather Wakelee[1], Jonathan Riess[1], Melanie San Pedro-Salcedo[1], Sukhmani Padda[1], Kavitha Ramchandran[1], Matthew Gubens[2], Joel Neal[1]
[1]Medicine, Oncology, Stanford University, Palo Alto/California/UNITED STATES OF AMERICA, [2]Medicine, Oncology, University of California, San Francisco, San Francisco/UNITED STATES OF AMERICA

Background: There are few treatment options for patient with advanced thymic malignancies and utility of many of the available chemotherapies are limited by cumulative toxicity such as neuropathy (taxanes) and cardiomyopathy (anthracyclines). We designed this study to look at single agent amrubicin, a third generation anthracycline and topoisomerase II inhibitor with limited cardiac toxicity, in patients with advanced thymic malignancies.

Methods: Eligible patients have confirmed thymic malignancy (thymoma (T) or thymic carcinoma (TC)) with progression or relapse after at least 1 prior chemotherapeutic regimen, and adequate organ function including left ventricular ejection fraction (LVEF) of >50%. The initial treatment plan consisted of amrubicin at 40 mg/m^2 IV days 1-3 repeated in 3-week cycles. The study is a Simon 2-stage design based on a null hypothesis of a true response rate <5%, with 90% power to detect a 20% true response rate and a plan to accrue 12 evaluable patients in stage 1, then if at least 1 response is seen, to add 25 additional evaluable patients in stage 2 for a total of 39 patients.

Results: Enrollment was initiated in July 2011. Here, we report on the first 12 patients, all enrolled at Stanford University over a 19-month period. Of the first 12 patients enrolled, 11 were dosed. All were pre-treated (5 with prior anthracycline). There were 5 women and 7 men; age range of 30-67 years old; 6 were of Asian ethnicity, 5 were non-Hispanic White and 1 was Hispanic. After enrollment of the first 8 patients, of whom 3 were hospitalized with febrile neutropenia (FN) (38%), the study was amended to a starting dose of 35 mg/m^2 days 1-3 repeated in 3-week cycles. Other than FN in those 3 patients, G4 thrombocytopenia in 1 patient, and treatment-related G3 fatigue in 2 patients, other toxicities were generally mild and well tolerated. No significant changes in LVEF have been noted on serial echocardiograms. Of the 11 treated patients, there were 3 partial responses (2 T and 1 TC), 7 with stable disease for at least 4 cycles, and 1 with progressive disease (PD) after 2 cycles (TC). Of the 11 treated patients, only 1 patient, with PD after C2, has stopped before completing 6 cycles, and 5 to date have tolerated >10 cycles (others are still on treatment and may reach that number), with 15 cycles as the highest number to date.

Conclusion: Amrubicin, at 35 mg/m^2 IV days 1-3 on a 3-week cycle, shows promise as a single agent in pre-treated patients with thymoma and thymic carcinoma with a 27% RR in the first 11 treated patients. This exceeded the threshold for proceeding to step 2 and the study will now continue to a total of 39 patients and has expanded to other sites including Indiana University.

Keywords: amrubicin, advanced thymic malignancy, chemotherapy

O3.3: INTENSITY MODULATED RADIOTHERAPY FOR THYMOMA WITH PLEURAL RELAPSE

Changlu Wang[1], Wentao Fang[2], Lanting Gao[1]
[1]Radiation Oncology, Shanghai Chest Hospital, Shanghai/CHINA, [2]Department Of Thoracic Surgery, Shanghai Chest Hospital, Shanghai/CHINA

Background: It is always challenging to deal with a primary stageⅣa thymoma with pleural involvement or pleural recurrence after thymectomy. We tried IMRT for some patients after we found extended surgery is impossible for them and systemic chemotherapy resulted in failure.

Methods: From Apr 2009 to Feb 2013, totally 27 patients have been irradiated in our department with IMRT, targeting at pleural implants. The gender ratio was 18:9(male vs female). There were 3 B1, 2 B2, 21 B3 and 1 carcinoid respectively, categorized by WHO classification. Two patients were primary stageⅣa, while the other 25 were diagnosed as post operative recurrence. The median time of recurrence was 40 (6-96) months The GTV countering covered visible lesions and the smooth pleura among them, usually forming an arch-shaped field. Prophylactic dose was given below 30Gy, and boost dose to visible tumor was given below 50Gy. Once out-field recurrence occurred, a second or third course of IMRT would also be given.

Results: Among all 27 patients, 25 (92.6%) showed a more than 50% tumor regression within 3 months after IMRT. One patient showed tumor progression after 18Gy radiation, because myasthenia gravis exacerbation prevented her from further radiotherapy. One carcinoid patient showed no response 4 months after a 40Gy IMRT. Five patients developed out-field recurrence and received a second course of IMRT. The median progression free survival time was 27 months (3-45). Four patients suffered from radiation induced peumonitis of 3 degree, and symptoms were well relieved after medical control. Three patients developed ipslateral thorax contracture about 3 years after radiotherapy.

Conclusion: IMRT has excellent effect on local tumor control for thymoma with pleural relapse. Prophylactic dose is advised to be blow 30Gy for concern of dose hot-spot when part-field of the first IMRT overlaps that of the second IMRT. RT induced peumonitis is the main toxicity.

Keywords: radiotherapy, thymoma, pleural dissemination

O3.4: DOES POST-OPERATIVE RADIATION IMPACT SURVIVAL AFTER COMPLETE SURGICAL RESECTION OF MASAOKA STAGE IIB THYMOMA? A POPULATION BASED ANALYSIS IN 228 PATIENTS

Benny Weksler, Manisha Shende, Katie Nason, Arjun Pennathur
Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh/PA/UNITED STATES OF AMERICA

Background: While postoperative radiation is commonly advocated in patients with Masaoka Stage IIB thymoma, the benefit of adjuvant radiation is unclear in patients who have undergone a complete surgical resection. The rarity of the disease has prevented proper randomized controlled studies. The goal of this study was to determine the effect of adjuvant radiation therapy (RT) in overall and disease-specific survival in patients with Masaoka stage IIB thymoma, who have undergone a complete resection.

Methods: The SEER (Surveillance, epidemiology and end result) database is a NCI sponsored registry that covers 28% of the U.S. population and captures 98% of all cancer cases within the surveyed areas. We queried SEER for all patients with stage IIB thymoma who underwent complete surgical resection and survived more than 30 days after diagnosis. Both overall survival and disease specific survival was determined using the Kaplan-Meier method and compared using the log-rank test. The hazard ratio for death, controlling for confounding variables, was determined using a Cox proportional hazard model. Significance was set as $p<0.05$.

Results: We identified 228 patients with stage IIB thymoma who underwent complete resection. Adjuvant postoperative radiation therapy was given to 137 (60.1%). Groups were similar in age, sex, and tumor size, but there were more Caucasians in the RT group 48/101 (57.8%) vs 100/167 (73.5%), p=0.018. Overall survival for patients receiving adjuvant RT was 169.7 months (95% CI, 150.0-189.5) versus 153.4 months (95% CI, 121.6-185.2) in patients not receiving RT (p=0.664). Thymoma specific survival was also not improved with adjuvant RT (p=0.521). Multivariate analysis did not show radiation therapy, sex, tumor size, and WHO histology to significantly affect overall survival.

Conclusion: This large population based study shows that postoperative adjuvant radiation therapy does not appear to improve survival in completely resected patients with stage IIB thymoma. Further studies on the role of postoperative radiation therapy in stage IIB thymoma are needed.

Keywords: radiation therapy, Stage IIB thymoma, Survival, Population based study

POSTER SESSION 1
Display Time:
Friday, September 6, 2013 – 09:00 – 15:30

P1.01: GLI1, NOTCH1 AND CTNNB1 EXPRESSION BY AUTOMATED QUANTITATIVE IMMUNOFLUORESCENCE (AQUA) IN A THYMIC MALIGNANCY TISSUE MICROARRAY (TMA)

Jonathan Riess[1], Robert West[2], Sukhmani Padda[1], Michelle Dean[3], Alexander Klimowicz[3], Chuong Huong[4], Joel Neal[1], Heather Wakelee[1]
[1]Medicine, Division Of Oncology, Stanford University School of Medicine, Stanford/California/UNITED STATES OF AMERICA, [2]Pathology, Stanford University School of Medicine, Stanford/California/UNITED STATES OF AMERICA, [3]Functional Tissue Imaging Unit, Tom Baker Cancer Center, University of Alberta, Alberta/CANADA, [4]Cardiothoracic Surgery, Division Of Thoracic Surgery, Stanford University School of Medicine, Stanford/California/UNITED STATES OF AMERICA

Background: Thymoma is a rare malignancy, with a paucity of data on its biology and on the role of targeted therapeutics. Wnt, notch and sonic hedgehog pathway interactions between thymocytes and thymic stroma are important to both thymus and T-cell development. AQUAnalysis® is a digital image analysis software that continuously measures multiplexed protein expression and has the potential to overcome limitations of small sample sizes and tissue heterogeneity in the tumor microenvironment. We analyzed a thymoma TMA for gli1, notch1 and CTNNB1 expression by AQUA® as surrogate markers of activity of the sonic hedgehog, notch and wnt pathways, respectively. We hypothesized this preclinical screen may provide rationale for attacking these pathways with targeted therapeutics in thymoma.

Methods: A TMA was constructed from 68 patients with thymic malignancies and 8 benign thymic controls at Stanford University School of Medicine (Stanford, CA). Gli1, notch1 and beta-catenin expression were assayed using quantitative fluorescent immunohistochemistry at the Tom Baker Cancer Center (Alberta, Canada). The TMA was stained with anti-gli1 rabbit mAb (monoclonal antibody), clone EPR4523 (Epitomics, Burlingame, CA, USA); anti-Notch1 rabbit mAb, clone EP1238Y (Epitomics, Burlingame, CA, USA); and anti-beta-catenin mouse mAb, clone β-Catenin-1 (Dako Mississauga, ON, Canada) using a Dako autostainer. To isolate expression of these stem-cell pathway proteins separately in the tumor and the lymphocytes, the TMA was also stained with anti-pan-cytokeratin guinea pig mAb (Acris, San Diego, CA, USA); anti-vimentin rat mAb, clone 280618 (R&D Systems, Minneapolis, MN, USA); and anti-CD45 rabbit mAb, clone EP322Y (Epitomics, Burlingame, CA, USA). Automated image acquisition was performed using an Aperio Scanscope FL (Aperio Inc., Vista, CA, USA). Images were then analyzed using the AQUAnalysis® program, version 2.3.4.1. A tumor-specific mask and a tumor cytoplasmic mask were generated to distinguish thymoma cells from surrounding stromal tissue by thresholding the pan-cytokeratin images to identify pan-cytokeratin positive cells as tumor cells and define the tumor cytoplasm Statistical analysis was performed using SAS Enterprise Guide v5.0 (Cary, NC). Two-tailed t-tests were used to compare the differences between thymic tumor and benign control tissue. ANOVA and Dunnett's t-test was used to compare differences in gli1, notch1, and CTNNB1 expression by WHO histology.

Results: Demographics for 68 patients: M:F (53%/47%), Mean age at diagnosis: 55 years, WHO Histology: A (10%), B (57%), AB (24%), C (4%), unclassified (4%), Pathologic Masaoka Stage: I (46%), IIa (18%), IIb (4%), III (18%), IVa (9%) IVb (6%). No difference in gli1 (mean 211 vs. 201, p=0.31), CTNNB1 (mean 396 vs. 418, p=0.66) or notch1 expression (mean 317 vs. 325, p=0.82) was noted between thymic tumors and controls. In a subset analysis, we found no significant differences by WHO histology compared to controls.

Conclusion: AQUA® was used to help overcome limitations of analyzing protein expression in histologically heterogeneous thymic tumors and small sample sizes. We found no clinically or statistically significant increased expression of gli1, notch1, and CTNNB1 in thymoma compared to benign thymic tissue. Thus, this study provides no evidence for upregulation of the sonic hedgehog, notch or beta-catenin pathways in thymic tumors.

Keywords: stem cell, tissue microarray, thymoma

POSTER SESSION 1
Display Time: Friday, September 6, 2013 – 09:00 – 15:30

P1.02: INCREASED GALECTIN-1 EXPRESSION IN A THYMIC EPITHELIAL TUMOR TISSUE MICROARRAY (TMA)

Jonathan Riess[1], Peiwen Kuo[2], Christina Kong[3], Robert West[3], Sukhmani Padda[1], Heather Wakelee[1], Quynh Le[2]
[1]Medicine, Division Of Oncology, Stanford University School of Medicine, Stanford/California/UNITED STATES OF AMERICA, [2]Radiation Oncology, Stanford University School of Medicine, Stanford/CA/UNITED STATES OF AMERICA, [3]Pathology, Stanford University School of Medicine, Stanford/CA/UNITED STATES OF AMERICA

Background: Thymoma is a rare malignancy with a paucity of data on biology. Thymic epithelial tumors are often admixed with developing T-lymphocytes in the microenvironment. Galectin-1 (gal-1) is a beta-galactosidase binding protein involved in T-cell development via thymic stromal and thymocyte interaction as well as thymocyte development through negative selection. Gal-1 also induces apoptosis of effector T-lymphocytes, promotes angiogenesis, and is a poor prognostic indicator when overexpressed in several tumor types. To our knowledge expression of gal-1 has not been examined in thymic epithelial tumors.

Methods: A TMA was constructed from 68 patients with thymic malignancies and 8 benign thymic controls at Stanford University School of Medicine (Stanford, CA). Immunohistochemical stains for galectin-1 (1:200 dilution; citrate pre-treatment; mouse monoclonal; Novocastra) were performed on 4 µM-thick TMA sections. Galectin-1 cytoplasmic staining of the epithelial cell component was scored as negative (0), focal positive (1+), or strong positive (2+) by a Stanford pathologist, who was blinded to the clinical data. Gal-1 expression (0, 1, 2) was averaged for each patient sample. Statistical analysis was performed using SAS Enterprise Guide v5.0 (Cary, NC). Non-parametric statistical analyses were used to compare average patient gal-1 expression between thymic tumors and benign thymic controls.

Results: Demographics for 68 patients: M:F (53%/47%), Mean age at diagnosis: 55 years, WHO Histology: A (10%), B (57%), AB (24%), C (4%), unclassified (4%), Pathologic Maseoka Stage: I (46%), IIa (18%), IIb (4%), III (18%), IVa (9%) IVb (6%). Gal-1 expression was increased among thymic tumor tissue compared to unpaired controls (mean avg gal-1 expression 1.5 vs. 0.125, p=0.0012, Kruskal-Wallis test). Logistic regression of tumor vs. control thymus by gal-1 generated a C-statistic of 0.845. A significant increase in gal-1 expression was noted across all WHO thymoma subtypes except thymic carcinoma (type C) ($p < 0.05$, non-parametric ANOVA with post-hoc ranked Dunnett's t-test). Among 11 thymic tumors analyzed with paired adjacent resected benign thymus tissue from the same patient, a significant increase was noted in gal-1 expression among tumor compared with adjacent resected benign thymus (mean avg gal-1 1.82 vs. 0.35, p=0.004, sign-rank test).

Conclusion: Gal1 expression was increased among thymoma compared with benign thymus controls and paired resected benign thymus tissue. A robust C-statistic of 0.845 indicates that gal-1 expression may discriminate tumor from benign thymus. Increased gal-1 expression was conserved across WHO histologic subtype except for thymic carcinoma—whose analysis was limited due to small sample size. We are continuing to investigate the biologic and clinical significance of increased gal-1 expression in thymoma.

Keywords: galectin-1, immune markers, thymoma, tissue microarray

POSTER SESSION 1

Display Time: Friday, September 6, 2013 – 09:00 – 15:30

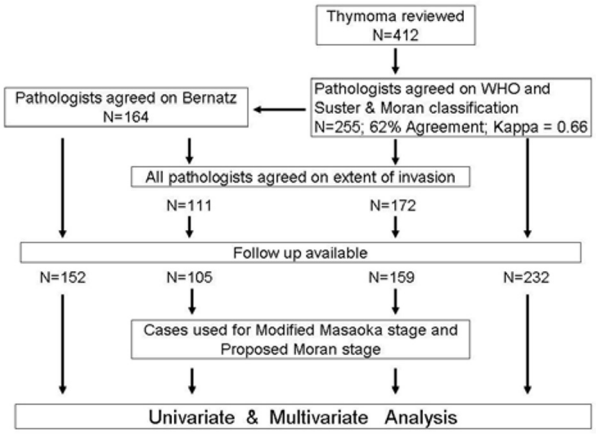
P1.03: MODIFIED MASAOKA STAGE AND THYMOMA SIZE ARE INDEPENDENT PROGNOSTIC PREDICTORS IN THYMOMA

Anja Roden[1], Eunhee Yi[1], Sarah Jenkins[2], Kelly Edwards[2], Stephen Cassivi[3], Randolph Marks[4], Yolanda Garces[5], MarieChristine Aubry[1]
[1]Laboratory Medicine And Pathology, Mayo Clinic Rochester, Rochester/MN/UNITED STATES OF AMERICA, [2]Division Of Biomedical Statistics And Informatics, Mayo Clinic Rochester, Rochester/MN/UNITED STATES OF AMERICA, [3]Division Of General Thoracic Surgery, Mayo Clinic Rochester, Rochester/MN/UNITED STATES OF AMERICA, [4]Division Of Medical Oncology, Mayo Clinic Rochester, Rochester/MN/UNITED STATES OF AMERICA, [5]Department Of Radiation-oncology, Mayo Clinic Rochester, Rochester/MN/UNITED STATES OF AMERICA

Background: Modified Masaoka staging has been suggested as a prognostic parameter for thymoma, although Moran et al proposed a new staging system. The prognostic role of histopathologic classifications and clinical features are controversial. Moderate interobserver agreement in morphologic classification hampers studies. We studied clinicopathologic parameters of thymoma in which multiple pathologists agreed upon a morphologic diagnosis.

Methods: Three pathologists reviewed 412 thymoma (1942-2008) and classified them according to WHO, proposed Suster & Moran (S&M) and Bernatz classifications. Cases in which all pathologists agreed were studied further. Outcomes were analyzed with Cox proportional hazards regression models.

Results: Figure 1 presents numbers of reviewed thymomas, morphologic agreement, available follow up and statistically analyzed cases. Follow-up (median 7.5 years, range 0-44) was available for 121 women and 111 men; 33 had recurrence and/or metastasis (5-year estimate 9.2%). 121 patients died (5-year estimate 23.9%), 11 of disease.



		Overall Survival		Recurrence Free Survival	
		HR	P-Value	HR	P-Value
Age, median years (range)	56.6 (18-90)	**1.02**	**0.001**	0.98	0.09
Thymoma Size, median cm (range)	7.0 (1.5-25.8)	**1.10**	**0.0008**	**1.17**	**0.0007**
Weight loss, n (%)	14 (6.1)	**2.47**	**0.003**	**3.20**	**0.02**
Resection status[a]		**0.43**	**0.03**	0.36	0.15
WHO[b]					
A	12.9%	**1.0**	**0.001**	**1.0**	**0.001**
AB	24.1%	**0.68**		**0.33**	
B1	19.0%	**0.52**		**1.19**	
B2	30.2%	**1.22**		**1.99**	
B3	10.3%	**1.79**		**4.37**	
S&M					
Typical thymoma	89.7%	**2.14**	**0.004**	**3.93**	**0.0003**
Atypical thymoma	10.3%				
Bernatz					
Lymphocyte	19.1%	**1.0**	**0.017**	1.0	0.09
Spindle	25.7%	**1.73**		0.39	
Mixed	41.4%	**2.13**		0.92	
Epithelial	13.8%	**3.30**		2.03	
Modified Masaoka Stage					
I	37.1%	**1.0**	**<0.0001**	**Non-estimable**	
II	27.7%	**2.41**			
III	28.3%	**2.08**			
IV	6.9%	**6.97**			
Continuous		**1.61**	**<0.0001**	**4.27**	**<0.0001**
Proposed Moran Stage					
0	43.2%	**1.0**	**<0.0001**	**Non-estimable**	
I	18.9%	**2.58**			
IIa/b	23.0%	**1.58**			
IIc	6.8%	**5.18**			
IIIa/b	8.1%	**8.10**			
Continuous		**1.59**	**<0.0001**	**3.14**	**<0.0001**

Table 1

Table 1 summarizes the univariate analysis for overall (OS) and recurrence free (RFS) survival. Year of treatment was not significant. Multivariate analysis adjusted for WHO, S&M or Bernatz showed age, thymoma size and Masaoka as independent predictors of OS; thymoma size and Masaoka independently predicted RFS. Weight loss and resection status were additional predictors of OS; weight loss was an additional predictor of RFS when adjusted for S&M. Resection status was also an independent predictor for OS when adjusted for Bernatz.

If adjusting for WHO or S&M and Masaoka and resection status, only Masaoka remained an independent predictor of RFS and OS. If adjusted for Masaoka, age and thymoma size were independent prognostic predictors of OS. A strong correlation between Masaoka and proposed Moran staging (correlation coefficient, 0.95) suggested that proposed Moran staging has similar prognostic strength as Masaoka. Table Legend: [a]Complete resection in 92.1% cases. [b]Micronodular (3.0%) and metaplastic (0.4%) thymoma were also identified

Conclusion: Modified Masaoka staging is the strongest predictor of OS and RFS of thymoma when compared to resection status and morphologic classifications. Thymoma size is a prognostic parameter independent of Masaoka and morphology and should be considered for any new staging system.

Keywords: WHO classification of thymoma, Modified Masaoka Stage, Thymoma size, Prognostic Predictors of thymoma

POSTER SESSION 1

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P1.04: IMPACT OF THE RECOMMENDATIONS OF THE INTERNATIONAL THYMIC MALIGNANCY INTEREST GROUP (ITMIG) ON THE MASAOKA- KOGA'S CLASSIFICATION OF THYMOMAS.

Juan Carlos Trujillo[1], Ramon Rami-Porta[1], Sergi Call[1], Carme Obiols[1], Cynthia Jose Baez[2], Guadalupe Gonzalez[2], Mireia Serra[1], Roser Saumench[1], Josep Belda[1]

[1]Thoracic Surgery, Hospital Mutua de Terrassa, Terrassa/SPAIN, [2]Pathology, Hospital Mutua de Terrassa, Terrassa/SPAIN

Background: The objective of this study is to see how the ITMIG recommendations changed the original Masaoka-Koga's classification of thymomas in our series.
Methodes: Retrospective descriptive study of a series of patients who underwent resection of thymic tumors from June 1995 to May 2013. The original Masaoka-Koga's classification was modified following the ITMIG recommendations (J Thorac Oncol. 2011;6 S1710-S1716).

IIb	1	5	4/14 (29%)
III	6	2	4/14 (29%)
IVa	4	3	1/14 (7%)
IVb	1	1	0/14 (0%)
			All patients with cha 14

Resection approaches: 26 (72.2%) sternotomies, 5 (13.8%) posterolateral thoracotomies, 3 (8.3%) VATS (video-assisted thoracic surgery) resections, 1 (2.7%) anterolateral thoracotomy, 1 (2.7%) transcervical approach. In all cases but three complete resection was possible. Two patients (5.5%) presented with recurrence; one of them had a stage IVb thymoma. Both underwent a new resection. As for the 8 patients with MG, 5 (62.5%) had a complete remission. One patient (2.7%) died in the postoperative period from sepsis by Staphylococcus aureus. After a mean follow-up of 88.3 months (range from 1 to 193 months), 29 (80%) patients were alive. In the group of patients with thymoma, 5 died from non-related causes. From the 4 patients with thymic carcinoma, one is free from disease (after 5 months of follow-up), one patient was missing after 132 months of follow-up, one died from non-thymoma related and the other one died intraoperatively from rupture of the aortic arch. This last patient had been treated with induction chemo-radiotherapy.

Conclusion: The ITMIG recommendations modified the original Masaoka-Koga's classification in more than a third of cases. We need larger series to see how this change in staging impacts survival.

Keywords: Masaoka-Koga's classification, Thymic tumors, staging

POSTER SESSION 1

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P1.05: PLEURAL METASTASES OF THYMOMA IN PLEURODESED HEMITHORAX - DO WE NEED TO RETHINK THE TRANSCOELOMIC MECHANISM OF METASTATIC SPREAD?

Sarah Hunt, Alan Kirk, Khalid Amer
Thoracic Surgery, Golden Jubilee National Hospital, Glasgow/UNITED KINGDOM

Background: Disseminated disease in thymic malignancy is typically confined to the thorax. The route of metastatic spread has been attributed to multiple mechanisms including; transplantation, implantation, lymphatic, haematogenous and most commonly transcoelomic – particularly where pleura is involved. This case report and literature review explores the nature of metastatic spread to the pleura in a patient who had undergone previous talc pleurodesis, and considers whether established mechanisms need to be reconsidered.

Methods: Review of established literature on disseminated thymoma did not reveal a comparable case report. We searched literature databases PubMed and Cochrane, using search entries including; thymoma, dissemination, transcoelomic metastasis. We felt that this case report challenged the most current explantation of metatastic spread. A 53 year-old gentleman presented with pleuritic chest pain. His CTPA was negative. However the CT identified a large anterior mediastinal lobulated mass, extending into anterior pericardium. The mediastinum appeared to have associated pericardial thickening, with several pleural masses at the left hemithorax base. Biopsies identified thymoma tissue, stage B1. In 1998 and 2000 he was admitted to hospital with left-sided spontaneous pneumothoraces, and underwent a successful talc pleurodesis(2000) which obliterated the left pleural cavity and prevented any reoccurrence. In 2008 the gentleman underwent a routine chest x-ray for shortness of breath, this identified; abnormalities distorting the cardiac contours, thought not to be suspicious at this time, and otherwise normal. The man commenced neo-adjuvant chemotherapy which had limited effects on the size of the tumour. A radical thymectomy was performed on the 23/8/12. The mass was removed in two pieces plus three pleural lesions. Pleural options were limited due to pleurodesis. The histology identified a high grade B2 thymic tumour, with foci of squamous cell carcinoma(which were extensively present at the margins). No macroscopic disease was left in the

mediastinum. Due to the relative chemo insensitivity, further management included mediastinal radiotherapy and interval scans. The pleural lesions awaited a further surgical decision as to whether it would be possible to resect the tissue via thoracotomy.

Results: The regionalised nature of pleural involvement in this patient, in the context of an obliterated pleural space, suggested that transcoelomic mechanisms of metastatic spread was less likely. Literature has suggested that lymphogenous and haematogenous dissemination are less common in thymic malignancies, however this case may suggest that other methods of dissemination may be more significant than previously thought.

Conclusion: This case prompts reconsideration of the predominant route of metastatic spread in thymic malignancy. Invasion and transcoelomic spread are reported frequently however it has been rarely seen to disseminate via the blood and lymph systems. Pleural dissemination is seen most frequently in thymic malignancy(in some series up to 25%). This case questions the route of dissemination via the transcoelomic route in an obliterated pleural space. Pathological studies of breast cancer spreading to pleura found them to be mostly lymphatic. With this in mind and the case discussed, some interesting questions are raised into the metastatic spread of thymic malignancies.

Keyword: Thymoma, transcoelomic metastases, pleurodesis

POSTER SESSION 1

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P1.06: THE ROLE OF HAEMATOLOGICAL MARKERS IN PATIENTS UNDERGOING THYMECTOMY: A STUDY FROM UNITED KINGDOM.

Luke Kelly, Felice Granato, Stephan Dreyer, Matthew Wickham, Alan Kirk
Thoracic Surgery, Golden Jubilee National Hospital, DY/UNITED KINGDOM

Background: Thymomas and thymic carcinomas are epithelial tumours arising from the thymic gland (TETs). The incidence in the United States is 0.15 per, 100,000 person years. In 10-15% of cases, TETs are associated with Myasthenia Gravis (MG).

The role of haematological markers, such as acute phase proteins (APP), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) is still uncertain. The aim of this retrospective study is to evaluate the pre-operative significance of APP, haemoglobin, NLR and PLR in patients with TETs undergoing thymectomy and to assess their impact on the clinical outcome of MG.

Methods: Sixty consecutive patients undergoing thymic resection at a single institution from November 2008 to May 2013 were retrospectively analysed. Age, gender, pre-operative CRP, NLR, PLR, haemoglobin, albumin, myasthenia status and post-operative medical treatment were evaluated. Two patients with diagnosis of malignancy other than TETs were excluded from our study. Two groups were identified; Group A (patients with ETTs), Group B (patients with benign thymic disease or normal pathology). A subgroup of patients with myasthenia gravis and their medical management following thymectomy was also assessed.

Results: There was no statistical significant difference in the preoperative mean values of haemoglobin, albumin, CRP, PLR and NLR between Group A and B ($p>0.05$). In patients with a diagnosis of myasthenia gravis, patients with no reduction in post-operative medical treatment following thymectomy were shown to have higher mean values of CRP and lower PLR values but these differences did not reach statistical significance ($p>0.05$) whereas mean NLR was approaching statistical significance ($p=0.06$).

Conclusion: In this study, the pre-operative haematological markers evaluated did not show a significant elevation in patients with TETs when compared to those with benign thymic pathologies. Preliminary evidence suggests there may be a neutrophil mediated response in MG and this could influence the clinical improvement of these patients after thymectomy. Further studies are warranted in order to make definitive conclusions.

Keyword: Thymic malignancy myasthenia markers

POSTER SESSION 1

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P1.07: RIGHT PARATRACHEAL LYMPH NODES GROUP IS IMPORTANT PATHWAY OF LYMPHATIC METASTASIS IN MALIGNANT THYMIC EPITHELIAL TUMORS

In Kyu Park[1], Jae Hyun Jeon[2], Yoohwa Hwang[2], Hey-Seon Kim[2], ChangHyun Kang[1], YoungTae Kim[1]
[1]Seoul National University Hospital, Seoul National

University College of Medicine, Seoul/KOREA, [2]Seoul National University Hospital, Seoul/KOREA

Background: Lymph node metastasis is not uncommon and important prognostic factor in thymic epithelial tumors. However, lymphatic metastasis pattern is still unknown. We investigated lymph node metastasis pattern of thymic epithelial tumors.

Methods: Total of 223 patients underwent thymectomy for malignant thymic epithelial tumors were retrospectively reviewed. Stations of lymph node metastasis in patients who underwent lymph node dissection and station of lymph node recurrence in patients without initial lymph node metastasis were investigated. Lymph node station was divided into anterior mediastinal lymph nodes (perithymic lymph nodes), intrathoracic lymph nodes (any intathoracic lymph nodes except anterior mediastinal lymph nodes) and extrathoracic lymph nodes. Nomenclature of each station of intrathorcic lymph nodes follows that of generally used lung cancer lymph node station.

Results: Lymph node metastasis was confirmed in 12 patients. Eleven patients had metastasis in dissected lymph node during total thymectomy and one patient had recurrence at lymph node during follow-up. Lymph node metastasis rate according to the WHO type were 71% (3/42) in B2, 9.1% (3/33) in B3 and 16.2% (6/37) in C. There was no lymph node metastasis in 101 type A, AB and B1. Metastasis rate according to the Masaoka-Koga stages excluding lymph node factor were 28.1% (9/32) in III, 10.5% (2/19) in IVa and 33.3% (1/3) in IVb. There was no lymph node metastasis in 169 patients with stage I or II tumors. Mean tumor size was 8.9cm (4 -14). Lymph node metastases were confirmed at anterior mediastinal lymph nodes in 6 patients and at intrathoracic lymph nodes in 7 patients. One patient had metastasis at both areas. Five patients (71.4%) with intrathoracic lymph node metastasis had metastasis at right paratracheal area. One patient with B2 thymoma invading chest wall had metastasis at right internal mammary lymph node and right hilar lymph node. One patient with right paratracheal lymph node metastasis also had metastasis at subcarinal lymph node. One patient with completely resected stage IIb type B3 thymoma had recurrences at subcarinal node and right middle lobe. Two patients with right paratracheal lymph node metastasis had recurrences at cervical lymph nodes.

Conclusion: Anterior mediastinal and intrathoracic lymph node metastasis is not uncommon in malignant thymic epithelial tumors. Right paratracheal lymph nodes group is crucial station of lymphatic metastasis pathway in malignant thymic epithelial tumors. Right paratracheal lymph node should be dissected in locally advanced malignant thymic epithelial tumors.

Keywords: right paratracheal node, lymph node metastasis, thymoma

POSTER SESSION 1

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P1.08: PET-CT EVALUATION OF METABOLIC TUMOR VOLUME IN EARLY AND INVASIVE THYMOMAS

Marcelo Benveniste[1], Cesar Moran[2], Osama Mawlawi[3], Stephen Swisher[4], Patricia Fox[5], Reginald Munden[1], Edith Marom[1]

[1]Diagnostic Imaging, MDAnderson Cancer Center, Houston/TX/UNITED STATES OF AMERICA, [2]Pathology, MDAnderson Cancer Center, Houston/UNITED STATES OF AMERICA, [3]Physics, MDAnderson Cancer Center, Houston/UNITED STATES OF AMERICA, [4]Surgery, MDAnderson Cancer Center, Houston/UNITED STATES OF AMERICA, [5]Statistics, MDAnderson Cancer Center, Houston/UNITED STATES OF AMERICA

Background: Metabolic tumor volume assessment using positron-emission tomography (PET)–CT has a role for monitoring response to therapy in oncologic patients. Assessment of tumor volume above a specific SUV threshold has a potential promise to distinguish between early (Stage I and II) and advanced thymoma (stage III and IV) as well as high risk thymoma (Type B3) from low risk according to WHO Classification. It is important to differentiate these neoplasms before surgery, as patients with a worst histological type or locally advanced tumors require neoadjuvant chemotherapy that enables effective resection. Thus, tumor volumetric assessment could be used to direct those patients. This study assessed whether the volumetric standardized uptake value (SUV) measurements can predict advanced thymoma and whether it can separate type B3 thymoma from low risk thymoma.

Methods: We retrospectively reviewed FDG positron emission tomography (PET)-CT scans of 51 consecutive newly diagnosed patients with thymic epithelial malignancy. PET-CT findings documented were focal FDG activity: SUVbwmax, SUVbwmean, SUVbwpeak and total body volumetric standardized uptake value (SUV) measurements.

These were correlated with Masaoka-Koga staging and WHO classification. Wilcoxon rank-sum tests were used to assess association between SUV and pathological stage, cancer type, and classification.

Results: Among the study patients, 37 had thymoma, 12 thymic carcinoma, and 2 thymic carcinoid. Higher total tumor volume above SUV 3.5 was seen in patients with type B3 thymoma than in those with type A, AB, B1, or B2 thymoma (p=0.0408). Total tumor volume above SUV 3.5 was higher in patients with advanced stage than in early stage disease (p=0.0008). Additionally, patients with thymic carcinoma or carcinoid demonstrated a higher total tumor volume above SUV 3.5 than in those with thymoma (p=0.0212).

Conclusion: Metabolic tumor volume assessment is helpful in distinguishing early from advanced stage thymoma, low-risk thymoma from more aggressive thymoma (type B3) and thymic carcinoma/carcinoid tumors from thymoma.

Keywords: PET-CT, Metabolic Tumor Volume, thymoma

POSTER SESSION 1

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P1.09: ^{68}GA-DOTA-CONJUGATE PEPTIDES AND [^{18}F]FDG PET/CT IN THYMIC MALIGNANCIES

Martina Sollini[1], Armando Froio[1], Antonio Chella[2], Marco Lucchi[3], Federico Rea[4], Giulia Atti[1], Roberto Boni[5], Massimo Roncali[1], Annibale Versari[1], PaolaAnna Erba[5]

[1]Nuclear Medicine, Arcispedale Santa Maria Nuova - IRCCS, Reggio Emilia, Reggio Emilia/ITALY, [2]Pneumology, Azienda Ospedaliero-Universitaria Pisana, Pisa/ITALY, [3]Thoracic Surgery, Azienda Ospedaliero-Universitaria Pisana, Pisa/ITALY, [4]Thoracic Surgery, University of Padua, Padua/ITALY, [5]Nuclear Medicine, University of Pisa, Pisa/ITALY

Background: Thymic malignancies include different type of neoplasms characterized by different morphology of epithelial cells and degree of atypia. Variable different degree of somatostatin receptors (SSTR) expression may be present on cell surface and despite the in vitro demonstration of its inhibitory effect in thymic epithelial cells as well as on T-lymphocyte development through paracrine mechanisms, the use of octreotide alone or in combination with prednisone is still controverse even in presence of positive Octreoscan. Although Octreoscan shows high efficacy for whole body imaging (reported detection rate of 80-100%), there are some limitations. More recently, PET with ^{68}Ga-DOTA-conjugate peptides has brought about dramatic improvements in spatial resolution with promising results for the detection of SSTR expressing tumours, and provides prognostic information. The aim of this study is to investigate the pattern of ^{68}Ga-DOTA-conjugate peptides and [^{18}F]FDG uptake at PET/CT for thymic malignancies restaging and to compare their performances to CT findings as gold standard.

Methods: We retrospectively evaluated 29 thymic malignancies patients (M/F=12/17; mean age 57 years; median age 60 years; range 35-78 years) affected by thymic neoplasms (type A n=2, AB n=2, B1 n=4, B2 n=4, B2/B3 n=2, B3 n=7, C n=8). All patient after histological confirmation, performed both ^{68}Ga-DOTA-conjugate peptides PET/CT and [^{18}F]FDG PET/CT one month a part. Results of ^{68}Ga-DOTA-conjugate peptides and [^{18}F]FDG PET/CT examinations were compared using CT findings as gold standard and correlate to histological type. The maximum standard uptake value (SUV_{max}) was calculated for both ^{68}Ga-DOTA-conjugate peptides and [^{18}F]FDG PET/CT images.

Results: ^{68}Ga-DOTA-conjugate peptides PET/CT was able to correctly identify site of disease in 12(1/2 AB; 2/4 B1; 1/4 B2; 4/7 B3; 4/8 C) cases and negative in 17 (2/2 A; 1/2 AB; 2/4 B1; 3/4 B2; 2/2 B2/B3; 3/7 B3 and 4/8 C) while [^{18}F]FDG PET/CT results negative in only 5 cases (1/2 AB;1/4 B2; 2/7 B3; 1/8 C). Comparison between ^{68}Ga-DOTA-conjugate peptides and [^{18}F]FDG PET/CT are as follow: 14/29 ^{68}Ga-DOTA-conjugate peptides-/[^{18}F]FDG+; 2/29 ^{68}Ga-DOTA-conjugate peptides+/[^{18}F]FDG-; 10/29 both positive and 3/29 both negative (Table 1).

Table 1

PET/CT	FDG +	FDG -	Total
^{68}Ga-DOTA +	10	2	12
^{68}Ga-DOTA -	14	3	17
Total	24	5	29

SUV_{max} values not showed significant difference between ^{68}Ga-DOTA-conjugate peptides and [^{18}F]FDG PET/CT (2.2-9.1 and 2.1-9.8, respectively). In 5 patients all the CT detectable lesions presented ^{68}Ga-DOTA-conjugate peptides uptake while for [^{18}F]FDG this was observed in 14 cases. In the other cases we observed at least one measurable CT lesion without either ^{68}Ga-DOTA-conjugate peptides and/or [^{18}F]FDG uptake. Finally, in 5 cases ^{68}Ga-DOTA-conjugate peptides and [^{18}F]FDG PET/CT identify more lesions as

compared to CT, mainly localized at bone. No false positive findings were observed at ^{68}Ga-DOTA-conjugate peptides PET/CT.

Conclusion: In this series of thymic neoplasm at restaging a predominant [^{18}F]FDG positivity was observed as compared to ^{68}Ga-DOTA-conjugate peptides at PET/CT. ^{68}Ga-DOTA-conjugate peptides remains most frequently positive in AB, B1, B3 and C even. Concordant [^{18}F]FDG-PET/CT and CT results were observed in 14/29 patients, detecting additional bone lesions in 5/29 cases. These findings may suggest a relative loss of SSTR expression during thymic malignancy progression and should be considered when planning SSTR-analogues therapy.

Keywords: [18F]FDG PET/CT, thymic malignancies, 68Ga-DOTA-conjugate peptides PET/CT, somatostatin receptors expression

POSTER SESSION 1

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P1.10: ANALYSIS OF PROTEIN EXPRESSIONS AND GENETIC MUTATIONS OF THE C-KIT GENE IN 19 PATIENTS WITH THYMIC CANCER - AN EXPERIENCE OF ONE C-KIT MUTATION POSITIVE PATIENTS TREATED WITH IMATINIB

Takashi Seto[1], Fumihiko Hirai[1], Gouji Toyokawa[1], Yoko Takeda[1], Kenichi Taguchi[2], Ryo Toyozawa[1], Eiko Inamasu[1], Tsukihisa Yoshida[1], Yoshimasa Shiraishi[1], Tomoyoshi Takenaka[1], Masafumi Yamaguchi[1], Mitsuhiro Takenoyama[1], Yukito Ichinose[2]

[1]Department Of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka/JAPAN, [2]Clinical Research Institute, National Kyushu Cancer Center, Fukuoka/JAPAN

Background: Thymic cancer (TC) is a rare malignancyamong thymic tumors, and c-kit serves as one of the immunohistochemical (IHC) markers of TC. Although mutations of the *c-kit* gene are frequently observed in gastrointestinal stromal tumor (GIST), and the patients with *c-kit* positive GIST have been successfully treated with c-kit inhibitors such as imatinib, several reports recently identified mutations of the *c-kit*gene in patients with TC. Thus,we investigated mutations and protein expressions of the *c-kit* gene in patients with TC.

Methods: IHC and genetic analyses (PCR and direct sequencing) were performed in nineteen patients with TC.

Results: One of 19 (5%) patients with TC was identified to harbor the *c-kit* mutation, while c-kit protein expressionswere observed in 10 of 19(53%) TCs.Among the 10 c-kit positive TCsat protein levels,fourTCs were judged to be weaklyor focally stained. **Case report:** A 32-years-old female without any symptomswas diagnosed with TC (poorly differentiated squamous cell carcinoma) by thymicfine needle biopsy. Since the disease progressed even after treatments with carboplatin pluspaclitaxel and some investigational drugs, VATS lung biopsy was performed fora metastatic lung tumor, and revealed the tumor to be the same histology as that of the initial biopsy. The tumor showed immunoreactivity for CK903, P63, CD5, chromograninA, CD56, bcl-2 and c-kit, while no expressions of synaptophysin and hCG were observed. Furthermore, genetic analyses detected mutations of the *c-kit* gene in exon11 V559G (substitution-missense) and 1676 T> G (substitution). Based on this result, treatment with imatinib 400mg/day p.o. was administered from 28/Mar/2013 and 20% of tumor regression was achieved approximately 3 month after the administration of the drug.

Conclusion: The frequency of the *c-kit* sensitive mutationshas yet to be established; however, patients with TC harboring the *c-kit*mutations could benefit much from c-kit inhibitors. Since *c-kit* is one of the driver oncogenesin TCs, c-kit inhibitors such as imatinib could be one of the key-drugs for *c-kit* mutatedpatients with TC. A prospective global study is warranted to investigate the efficacy and safety of c-kit inhibitors for TCs harboring the *c-kit* mutations.

Keywords: thymic cancer, c-kit, imatinib

POSTER SESSION 1

Display Time: Friday, September 6, 2013 – 09:00 – 15:30

P1.11: EXPRESSION OF EZRIN IN TUMOR CELLS CORRELATES WITH THE THYMOMA SUBCLASSIFICATION

Qiangling Sun[1], Wentao Fang[2]

[1]Basic Research Laboratory, Shanghai Chest Hospital, Shanghai/CHINA, [2]Department Of Thoracic Surgery, Shanghai Chest Hospital, Shanghai/CHINA

Background: The histologic classification of thymoma has been attracting more controversy on account of morphological variation and tumor epithelial heterogenicity for the past several decades. Molecular profiling at gene or protein levels may elucidate the biological variance of tumors

and contribute to the pathological classification system that correlates better with biological, clinical and prognostic parameters.

Methods: To investigate the roles of ezrin in thymic epithelial tumors, we examined the expression of ezrin in 39 type B tumors by tissue array and immunohistochemistry. The tumors consisted of 18 type B1, 11 type B2 and 10 type B3 according to the World Health Organization histologic classification system and of 13 stage Ⅰ, 13 stage Ⅱ and 11 stage Ⅲ thymomas according to the Masaoka staging system.

Results: In the positive cases, ezrin were expressed in epithelial cells. The statistical analysis demonstrated that the significant difference in the positive rate of ezrin between type B1 thymoma and type B3 thymoma (Z=-2.963, P= 0.003). However, there is no difference between ezrin expression in type B1 and B2 thymoma (Z=-1.814, P=0.070) or between type B2 and B3 (Z=-1.047, P=0.295). The ezrin showed a tendency to be expressed in higher classification tumors from type B1 to B3. There is correlation between ezrin and WHO classification from type B1 to type B3 (Spearman's correlation coefficients: 0.515, P=0.002). Statistical analysis showed that there is correlation between ezrin expression and clinical stage (Spearman's correlation coefficients, Ezrin: 0.481, P=0.032;).

Conclusion: In all, these results suggest that the elevated expression of ezrin, likely contribute to the discrimination of type B1, B2 and B3 thymoma tissues. Moreover, the above results showed that the increased expression of ezrin were in accordance with the tumor aggravation.

Keyword: Thymoma; Ezrin; Tissue array; Immunohistochemistry.

POSTER SESSION 1

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P1.12: CLASSIFICATION OF THYMIC NEUROENDOCRINE CARCINOMAS BY A KI67-BASED DIGITAL IMAGE PROCESSING APPROACH

Cleo-Aron Weis[1], Benedict Griessmann[1], Philipp Ströbel[2], Alexander Marx[1]

[1]Institute Of Pathology, University Medical Centre Mannheim, Mannheim/GERMANY, [2]Institute Of Pathology, University Medical Center Göttingen, Göttingen/GERMANY

Background: The 2003 WHO-classification of neuroendocrine carcinomas (NEC) in the thymus is based on the nomenclature of neuroendocrine tumour occurring in the lung distinguishing typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma (SCC). The classification of NEC especially pulmonary ones further developed in the last years. Meanwhile, the ki67-index has been suggested as an alternative approach to classify pulmonary NEC. In the thymus respective data are missing. In the present study we describe a method to automatically measure the ki67-index. Our aim is to correlate the classification of thymic NEC with the obtained ki67-index.

Methods: The patient collective comprises 35 cases of confirmed thymic NEC. These were assigned according to the actual WHO-criteria (morphology, necrosis, mitoses) to typical carcinoid, atypical carcinoid, LCNEC and SCC. Evaluation of the ki67-index for these cases was based on digital image processing. Therefore, the immunohistochemically stained sections were fully digitalized using an Aperio ScanScope.

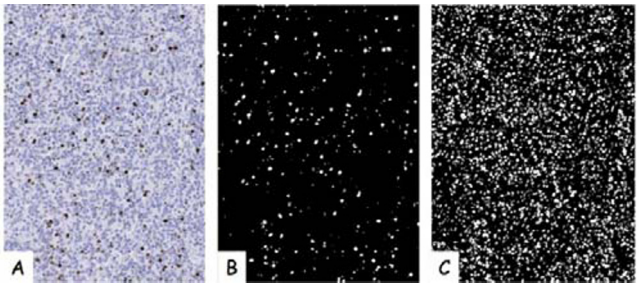

Fig.: Image processing workflow A shows the original image. B visualizes the segmentation of brown nuclei whereas C shows the segmentation of all nuclei. Subsequently, the slides underwent further processing using MATLAB, which resulted in two binary images, one comprising all nuclei stained for ki67 (B) and another one comprising all nuclei (C). The number of nuclei per binary image can be easily calculated by implemented functions and the ki67 can be calculated by dividing the results. This method was validated by comparing the results of evaluation by hand and by image processing.

Results: Digital image processing based calculation of the ki67-index in thymic NEC is possible and leads to similar results as by-hand evaluation. Furthermore, there is a good inter- and intraobserver reproducibility of the results.

Conclusion: The ki67-index can be calculated in a full automatic way and leads to reliable results. In analogy to the recent development in pulmonary NEC, we are going to map

the classification by individual ki67-indeces. Thereby, we plan to define certain thresholds for the classification of thymic NEC. The numeric values of these thresholds will be compared to the pulmonary ones to confirm the commonalities or, if the results are different, to question them.

POSTER SESSION 1

Display Time: Friday, September 6, 2013 – 09:00 – 15:30

P1.13: RYTHMIC: A NATIONWIDE NETWORK FOR THYMIC MALIGNANCIES IN FRANCE

Benjamin Besse[1], Eric Pichon[2], Pascal-Alexandre Thomas[3], Hervé Léna[4], Eric Dansin[5], Gilbert Massard[6], Gérard Zalcman[7], Julien Mazières[8], Luc Thiberville[9], Virginie Westeel[10], Pierre Fournel[11], Christelle Clément-Duchêne[12], Xavier Quantin[13], Jaafar Bennouna[14], Thierry Molina[15], Nicolas Girard[16]

[1]Institut Gustave Roussy, Villejuif/FRANCE, [2]Centre Hospitalier Régional Universitaire, Tours/FRANCE, [3]Assistance Publique, Hôpitaux de Marseille, Marseille/FRANCE, [4]Centre Hospitalier Universitaire, Rennes/FRANCE, [5]Centre Oscar Lambret, Lille/FRANCE, [6]Hôpitaux Universitaires de Strasbourg, Strasbourg/FRANCE, [7]Centre Hospitalier Universitaire, Caen/FRANCE, [8]Centre Hospitalier Universitaire, Toulouse/FRANCE, [9]Centre Hospitalier Universitaire, Rouen/FRANCE, [10]Centre Hospitalier Régional Universitaire, Besançon/FRANCE, [11]Institut de Cancérologie Lucien Neuwirth, Saint-Priest en Jarez/FRANCE, [12]Centre Hospitalier Universitaire, Vandoeuvre-les-Nancy/FRANCE, [13]Centre Hospitalier Universitaire, Montpellier/FRANCE, [14]Institut de Cancérologie de l'Ouest, Nantes/FRANCE, [15]Assistance Publique-Hôpitaux de Paris, Paris/FRANCE, [16]Hospices Civils de Lyon, Lyon/FRANCE

Background: RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a nationwide network for thymic malignancies, which was appointed in 2012 by the French National Cancer Institute, as part of its rare cancer program. The objectives of the network include a territorial coverage by regional expert centers, the dissemination of highest standards for the diagnostic and therapeutic management of patients, and the promotion of collaborative research. Registration in RYTHMIC of all patients diagnosed with thymic malignancy is recommended as part of good clinical practice for oncologists.

Methods: Starting January 2012, the management of all patients diagnosed with thymic malignancy in France has been discussed on a real-time basis at a reference national multidisciplinary tumor board (MTB), which is organized twice a month using a web-based conferencing system. Decision-making is based on consensual recommendations, that were originally established using available evidence, and are updated and approved each year by all members of the network. A prospective database of all patients is hosted by the French Thoracic Cancer Intergroup. We report the characteristics and treatment modalities of patients included during the first year.

Results: From January to December 2012, 257 patients were enrolled in RYTHMIC. There were 126 (49%) men and 131 (51%) women; mean age at diagnosis was 54.5 years. Among 214 cases, histology was thymoma for 146 (56%) patients (11 (5%) type A, 28 (13%) type AB, 22 (10%) type B1, 35 (16%) type B2, 24 (11%) type B3, 26 (12%) mixed type), and thymic carcinoma for 33 (15%) patients, 8 of which were neuroendocrine carcinomas; other histologies were diagnosed for 35 (16%) patients. Among 144 cases, Masaoka-Koga stage was I, IIA, IIB, III, IVA, and IVB in 34 (24%), 19 (13%), 20 (14%), 22 (15%), 35 (24%), and 14 (10%) patients, respectively. 44 (17%) patients presented with autoimmune disorder, consisting of myasthenia gravis in 28 cases. Surgery was performed for 166 patients, mostly using a median sternotomy approach (52% of cases). Postoperative radiotherapy was delivered to 42 patients; 71 patients received perioperative chemotherapy. Exclusive chemotherapy/radiotherapy was administered to 20 and 4 patients, respectively. Mature data will be presented at the meeting.

Conclusion: This first analysis of the RYTHMIC prospective cohort demonstrates the feasibility of a national MTB for thymic malignancies, that, besides ensuring all patients an equal access to highly specialized treatment, provides with a comprehensive tool to monitor dedicated actions to improve the management of patients in the future, increase the quality-of-care, and screen patients for future translational research and clinical trials. Supported by Institut National du Cancer

Keywords: network, Tumor board, thymic tumor

POSTER SESSION 1

Display Time: Friday, September 6, 2013 – 09:00 – 15:30

P1.14: RESULTS AND PROGNOSTIC FEATURES OF RECURRENT THYMOMA

Cai Xu, Qin Feng, Cheng Fan, Yi Zhai, Yi Chen, Hong Zhang, Ze Xiao, Zong Zhou, Jun Liang, Zhou Hui, Dong Chen, Jie He, Lu Wang

Radiation Oncology Department, Cancer Institute & Cancer Hospital Chinese Academy of Medical Science, Peking Union Medical College, Beijing/CHINA

Background: This study sought to analyse the results and prognosis of recurrent thymoma.

Methods: Between 1991 and 2012, 32 patients who developed recurrence after radical resection of thymoma were reviewed.

Results: The initial Masaoka staging was stage I, 3; stage II, 14; stage III, 10; stage IVa, 4;and stage IVb, 1. World Health Organization tumor type: A and AB, 5; B1, 7; B2, 6; B3, 12; and unknown, 2. Among the 32 patients, relapses were found in the following sites: pleura (20 cases), tumor bed (10),non-tumor bed in mediastinum (one), lung (seven), chest wall (six), lymph node metastasis (four) , abdominal node metastasis (one),liver (one), pleural effusion (four), and overlapped recurrence (14).The patterns of recurrence: local recurrence, 6; regional recurrence, 8; distant recurrence, 5; local and regional recurrence, 6; regional and distant recurrence, 4; local, regional and distant recurrence, 3. The median recurrence interval was 42 months (range, 5–193 months). The median follow-up time after recurrence was 49.5 months (range, 1-136months). Overall 5-year survival after recurrence was 65.5%. 7 patients with relapse in the thorax are still alive after re-resection, with a median survival time of 26 months (range, 6-95 months). The perioperative mortality was 0% and the morbidity was 14%. 4 patients with local relapse were given radiotherapy (RT) alone, with a median survival of 60 months (range, 51-107months) and one was dead of progressive disease, probably due to lower reirradiation dose (50Gy), compared to others with radiation dose (60Gy). In patients with regional and/or distant relapse, 6 patients received chemotherapy, and had 37.5% of overall 5-year survival. 5 patients without re-treatment had 50% of overall 1-year survival, with median survival 3 months (range,1-20months). After re-treatment, 9 patients had re-relapse, and the re-relapse free survival rate was 63% at 5 years, with a median re-relapse free survival of 53 months (range, 11-69months). 1 of 15 patients with RT had radiation pneumonitis and recovered after management. In univariate analysis, age (<55y, ≥55y; p=0.009), patterns of relapse (p=0.042), and recurrence-free interval (<20months, ≥20months; p=0.038) were prognostic factors.

Conclusion: Reoperation for resectable thymoma recurrences is associated with better outcome and relative safety, and it should be recommended. In patients with local recurrence of thymoma, RT may get comparable survival to re-operation. RT/CT probably is the treatment of choice when re-resection is not feasible. Younger age, local and regional recurrence, and longer relapse-free interval are associated with positive prognosis.

Keyword: Recurrent Thymoma, Management, outcomes, Prognosis.

POSTER SESSION 1

Display Time: Friday, September 6, 2013 – 09:00 – 15:30

P1.15: CLINICAL OUTCOMES AND PROGNOSTIC FACTORS FOR PATIENTS WITH MASAOKA STAGE III THYMOMA

Chengcheng Fan[1], Qin Feng[1], Yi Chen[1], Yi Zhai[1], Zong Zhou[1], Dong Chen[1], Ze Xiao[1], Hong Zhang[1], Jun Liang[1], Ji Lv[1], Zhou Hui[1], Jie He[2], Lu Wang[1]

[1]Radiation Oncology, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing/CHINA, [2]Thoracic Surgery, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing/CHINA

Background: We aimed to analyze the long-term survival rates, recurrence rates and prognostic factors for patients with Masaoka stage III thymomas.

Methods: A total of 111 patients with stage Ⅲ thymoma treated in our hospital between January 1966 and December 2010 were retrospectively analyzed. Sixty-eight patients (61.3%) were with complete resection, while 23 patients (20.7%) with incomplete resection and 20 patients (18%) with pure biopsy (18 patients with thoracic exploration surgery and 2 patients with CT-guided fine needle puncture biopsy). Fifty-six patients with complete resection (50.5%) and 10 patients with incomplete resection (9%) had postoperative radiation. Twenty patients with pure biopsy received post or preoperative radiation or chemotherapy with or without surgery.

Results: The median follow-up time was 66 months (5-540). The total overall survival (OS) rates、disease free survival（DFS）rates and disease specific survival (DSS) rates at 5 and 10 year were 75.3%、60.8%、81.9% and 54.7%、41.3%、67.1%, respectively. The total failure rate was 36% (40/111), including 30.6% locoregional recurrence and 9% distant metastasis. The DFS at 5 and 10 year among the patients with complete resection、incomplete resection and pure biopsy were 73.9%、40.1%、41.2% and51.5%、26.7%、30.9%, respectively（p=0.003）. The DSS at 5 and 10 year were 93.9%、69.2%、59.7% and 78.9%、46.2%、59.7%, respectively（p=0.004）. On multivariate analysis, resection completeness (p=0.000) and lung involvement (p=0.024) were independent prognostic factors for DFS, and resection completeness (p=0.002)、age (p=0.028) and myasthenia gravis (p=0.038) were independent prognostic factors for DSS.

Conclusion: Patients with completely resected thymoma had a better survival and lower recurrence rates than patients with tumor incompletely resected. Resection completeness and lung involvement were prognostic factors for DFS, and resection completeness、age and myasthenia gravis were
prognostic factors for DSS.

Keywords: thymoma, Surgery, radiotherapy, thymic tumor

POSTER SESSION 1

Display Time: Friday, September 6, 2013 – 09:00 – 15:30

P1.16: A GENE SIGNATURE TO DISTINGUISH THYMIC CARCINOMA FROM THYMOMA

Yesim Gökmen-Polar[1], Robert Cook[2], Jeff Wilkinson[3], Derek Maetzold[2], John Stone[3], Kristen Oelschlager[2], Wei Lu[4], Ioan Vladislav[5], Kenneth Kesler[6], Patrick Loehrer[7], Sunil Badve[1]

[1]Pathology And Laboratory Medicine, Indiana University School of Medicine and Simon Cancer Center, Indianapolis/IN/UNITED STATES OF AMERICA, [2]Castle Biosciences Incorporated, Friendswood/UNITED STATES OF AMERICA, [3]St. Joseph's Hospital And Medical Center, The DNA Diagnostics Laboratory, Phoenix/UNITED STATES OF AMERICA, [4]Indiana University Simon Cancer Center, Indianapolis/UNITED STATES OF AMERICA, [5]Pathology & Laboratory Medcine, Indiana University School of Medicine, Indianapolis/UNITED STATES OF AMERICA, [6]Surgery, Indiana University School of Medicine and Simon Cancer Center, Indianapolis/IN/UNITED STATES OF AMERICA, [7]Hematology/oncology, Indiana University School of Medicine and Simon Cancer Center, Indianapolis/IN/UNITED STATES OF AMERICA

Background: Thymomas and thymic carcinomas (TCs) are rare epithelial tumors derived from the thymic gland that can be at times histologically difficult to distinguish from each other. However, thymic carcinomas are more aggressive and metastasize more frequently than thymoma. Our prior work has resulted in the development of a commercially available prognostic 9-gene signature that can accurately identify patients at high or low risk for metastases from thymomas (Gökmen-Polar et al. PLoS One, 2013; in press). However, the signature is not prognostic for TCs (J Clin Oncol 31, 2013 (suppl; abstr 7605)) highlighting the need to reliably distinguish thymomas from TCs. In the current study, we sought to identify molecular characteristics that distinguish thymomas and TCs.

Methods: qRT-PCR assay for 23 genes (19 test and four reference genes) was performed on formalin-fixed, paraffin-embedded primary thymomas (*n*=111) and TCs (*n*=35) including neuroendocrine carcinomas. All procedures were carried out under CLIA approved and CAP accredited laboratory guidelines. Expression data and biostatistical analysis were performed using JMP Genomics (SAS). Predictive modeling using Radial Basis Machine (RBM) analysis was performed.

Results: Median ages for the thymoma and TCs cohorts were 49 years (range 18-85; Male:Female 1:1.5) and 54 years (range 22-81; Male:Female 1.2: 1), respectively. The distribution for thymoma WHO schema consisted of 37 type B2 and 17 type B3, whereas type A, AB and B1 exhibited less aggressive type with being 8, 26 and 22, respectively. A12-gene signature was found to have strong diagnostic accuracy for identifying thymomas and thymic carcinomas. RBM analysis using the 12-gene signature distinguished the two malignancies with 100% accuracy (ROC=1.0). Resampling of the data was performed to validate the ROC accuracy using 5-fold cross-validation, repeating the validation 20 times. The 12-gene model had a corrected ROC = 0.962, with a mean accuracy of 87%.

Conclusion: A diagnostic gene expression profile was identified that can accurately distinguish thymomas and thymic carcinomas. This objective molecular classification can assist in the accurate categorization of difficult cases and add valuable information to current WHO histological schema. The accurate classification of tumors will not only

enable better prognostication of tumors but also lead to more effective, and precise treatment options for patients.

Keywords: gene signature, thymoma, thymic carcinoma, distinction

POSTER SESSION 2
Display Time:
Saturday, September 7, 2013 – 09:00 – 15:30

P2.01: PERCUTANEOUS CRYOABLATION IN TREATMENT OF RECURRENT THYMOMA: EFFICACY AND SAFETY.

Fereidoun Abtin[1], Leyla Nasehi[1], Robert Suh[1], Simon Han[1], William Hsu[1], James Sayre[1], Robert Cameron[2]
[1]Radiology, UCLA, Los Angeles/UNITED STATES OF AMERICA, [2]Thoracic Surgery, UCLA, Los Angeles/UNITED STATES OF AMERICA

Background: Thymoma is the most common anterior mediastina tumor (incidence: 0.15 - 0.5 in 100,000 person year). Following resection, recurrence occurs mostly in pleura or mediastinum, with re-resection as standard of care. Not all patients are candidates for re-resection and often multiple sites or recurrence limits surgical intervention. Percutaneous Cryoablation Technique (PCT) is a locally ablative minimally invasive technique, which has been used in management of lung cancer and metastasis with relative success. Here we describe our experience with use of PCT in management of recurrent Thymoma, and assess this procedure's safety and efficacy.

Methods: This is a retrospective observational study of thymoma patients with recurrence and drop metastasis after thymectomy treated with PCT from 2008 to 2012. Patients were followed up with imaging. Imaging was used as indicator of local recurrence. Multiple technical and clinical variables were assessed and stepwise multiple variable logistic regression model was used to identify significant imaging and clinical predictors of local control. Safety spectrum of Cryoablation was also assessed.

Results: PCT was performed on 5 patients with 25 lesions (1-16 per patient) at: 8 (32%) Chest wall , 12 (48%) pleura , 2 (8%) mediastinum and 3 (12%) lung lesions. Conscious sedation was used for 19 (76%) and general anesthesia for 6(24%) ablations, with 1-3 (median:1) ablations per session. Median hospital stay was <1 day and it didn't exceed 2 days. Median 2 freeze cycles (range 2-6) per lesion for median duration of 20 minutes (range 10-40). Median size of tumor at long axis was 34.6 mm (range 12-81) and at short axis was15.4 mm (6-25). 5/25 (20%) cryoablations had 0 mm margin, 3/ 5 cryoablations were on single lesion abutting aorta which recurred twice. Patients were followed up for median 331 days (Range=14-1495). On follow up imaging 2/25 (8%) recurred as shown by increased size and nodular enhancement. Immediate complications was absent in 23/25 (92%) ,with 1 pneumothorax and 1 pulmonary hemorrhage. After 24 hours 5/25 (20%) ablations had following complications: 1 pneumonitis, 1 pain, 2 (8%) rib fracture, 1 myasthenia gravis flare, and 1 delayed pneumothorax and moderate left pleural effusion requiring thoracenthesis.

Conclusion: Percutaneous cryoablation for metastatic thymoma allows treatment of multiple lesions with (23/25) 92% local control rate. Proximity of tumor to aorta is possible cause for sink effect and local recurrence. The complications are limited and managed during the ablation.

Keywords: Thymoma treatment, Thymoma recurrence, Percutaneous Cryoablation Technique, minimal invasive surgery

POSTER SESSION 2
Display Time: Saturday, September 7, 2013 – 09:00 – 15:30

P2.02: AN OBSERVATIONAL DATABASE ON THYMOMA PATIENTS FOR STUDYING CRYOABLATION OUTCOMES

Simon Han[1], Leyla Nasehi[2], Fereidoun Abtin[2], William Hsu[1]
[1]Medical Imaging Informatics - Dept Of Radiological Sciences, University of California, Los Angeles, Los Angeles/UNITED STATES OF AMERICA, [2]Radiology, University California Los Angeles, Ronald Reagon hospital, Los Angeles/UNITED STATES OF AMERICA

Background: Increasingly, electronic health records have become an important source for clinical phenotypes in understanding the natural course of diseases and the effectiveness of treatments. The objective of this work is to implement an observational database for capturing and standardizing detailed clinical information about individuals treated for thymomas at our institution. We have developed a web-based application for inputting, storing, and reviewing data on thymoma patients for the purposes of knowledge discovery and outcomes analysis. The platform was designed to be extensible to other cancers (e.g., mesotheliomas) and has been demonstrated as part of a retrospective study of percutaneous cryoablations (PCT) study (Abtin et al, 2013). A standardized vocabulary was created to represent each variable and presented as a series of dropdown menus to facilitate data entry, reduce errors,

and eliminate variability in reporting. Physicians and fellows, the primary users, were involved in defining the data elements and refining the user interface (UI).

Methods: The database was implemented using an iterative approach. First, clinical investigators were asked to define a set of relevant variables and standardized set values. Refinement to the database was guided by feedback provided by clinicians who reviewed the data model and web-based UI. A fellow extracted patient records for retrospective data and organized the variables into categories, as well as listing expected values and standardizing them to ensure the consistency of data. The lists are set up in the database to be easily modifiable. Non-standardized values can be entered via selection of "Other" and entering a user defined value. An automated information extraction pipeline using the Unstructured Information Management Architecture (UIMA) is being explored to automate some of the annotation tasks (e.g., extract patient characteristics, cryoablation details, complications).

Results: A total of 89 data elements are grouped into the following categories: demographics (e.g., age, gender), clinical characteristics (e.g., date of diagnosis, lesion location), procedure characteristics (e.g., complications), imaging characteristics (e.g., measurements, PET findings), and follow-up (e.g., date, outcome). Each patient is associated with demographic information, clinical characteristics, and one or more PCT procedures. Each PCT is associated with a description about the procedure, image findings, and follow-up information. Presently, the database contains five patients with a total of 25 PCTs and 56 imaging follow-ups. The web-based UI provides an intuitive means for inputting and validating data. A dashboard allows users to easily query the database and export inputted information for further study.

Conclusion: Observational databases populated with structured clinical information play an important role in supporting research. Appropriate infrastructure that integrates clinical and research findings are important moving forward. We have developed a database that is configured to the specific needs of a retrospective percutaneous cryoablation study. While the current cohort size is small, our intent is to provide this database as a resource to the community, spur discussion on how to standardize data collection across institutions, and partner with existing efforts such as the ITMIG registry (Huang, 2012) to provide high quality clinical, intervention, and outcome information for thymoma patients undergoing PCT.

Keywords: database, web application, percutaneous cryoablation, PCT

POSTER SESSION 2

Display Time: Saturday, September 7, 2013 – 09:00 – 15:30

P2.03: ORAL ETOPOSIDE IN PRETREATED ADVANCED THYMOMA AND THYMIC CARCINOMA. A FRENCH EXPERIENCE.

Celine Boutros, Florence Fayard, Benjamin Besse
Department Of Cancer Medicine, Institut Gustave Roussy, Villejuif/FRANCE

Background: Thymomas and thymic carcinomas, also named thymic epithelial tumors (TET), are rare tumor entities. There is no standard systemic treatment for pretreated advanced, recurrent TET. Here, we review the efficacy and tolerability of oral etoposide in this setting.

Methods: We reviewed the files of patients who were treated for TET in our institution from November 1992 through December 2012. Patients who received oral etoposide (25 mg 3 times a day, 3 weeks out of 4) for advanced recurrent disease were included in this retrospective study. We assessed response rates using RECIST (Response Evaluation Criteria in Solid Tumors) 1.0 criteria, and collected overall survival (OS), progression-free survival (PFS), and toxicities.

Results: A total of 46 patients were treated for TET. Thirteen patients with recurrent TET received oral etoposide. The median age of patients was 59 years (range 33-85). Eight patients (61%) had thymic carcinoma and 5 patients (39%) had thymoma. The median number of prior chemotherapy regimens was 2 (range 0-8). The median follow-up was 133 months, and the median duration of oral etoposide treatment was 9 months. A partial response (PR) and stable disease (SD) occurred in 2 (15%) and 9 patients (70%) respectively. No complete response was observed. The median PFS was 9 months. The median OS was 69 months since diagnosis and 40 months since the initiation of oral etoposide. Among patients with thymic carcinoma, 1 achieved a PR and 5 achieved SD, whereas 2 progressed. Among patients with thymoma, 1 achieved PR and 4 achieved SD. The median PFS was 4 and 53 months for thymic carcinoma and thymoma cohorts, respectively. The median OS since the diagnosis was 50 and 169 months for thymic carcinoma and thymoma, whereas the median OS since oral etoposide initiation was 22 and 98 months for the same cohorts,

respectively. Grade 3 and 4 toxicities included anemia (15%), neutropenia (23%) and thrombocytopenia (8%). No toxicity-related death occurred.

Conclusion: Our data suggest potential activity of oral etoposide in patients with pretreated thymoma and thymic carcinoma. The treatment is well tolerated. Additional evaluation of oral etoposide in this rare disease is warranted.

Keywords: Thymic tumors, Recurrence, Oral etoposide, Response

POSTER SESSION 2

Display Time: Saturday, September 7, 2013 – 09:00 – 15:30

P2.05: NEOADJUVANT TREATMENT WITH A NOVEL OCTREOTIDE (PASIREOTIDE, SOM230 LAR) IN PATIENTS WITH PRIMARY INOPERABLE THYMOMA AND/ OR LOCAL RECURRENT THYMOMA TO REDUCE TUMOR SIZE - STUDY DESIGN AND FIRST RESULTS.

Berthold Schalke[1], Lukas Kirzinger[1], Rosmarie Kollanur[1], Hendrik Dax[1], Gerhard Schuierer[2], Berhard Kaiser[1], Michael Ried[3], Reiner Neu[4], Joerg Marienhagen[5], Alexander Marx[6]

[1]Dep Of Neurology At Medbo, University of Regensburg, Regensburg/GERMANY, [2]Dep Of Neuroradiology, MEDBO, Regensburg/GERMANY, [3]Dep Thoracic Surgery, University of Regensburg, Regensburg/GERMANY, [4]Nuclear Medicine, University of Regensburg, Regensburg/GERMANY, [5]Dep Of Nuclear Medicine, University of Regensburg, Regensburg/GERMANY, [6]Dep Of Pathology, Universityof Heidelberg/Mannheim, Mannheim/GERMANY

Background: Long term prognosis of patients with primary inoperable thymoma or local recurrent thymoma (Masaoka III - IVa) depends on complete resection (R0). Most thymoma express somatostatin receptors on the surface, detectable by nuclear medical methods. Octreoides have the capability to reduce tumor volume. In combination with corticosteroids the effect may be enhanced. Pasireotide (SOM230 LAR) a novel Octreotide, has a higher binding profile to human somatostatin receptor suptypes (sst), up to 30-40 times higher in sst1 + 5 and 5 times higher in sst3, only in sst 2the density is 2.5 times lower. Therefore SOM230LAR could offer a new treatment option for thymoma.

Methods: Inclusion criteria: Patients with diagnosed inoperable thymoma, defined as adherence to neighbored organs or suspicious to infiltrate neighbored organs or local metastasis and R0 resection can not be expected, >18years, WHO A – B3, Masaoka II – IVa and a positive nuclear medicine detection of somatostatin receptor at the tumor and with no exclusion criteria. The individual treatment phase will last up to 6 months. The role of prednisolon as an additional drug in the treatment of thymoma is not clearly understood, therefore we used the option to start the SOM230 treatment if possible without prednisolon. Prednisolon may be added to the therapeutic regime after 8 week if the therapeutic response is not adequate. Primary objective is tumor shrinkage defined as decrease in tumor volume of 20% as compared to baseline. Secondary objectives are resection status (R0,R1,R2), evaluation of morphological changes under treatment with SOM 230 and safety. It is a monocenter, single-arm, open label phase II trial.

Results: The aim is to treat 16 evaluable patients, till June 2013 8 patients started treatment, 3 patients completed study period regulary, 1 patient was withdrawn from the study because of good response so surgical removement of the tumor was possible, 3 patients completed the study regulary, 4 patients are still under treatment. Main side effects are gastrointestinal symptoms but always AE CTS are grade ≤2.

Conclusion: Pasireotide (SOM230) offers a good chance to reduce tumor volu´me in patients with primary inoperable thymoma or local recurrent thymoma.

Keyword: inoperable thymoma, Passireotide, SOM230

POSTER SESSION 2

Display Time: Saturday, September 7, 2013 – 09:00 – 15:30

P2.06: COMPARISON OF VIDEO-ASSISTED THORACOSCOPIC SURGERY AND MEDIAN STERNOTOMY APPROACHES FOR THYMIC TUMOR RESECTIONS AT A SINGLE INSTITUTION

Zhitao Gu[1], Teng Mao[2], Wenhu Chen[1], Wentao Fang[1]

[1]Department Of Thoracic Surgery, Shanghai Chest Hospital, Shanghai/CHINA, [2]Department Of Thoracic Surgery, Shanghai Chest Hospital, Shanghai/CHINA

Background: Surgical approaches for thymic tumors remain controversial. A variety of operative approaches have been introduced, each with its advantages and disadvantages. This study was designed to evaluate the feasibility and safety of video-assisted thoracoscopic surgery (VATS), and to compare the surgical results of VATS with the standard median sternotomy (MS) approach.This study was designed

to evaluate the feasibility and safety of video-assisted thoracoscopic surgery (VATS),
and to compare the surgical results of VATS with the standard median sternotomy (MS) approach.

Methods: Between April 2010 and April 2012, the data of 245 patients who underwent thymectomy for thymic tumors were prospectively collected. Among them, 93 patients with clinical stage I-II disease were retrospectively reviewed.

Results: Resection was planned for VATS in 49 cases, and for MS in 44 cases. During operation, there were 3 conversions to open surgery because of local invasion (conversion to thoracotomy in 1 patient, and sternotomy in 2). No transfusion was required in any patient. There was no significant difference in duration or amount of postoperative chest tube drainage between the two groups ($p>0.05$). Operative time, blood loss during operation, average length of the intensive care unit stay (LIS), and length of hospital stay (LHS) were significantly less in the VATS group than the MS group ($p <0.05$). There were no major perioperative complications or mortality. No recurrence was detected during a median follow-up of 27 months (range, 12–36 months).

Conclusion: VATS thymectomy for early-stage thymic tumors is safe and feasible. In comparison with standard median sternotomy, the VATS approach was associated with a shorter ICU stay and hospital stay. Prospective randomized multi-institutional trials with long-term follow-up are needed to compare the oncological outcomes.

Keywords: Video-assisted thoracoscopic surgery, median sternotomy, Thymectomy, Thymic tumors

POSTER SESSION 2

Display Time: Saturday, September 7, 2013 – 09:00 – 15:30

P2.07: INDOLEAMINE-2, 3-DIOXYGENASE (IDO) AS A POTENTIAL THERAPEUTIC TARGET IN THYMIC EPITHELIAL NEOPLASMS (TENS)

Vamsidhar Velcheti[1], Daniel Carvajal[2], Kurt Schalper[2], Daniel Morgensztern[1], Frank Detterbeck[3], David Rimm[2]

[1]Medical Oncology, Yale University, New Haven/UNITED STATES OF AMERICA, [2]Department Of Pathology, Yale University, New Haven/UNITED STATES OF AMERICA, [3]Department Of Surgery, Yale University, New Haven/CT/UNITED STATES OF AMERICA

Background: Thymic epithelial neoplasms (TENs) are rare mediastinal tumors with variable malignant potential and limited therapeutic options. Development of new treatment strategies for such rare diseases requires identification of actionable molecular targets. Indoleamine 2,3-dioxygenase (IDO) pathway is a mechanism for immune tolerance in tumors.IDO inhibitors are currently being evaluated in clinical trials with early signs of clinical activity. Herein, we validated an assay for IDO-1 measurement in formalin-fixed paraffin-embedded (FFPE) tissue and determine the expression of IDO-1 in TENs and the relationship with key clinico-pathological variables.

Methods: IDO-1 protein levels were measured in 31 TENs from Yale New Haven Hospital between1997-2012 represented in a tissue microarray (TMA). IDO-1 protein levels were determined in FFPE tissue samples using the mouse monoclonal antibody 1F8.2 (Millipore) and automated quantitative immunofluorescence (QIF). Antibody validation included immunoblot experiments and QIF analysis of human placenta (positive control) and HEK293 cells with inducible IDO-1 expression. TENs cases with IDO-1 levels above the median score were considered as high expressers. IDO-1 expression was correlated with clinico-pathological variables including age, gender, tumor size, development of myasthenia gravis, recurrence, WHO histotype and Masaoka stage. The limited number of cases and reduced events precluded a survival analysis.
Results: In immunoblot experiments, IDO-1 protein was detected as a single ~45 kDa band only in doxycycline-treated IDO-1 expressing HEK293 cells. Similarly, IDO-1 QIF levels were ~3 fold higher in doxycycline-treated HEK293 cells than in untreated parental cells. In human placental samples, IDO-1 staining was detected in trophoblastic cells. Reproducibility of IDO-1 measurement using QIF was high with a linear regression coefficient (R^2) of 0.8 in serial TMA sections. In TENs samples, IDO-1 signal allocated predominantly in the tumor compartment and showed perinuclear staining pattern. Elevated IDO-1 levels were detected in 16 TENs cases (52%). We find no correlations with WHO grade and Masaoka stage, however we are statistically underpowered to detect any associations with clinical characteristics or outcomes.

Conclusion: IDO-1 protein levels can be reproducibly measured using QIF in FFPE samples. Nearly half of TENs show elevated IDO-1 protein levels. IDO-1 is involved in the tumor-induced immune tolerance in patients with TENs and the therapeutic role of IDO-1 inhibitors in this patient population should be investigated.

Keyword: Thymic epithelial Neoplasms, IDO-1, Immune dysfunction

POSTER SESSION 2

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P2.08: THYMIC TUMORS: A RETROSPECTIVE REVIEW OF THE 10-YEAR OHSU KNIGHT CANCER INSTITUTE EXPERIENCE

Regan Duffy[1], Charles Thomas Jr[2], Brandon Tieu[3]

[1]Division Of Hematology And Medical Oncology, Oregon Health and Science University, Portland/UNITED STATES OF AMERICA, [2]Department Of Radiation Medicine, Oregon Health and Science University, Portland/UNITED STATES OF AMERICA, [3]Division Of Cardiothoracic Surgery, Oregon Health and Science University, Portland/OR/UNITED STATES OF AMERICA

Background: Study Design: Retrospective case-series of thymic malignancies treated at a NCI-Designated Cancer Center. **Objective:** To describe the clinical experience of patients (pts) with thymic tumors (TT) evaluated at Oregon Health & Science University (OHSU) over a ten-year period. **Summary of Background Data:** TT are rare and poorly understood tumors. TT are often asymptomatic until advanced stage, causing significant morbidity and treatment-related complications. Outcomes vary depending on the clinical stage and histologic subtype of TT. We reviewed all cases of TT treated at our institution over a 10 year period, including disease presentation and treatment response to inform potential future research in TT.

Methods: All pts, eighteen years old or older, with TT seen at OHSU between January 1, 2001 and June 30, 2011 were used in this analysis. Subjects were eligible for inclusion if they were seen during this period and diagnosed with any malignancy arising from the thymus gland, irrespective of histologic subtype. Using a case series design, data were collected in a retrospective manner. The medical record was systematically reviewed for pre-specified variables, including demographic data, tumor histology and stage, treatment history, and survival data.

Results: Twenty-eight pts were identified with a TT treated at the OHSU Knight Cancer Institute during the defined decade. The mean age at diagnosis was 55 yrs. 17 pts had thymoma (61%), 8 had thymic carcinoma (29%), and the remainder had other TT. Of the total cohort, the majority were male (61%), lifetime never smokers (61%), and Caucasian (96%). Nine pts had myasthenia gravis symptoms (32%). Symptoms at presentation were varied but many experienced chest discomfort/pain, dyspnea, cough, and/or fatigue. The majority were treated with surgery (93%) and radiation therapy (68%) with a mean dose of 54.2 Gy, while 54% received at least one type of chemotherapy (range 0-5). The median DFS was 110 months for thymoma, 30 months for thymic carcinoma, and 52.5 months for the other thymic tumors. The median OS has not been reached for the group of pts.

Conclusion: Using a retrospective design, we were able to capture the clinical course of pts with TT treated at our tertiary care institution over a ten-year period. Pts were treated with standard therapies, and survival (both disease-free and overall) is similar to historical reports. In addition to longer follow-up, these data suggest additional research should be undertaken to better characterize associated causes of TT. Future research should evaluate for tumor genetic abnormalities potentially amenable to targeted interventions which may improve DFS and OS, especially for aggressive variants of TT.

Keywords: thymic malignancies, Oregon Health and Science University, case-series

POSTER SESSION 2

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P2.09: EFFECTIVENESS OF COMBINATION OF CAPECITABINE AND GEMCITABINE IN PLATINUM-RESISTANT THYMIC EPITHELIAL TUMORS

Piera Federico, Carlo Buonerba, Pasquale Rescigno, Elide Matano, Lucia Nappi, Margaret Ottaviano, Filomena Calabrese, Vincenzo Damiano, Giuseppe Di Lorenzo, Giovannella Palmieri

University Federico II of Naples, Naples/ITALY

Background: Thymic epithelial tumors (TET) are a rare disease. Once loco-regional treatments have failed, platinum-based chemotherapy is employed to prolong survival and palliate symptoms. In November 2005, we started prospective multi-center trial to test capecitabine-gemcitabine in pretreated TET. Mature results are awaited. We here retrospectively review all patients with TET treated at our Institution with this schedule.

Methods: Patients with pathologically confirmed TET receiving at least one cycle of capecitabine-gemcitabine

were included in this analysis. Descriptive statistics and frequency counts were used to summarize characteristics of the study population. Median numbers were presented with interquartile ranges.

Results: Twenty-three patients were included in this single-center analysis. Six patients had a thymic carcinoma, while three, eight, two and four patients had a B1, B2, B2/B3 and B3 TET, respectively. Median age was 52 years (47-58).Eleven patients were female. Gemcitabine was delivered at the dose of 800-1,000 mg/m2 by 30-minute infusion on days 1 and 8 every 3 weeks along with oral capecitabine at the dose of 500-650 mg/m2 twice daily on days 1 to 14. Fourteen patients had an ECOG performance status of 0, one of 2, the remaining of 1. Seven patients had an IV a tumor, while the remaining had a IVb tumor. All patients, except for three for whom capecitabine-gemcitabine was the first line of therapy, had received a platinum-based regimen. Only one patient was primary refractory, while a complete response was obtained in 2 patients, a partial response in four patients, and the remaining had stable disease. Median PFS was 7 months (range, 4-9). Median survival was 12 months (6-20). Treatment was well tolerated. Twelve patients showed grade 3/4 toxicity, of whom two patients showed severe anemia, six severe neutropenia, four severe thrombocytopenia, two severe diarrhea and one severe fatigue.

Conclusion: In this retrospective analysis, gemcitabine-capecitabine was confirmed to have a high activity in TET. Mature results from the ongoing multicenter trial are awaited.

Keyword: capecitabine gemcitabine

POSTER SESSION 2

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P2.10: RECURRENCE RATE OF THYMIC EPITHELIAL TUMORS AFTER RADICAL SURGERY

Carlo Buonerba[1], Vincenzo Damiano[1], Lucia Nappi[1], Elide Matano[1], Ciro Candido[1], Pasquale Rescigno[1], Filomena Calabrese[1], Margaret Ottaviano[1], Piera Federico[1], Giuseppe Di Lorenzo[1], Mirella Marino[2], Michele Milella[2], Giovannella Palmieri[1]

[1]Center Of Rare Tumors Of Campania, University Federico II of Naples, Naples/ITALY, [2]Regina Elena Institute, Rome/ITALY

Background: According to the 2004 WHO classification, thymic epithelial tumors (TETs) comprise different histologies, including thymomas, thymic carcinoma, typical and atypical carcinoids. Histology classification of TETs has a dramatic impact on the prognosis and therapeutic strategy. We here review all TETs treated at two participating Institutions over the past 30 years

Methods: Eligible patients had a pathologically confirmed TET and had at least one access at either of the two participating Institutions. Relevant demographic and clinical data were retrieved. An exploratory analysis was conducted using a step-wise model in patients with completely resected tumors to seek for factors predictive of recurrence after radical surgery

Results: One hundred and ninety-one patients with TETs were included in this retrospective analysis. Eighty-eight were female, the remaining were male. Median age was 47 years (range 33-59). Sixty-three patients had myasthenia gravis. Five had a thymic neuroendrocrine tumor, 29 had a thymic carcinoma, while the remaining had a thymoma. Eighty-eight patients were alive at the time of analysis. Median overall survival was 5.25 years (range, 2.28-10.5). In the whole sample population, 113 patients had a completely resected tumor with clear pathological margins. In this sub-group of 113 patients (median age: 43, 34-53; 48 females, 65 males), 12 had a thymic carcinoma, with 41 patients presenting recurrent disease after radical surgery. At multivariate analysis, which included age, sex, adjuvant chemotherapy, adjuvant radiotherapy, maximum tumor diameter, presence of myasthenia gravis and stage, the only factor significantly predictive of recurrence was tumor histology (thymic carcinoma vs. other histologies, odds ratio: 3,57, 95% CI: 1,25 to 10,15; p = 0.01).

Conclusion: We showed that patients with thymic carcinomas are at increased risk of recurrence after radical surgery independently on adjuvant chemotherapy/radiotherapy treatment. Additional therapeutic options are required in the adjuvant setting of completely resected thymic carcinomas.

Keyword: thymic carcinoma, recurrence

POSTER SESSION 2

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P2.11: EVEROLIMUS PLUS SOMATOSTATIN ANALOGS IN THYMIC EPITHELIAL TUMORS

Giovannella Palmieri, Elide Matano, Lucia Nappi, Piera Federico, Pasquale Rescigno, Carlo Buonerba, Filomena Calabrese, Margaret Ottaviano, Giuseppe Di Lorenzo, Vincenzo Damiano

Referral Center of Rare Tumors of Campania, University Federico II of Naples, Naples, ITALY, Naples/ITALY

Background: Although anthracycline- and platinum-based chemotherapy is an active treatment for Thymic epithelial tumors (TETs) , novel systemic therapeutic options are especially needed for metastatic disease, which is virtually incurable. On the basis of the demonstrated activity of everolimus and octreotide in TETs, a phase II trial is currenlty undergoing at the Department of Molecular and Clinical Oncology and Endocrinology of University "Federico II of Naples" with the purpose to test combination of everolimus and octreotide LAR in TETs.
The mTOR complex is linked to downstream signaling of many soluble factors, including cytokines and growth factors, such as the epidermal growth factor and the insulin-like growth factor-1 (IGF-1). Both of these soluble factors may have a role in TETs biology. Although unsupported by in vitro experiences, these findings suggest that stimuli transduced by TK receptors, and consequently by mTOR, are important for thymoma growth, thus providing the biological rationale to support the use of everolimus in TETs. There is a strong rationale for combination therapy of everolimus with somatostatin analogs. In fact, the somatostatin receptors sst1 to sst5 activate different pathways that target the ERK1/2, PI3K and NOS pathways. The indirect effect of the sst receptors involves inhibition of the action of the receptor thyrosine kinases mentioned before, via tyrosine dephosphorylation of these receptors and/or their substrates and intracellular effectors. As a result, inhibition of cell proliferation, migration, invasion, and induction of apoptosis should be potentiated by combination therapy, and escape mechanism should be more difficult to develop. Importantly, we recently reported that everolimus was effective in two heavily pretreated patients with advanced TETs, with a progression-free survival longer than 1 year and minimal toxicity.

Methods: Adult patients with histologically confirmed TET that is metastatic and measurable according to RECIST criteria. All patients must give informed consent for their treatment.
The study is an open-label, nonrandomized, Italian single center, phase II study. The primary end point is response rate; secondary end points are safety, progression-free survival (PFS) and overall survival (OS). Treatment consists of oral everolimus (10 mg daily) and octreotide LAR (30 mg every four weeks). Treatment is continued until RECIST progression, unacceptable toxity or withdrawal of consent. Toxicity is assessed using the National Cancer Institute Common Toxicity Criteria (version 3.0).
For statistical considerations and study design, the primary end point is objective response. The RR is expected to be about 25%; a total of 35 assessable patients were needed for a two-stage design with a type I error (alpha) of 0.05 and a type II error (beta) of 0.2. In the first stage, 15 patients were to be enrolled. If >2 responses were observed, the design called for an additional 20 eligible patients to be accrued

Results: The study is ongoing.

Conclusion: Although clinical and biological evidence strongly suggest that a combination therapy of everolimus and somatostatin analogs might be highly effective in TET, our ongoing study is the first to be carried out to verify this hypothesis. Everolimus and octreotide LAR may display of high efficacy and low toxicity in TETs.

Keywords: everolimus, octreotide

POSTER SESSION 2

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P2.12: CONCURRENT CHEMORADIOTHERAPY FOLLOWED BY SURGICAL RESECTION FOR STAGE III THYMIC TUMORS - EARLY RESULT OF A PHASE II PROSPECTIVE CLINICAL TRIAL

Changlu Wang[1], Wentao Fang[2]

[1]Radiation Oncology, Shanghai Chest Hospital, Shanghai/CHINA, [2]Department Of Thoracic Surgery, Shanghai Chest Hospital, Shanghai/CHINA

Background: The optimal treatment for invasive stage Ⅲ thymic tumors remains controversial. The aim of this study is to assess the clinical efficiency of the trimodality approach.

Methods: From Nov 2008 to Dec 2012, totally 26 patients have been recruited in this trial. Of these patients there were 17 male and 9 female with mean age of 47.7(21-65). There

were 3 B2, 7 B3 and 16 carcinoma according to WHO classification. Patients were given radiation of intensity modulated radiotherapy at a dose of no more than 40Gy and a concurrent chemotherapy of docetaxol with cisplatin.(D: 65mg/m2, d1; P: 35mg/m2, d1-d2). Patients were re-evaluated after the induction treatment, surgical resection were given to those judged resectable and radical chemoradiotherapy (CRT)were given to those judged unresectable.

Results: Judging by CT images, the overall response rate of 26 patients were: complete response 3.8%; partial response 73.1% and no response 23.1%. Tumors of 14 patients were removed by surgery, while the other 12 patients received radical CRT. The 3 year overall survival and progression free survival of surgical group were both 78%, and the median progression free survival time is 13 months. However, the median PFS time was only 2.5 months for 3 patients with undifferentiated carcinoma, even the tumors responded very well to induction therapy.

Conclusion: Concurrent chemoradiotherapy is an effective and safe induction therapy for invasive stage Ⅲ thymic tumors. But it is not appropriate to apply this treatment to those patients with high grade thymic carcinomas, such as undifferentiated carcinoma.

Keywords: concurrent chemoradiotherapy, surgical resection, stage Ⅲ

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P2.13: A LARGE MICRORNA CLUSTER ON CHROMOSOME 19 IDENTIFIED BY RNA-SEQUENCING IS A TRANSCRIPTIONAL HALLMARK OF WHO TYPE A & AB THYMOMAS

Milan Radovich[1], Jeffrey Solzak[1], Madison Conces[2], Bradley Hancock[1], Rutuja Atale[1], Ryan Porter[2], Jin Zhu[3], Jarret Glasscock[3], Kenneth Kesler[1], Sunil Badve[4], Bryan Schneider[2], Patrick Loehrer[2]

[1]Surgery, Indiana University School of Medicine and Simon Cancer Center, Indianapolis/IN/UNITED STATES OF AMERICA, [2]Hematology/Oncology, Indiana University School of Medicine and Simon Cancer Center, Indianapolis/IN/UNITED STATES OF AMERICA, [3]Cofactor Genomics, LLC, St. Louis/MO/UNITED STATES OF AMERICA, [4]Pathology And Laboratory Medicine, Indiana University School of Medicine and Simon Cancer Center, Indianapolis/IN/UNITED STATES OF AMERICA

Background: Thymomas are one of the most rarely diagnosed malignancies. The challenge of histological subtyping of these tumors along with an inadequate understanding of the transcriptional biology is a hindrance to the development of prescriptive targeted therapies. To address this, we performed comprehensive next-generation RNA sequencing on a set of thymomas to examine the transcriptional landscape of this disease and to identify novel molecular hallmarks which can lead to more precise therapeutic interventions.

Methods: RNA was sequenced from 13 thymic malignancies and 3 normal tissues obtained from the Indiana University Simon Cancer Center using a Life Technologies SOLiD sequencer. The WHO subtypes of our samples were evaluated by a single pathologist (S.B.) blinded to the outcomes of the sequencing and include: (4) type A, (2) AB, (1) B2, (5) B3, (1) C, and (3) normal tissues. For gene expression, reads were mapped to the human genome (hg19) using the LifeScope software with outputs imported into Partek Genomics Suite for statistical analyses and subsequent pathway analyses was performed using IPA 9.0 (Ingenuity Systems). Validation of microRNA expression was performed using an additional set of 35 thymomas and a custom TaqMan Low Density Array (Life Technologies). For cell based studies, a thymoma AB cell line (IU-TAB1) was used and cells were treated with a panel of PI3K pathway inhibitors currently in clinical trial (BEZ235, BKM120, CAL-101, GDC-0980, GDC-0941, MK-2206, PF-04691502, XL-147). Cell viability was assessed using the Promega CellTiter-Flour assay, with statistical analysis using Prism Graphpad.

Results: Unsupervised hierarchical clustering of gene expression values revealed 100% concordance between gene expression clusters and WHO subtype. A subsequent unsupervised clustering of 705 precursor-microRNAs also showed substantial concordance between clusters and subtype. By analyzing the dendrograms, A & AB tumors were significantly different from other thymomas. Using differential expression analysis, a substantial differentiator was a large microRNA cluster on chr19q13.42 that is significantly over-expressed in all A & AB tumors and whose expression is virtually absent in the others thymomas. Over-expression of this microRNA cluster, which is normally silent in adult tissues, has been documented to result in hyperactivated PI3K/AKT Pathway. This was confirmed

using pathway analysis in the form of overexpression of PI3K-p110, PREX2, and down-regulation of FOXO in A & AB tumors. Treatment of IU-TAB1 cells, the only known thymoma AB cell line, with a panel of PI3K/AKT/mTOR inhibitors resulted in marked reduction of cell viability suggesting sensitivity to these agents.

Conclusion: Next-generation RNA sequencing showed concordance with the WHO thymoma histologic classification and support the notion that AB thymomas are a variant of type A thymomas. Furthermore, the expression of a large microRNA cluster on chr19q13.42 which affects the activity of PI3K pathway is altered only in type A & AB thymomas, suggesting the possible exploration of PI3K inhibitors in patients with these subtypes of tumor.

Keywords: thymoma, RNA-seq, microRNA, PI3K

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P2.14: SURGICAL TREATMENT OF THYMOMA

Sebastian Winiarski[1], Piotr Rudzinski[1], Renata Langfort[2], Małgorzata Szołkowska[2], Tadeusz Orlowski[1]

[1]Department Of Thoracic Surgery, National Research Institue of Tuberculosis and Lung Diseases, Warsaw/POLAND, [2]Department Of Pathology, National Research Institute of Tuberculosis and Lung Diseases, Warsaw/POLAND

Background: Thymoma is a neoplasm in which surgical resection is the treatment of choice.

Methods: A group of 116 patients with diagnosis of the thymoma which had surgical resection in the period of time between 2004 and 2012 was evaluated. 5-year survival rate was evaluated according to: - surgical techniques (sternotomy, thoracotomy, VATS thymectomy), - histopathological classifications and staging (WHO, Muller – Hermelink, Masaoka), - symptoms of myasthenia gravis, - postoperative treatment. 85 patients had sternotomy, 20 had thoracotomy and 9 had VATS thymectomy. 46 patients had symptoms of myasthenia gravis patients. There were 46 A/AB tumors, 27 B1 and 35 B2/B3 in WHO histopathological classification.The distribution of Masaoka staging system was 13 in I, 90 in II, 9 in III and 3 patients in stage IV.In Muller – Hermelink histologic classification 26 patients had thymoma corticale, 6 had thymoma medullarae, 5 had thymoma micronodulare, 39 had thymoma mixtum and 25 thymoma organoidum. After surgical resection 66 patients underwent radiation therapy and 19 patients were not able to get radiation therapy beacause of poor condition. Postoperative chemotherapy was administrated to 6 patients and 18 were not able to get chemotherapy.

Results: Five-year survival rate for patients who had sternotomy was 97.6%, thoracotomy - 89.4% and VATS thymectomy 77.8%. 5-year survival for patients with MG was 89% (41/46) wheras 87% - (61/70) forthose without MG. 5-year survival rate for patients with WHO histopathological diagnosis was: A/AB tumors - 90.9%, B1 – 96.3%, B2/B3 – 97.1%. Five-year survival rate for patients with Masaoka histopathological diagnosis was: I – 92.3%, II – 95.5%, III/IV – 90.9%. Five-year survival rate for patients with Muller – Hermelink histopathological diagnosis was: T.corticale – 96%, T.medullare – 83.3%, T.micronodulare – 100%, T.mixtum – 91.8%, T.organoidum – 100%. For patients who underwent radiation therapy 5-year survival was 98.5%, and those who were not able to get radiation because of poor condition was significantly worse (73.3%). The same result was observed in the group with postoperative chemotherapy 98% v. 71.8%. Overall 5-year survival rate for 116 patients with diagnosis of thymoma was 94.7%.

Conclusion: Five-year survival rate after surgical resection of thymoma is satisfying. The results are better when thymectomy is performed by sternotomy than VATS. The prognosis in B1-3 type thymoma is better then A/AB type and it is confirmed by Muller-Hermelink classification.

Keywords: five-year survival rate, thymoma, surgical treatment

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P2.15: FAVORABLE OUTCOME OF AGGRESSIVE SURGERY FOR THYMIC CARCINOMA: AN EXPERIENCE OF 23 CASES AT A SINGLE INSTITUTION

Tetsuzo Tagawa, Takahiro Nakajima, Takekazu Iwata, Hidemi Suzuki, Yuichi Sakairi, Junichi Morimoto, Takayoshi Yamamoto, Takamasa Yun, Yuki Sata, Toshiko Kamata, Terunaga Inage, Teruaki Mizobuchi, Shigetoshi Yoshida, Ichiro Yoshino

General Thoracic Surgery, Chiba University, Chiba/JAPAN

Background: Thymic carcinoma, a relatively rare entity, often presents locally advanced disease, or sometimes distant metastatic disease. The treatment strategy and

clinical prognostic factors have been yet to be fully elucidated.

Methods: Clinical charts of patients with thymic carcinoma who underwent surgery in Chiba University Hospital, Chiba, Japan, were retrospectively reviewed, and patient characteristics, surgical results, and survival were investigated.

Results: From 1991 to 2013, 23 patients (14 men, 9 women) underwent surgery at a mean age of 55 years. Preoperative histological diagnosis was obtained in 10 patients (43%). Preoperative Masaoka's stages were stage I in 6 patients (26%), II in 3 (13%), III in 9 (39%), IVa in 1 (4%) and IVb in 4 (17%). One patient had myasthenia gravis and another 1 patient had Multiple Endocrine Neoplasia type 1. Neoadjuvant chemotherapy was administered to 4 patients (17%) including 2 stage III and 2 stage IVb. Surgical resection was performed by median sternotomy in 19 patients (83%), anterolateral thoracotomy in 3 patients (13%), pasterolateral thoracotomy in 1 patient (4%) and thoracoscopic surgery in 1 patient (4%). Complete resection was achieved in 15 patients (65%) including 1 extrapleural penumonectomy. Ten patients (43%) underwent one or more combined resections; lung resection for 6 patients (26%), innominate vein resection for 6 patients (26%), pericardial resection for 5 patients (22%), chest wall resection for 3 patients (13%) and phrenic nerve resection for 2 patients (9%). Morbidity was experienced in 7 patients (30%), including 2 wound infections, 1 recurrent nerve palsy and 1 chylothorax. There were no perioperatie deaths. Eleven patients (48%) received post-operative therapy consisting of chemotherapy in 4 patients, radiotherapy in 5 and chemoradiotherapy in 2. WHO histologic types were determined by surgical patology; squamous cell carcinoma in 13 patients (57%), well differentiated neuroendocrine carcinoma in 4 (17%), sarcomatoid carcinoma in 1 (4%), papillary adenocarcinoma in 1 (4%), lymphoepithelioma like carcinoma in 1 (4%) and unknown in 3 (13%). The median follow-up time for the 19 surviving patients was 69 months (range, 1-219 months). The 5-year and 10-year overall survival rates were 76.2% and 63.5%, respectively. The 5-year survival rate of 15 patients who underwent complete resection was 88.9%. Of the 15 patients, 3 patients (20%) had recurrence including lung in 2 and supraclavicular lymph node in 1. Patients with preoperative Masaoka stage I-III showed significantly better survival than the patients with stage IV (p=0.029).

Conclusion: Even in the highly malignant disease, aggressive surgery provides a satisfactory outcome.

Keywords: thymic carcinoma, Surgery

POSTER SESSION 2

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P2.16: PATTERNS AND PREDICTORS OF RECURRENCE AFTER RADICAL RESECTION OF THYMOMA

Cai Xu, Qin Feng, Cheng Fan, Yi Zhai, Yi Chen, Hong Zhang, Ze Xiao, Zong Zhou, Jun Liang, Zhou Hui, Dong Chen, Jie He, Lu Wang

Radiation Oncology Department, Cancer Institute & Cancer Hospital Chinese Academy of Medical Science, Peking Union Medical College, Beijing/CHINA

Background: Even after complete resection, recurrence of thymoma is not uncommon, but the recurrent patterns remain controversial. This study sought to define the patterns and predictors of relapse after complete resection of thymoma.

Methods: A single-institution retrospective study was performed of 331 patients who underwent radical resection of thymoma from 1991 through 2012.

Results: After a median follow-up of 59 months (range, 3-256), the recurrence rates was 6.9% (23/331). Overall 5- and 10-year survival rates were 92.3% and 84.9%. Cancer specific survival rates were 95% and 89.4% at 5 and 10 years, respectively. Recurrence-free survival rates were 93.6% and 87.2% at 5 and 10 years, respectively. Among the 23 patients, relapses were found in the following sites: pleura (thirteen cases), tumor bed (six), lung (six), chest wall (four), lymph node metastasis (two) , abdominal node metastasis (one),liver (one), pleural effusion (three), and over-lapped recurrence (nine). According to the definition of the International Thymic Malignancy Interest Group, 10 (43.5%) patients had local recurrence, 15 (65.2%) had regional recurrence, 10 (43.5%) had distant recurrence (six lung, one liver, one abdominal node metastasis, and two lymph node metastasis), and 9 (39.1%) had over-lapped recurrence. The difference in survival after recurrence between lung and regional relapse was statistically significant (p=0.027), but it was insignificant between lung and distant relapse (p=0.808). Recurrence rates correlated with the initial Masaoka stage: I, 1.0% (2/196); II, 9.7% (9/93); III, 24.2% (8/33); IVa, 42.9% (3/7); and IVb, 100%

(1/1). The difference in recurrence between Masaoka stage I and II was stastically significant (p=0.000). And they also correlated with World Health Organization tumor type: A and AB, 3.2% (5/154); B1, 6% (4/67); B2, 6% (3/50); and B3, 22.7% (10/44). Tumor size demonstrated a step-up of recurrence at 8 cm (<8 cm, 62.8%; ≥8 cm, 37.2%; P=0.007). In multivariate analysis, Masaoka stage (p=0.005), tumor size (p=0.033), and WHO histology (p=0.046) were predictive of recurrence.

Conclusion: Pleura are the most common recurrent sites. Recurrence in the lung had poorer survival than the regional relapse, it should be included in the distant recurrence. Regional recurrence is the most common pattern of relapse, but local and distant recurrences are not infrequently observed. Advanced Masaoka stage, larger tumor size, and Type B3 were risk factors of recurrence.

Keyword: Thymoma, Recurrence, Patterns of Relapse, Predictors.

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P2.17: EXPERIENCE OF NEOADJUVANT THERAPY BY SURGERY FOR PATIENTS WITH ADVANCED STAGE THYMOMA

Mi Kyung Bae, Seong Yong Park, Chang Young Lee, Jin Gu Lee, Dae Joon Kim, Hyo Chae Paik, Kyung Young Chung

Thoracic And Cardiovascular Surgery, Yonsei University College of Medicine, Seoul/KOREA

Background: The treatment strategy for patients with advanced stage thymic epithelial tumor is still controversial. We reviewed our experience of induction therapy followed by surgery for patients with advanced stage thymic epithelial tumor.

Methods: From 2005 to 2013, twenty patients with histologically confirmed thymic epithelial tumor were treated with preoperative chemotherapy or chemoradiation followed by surgery. We reviewed these patients retrospectively

Results: Three patients received preoperative chemoradiation and 17 patients received chemotherapy (11 PAC protocol, 5 ADOC protocol, 4 other). Complete resection was achieved in 13 patients (65%). There were no surgery related deaths. Pathologic complete response was achieved in one patient. 8 patients had thymic carcinoma (WHO histologic type C) and 12 patients had thymoma (1 type B1, 3 type B2, 6 type B2+B3, 2 type B3). With a median follow-up of 31 months (range, 2 to 95 months), the overall 5-year survival was 87.5% and 5-year freedom from recurrence was 13.7%. In patients with type C thymoma, overall 5-year survival was 75.0 %; however, 5-year freedom from recurrence was 0.0 %. In patients with non-type C thymoma, there were no mortality during follow-up period and 5-year freedom from recurrence was 40.0%.

Conclusion: Neoadjuvant treatment followed by surgery might be considered in selected patients with non-type C thymoma.

Keywords: Multimodality treatment, thymoma, neoadjuvant therapy

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P2.18: ANALYSIS OF TREATMENT AND PROGNOSIS OF 150 THYMIC CARCINOMA PATIENTS

Yirui Zhai[1], Qin Feng[1], Wei Ji[1], Cheng Fan[1], Zhou Hui[1], Jun Liang[1], Zong Zhou[1], Yousheng Mao[2], Liqiang Zhou[3], Lu Wang[1]

[1]Department Of Radiotherapy, Cancer Hospital , Chinese Academy of Medical Sciences, Peking/CHINA, [2]Department Of Thoracic Sugery, Cancer Hospital,Chinese Academy of Medical Sciences, Peking/CHINA, [3]Department Of Medical Oncology, Cancer Hospital,Chinese Academy of Medical Sciences, Peking/CHINA

Background: Thymic carcinomas is characterized by more extensive local invasion, more frequent meatastasis and worse prognosis, compared with other subtypes of thymic tumor . The low incidence has precluded the development of randomized clinical trials. To investigate the clinical characteristics, treatment method a, prognosis and treatment induced toxicities of thymic carcinoma, we designed the retrospective research.

Methods: From June 1962 to December 2009, 150 patients diagnosed as thymic carcinoma histologically or cytologically were treated in Cancer Hospital , Chinese Academy of Medical Sciences. The median age was 52 years old (ranged from 13 to 79). Ninety-five were male and 55 were female. Patients with Masaoka's stage I, II, III, IV disease took 2.0%, 6.0%, 44.7% and 47.3%, respectively . Radical resection

was pursued in 33 patients (22.0 %). One hundred and thirty–five patients (90.0 %) received radiotherapy with median dose of 60 Gy, using conventional fractionations. Chemotherapy was delivered in 75 patients (50.0 %) with median of 4 cycles. Local control and overall survival rate was calculated by Kaplan-Meier method.

Results: The median follow up time was 12.5 years. Five-year and 10-year local control were 81.5% and 53.8%, respectively. The median survival time was 44.7 months. Five-year and 10-year overall survival rate was 40.6 % and 18.8%, respectively. The 5 year survival rate was 42.7%, 27.8 % and 17.1% for patients with disease of stage III, IVA and IVB, respectively. Seven of the 135 patients who received radiotherapy suffered radiation induced pneumonitis. All of the 7 patients received 2D conventional radiotherapy. Earlier stage and total resection were associated with better survival in both univariate analysis and Cox regression.

Conclusion: The prognosis of thymic carcinoma is poor. Masaoka staging, histology and type of tumor resection are significant prognosis factors. The complication of radiotherapy ,especially of the 3D conformal radiation was tolerable.

Keywords: thymic carcinoma, radiotherapy

POSTER SESSION 2

Display Time: Saturday, September 7, 2013 – 09:00 – 15:30

P2.19: OUTCOMES AND PREDICTORS OF RECURRENCE IN PATIENTS TREATED WITH RISK-ADAPTED, POST-OPERATIVE RADIOTHERAPY (RT) FOR THYMOMA - A SINGLE INSTITUTION, 30 YEAR RETROSPECTIVE STUDY

Nafisha Lalani[1], Najib Safieddine[2], David Hwang[3], Shaf Keshavjee[2], Andrea Bezjak[1], Anthony Brade[1]

[1]Department Of Radiation Oncology, Princess Margaret Hospital, Toronto/CANADA, [2]Surgery, University of Toronto, Toronto/CANADA, [3]Pathology, University of Toronto, Toronto/CANADA

Background: Thymoma is a rare epithelial cell tumour of the thymus, with an incidence of 0.15 per 100 000 persons[1]. Thymic carcinomas comprise a distinct subset and have a greater propensity for capsular invasion and distant metastases when compared to thymomas. Resection is the standard of care for localized disease but local recurrence is generally incurable, thus post-operative RT is often employed for high risk cases. The optimal dose of RT has not been established, nor whether lower doses can be utilized in a risk-adapted fashion for cases where RT is recommended but the risk of recurrence is felt to be at the lower end of the spectrum. Use of lower dose RT may help reduce the chances of late RT toxicity. Our institution employs such a risk adapted strategy and we present here our long term results.

Methods: Princess Margaret Cancer Center radiation and surgical oncology databases were queried from 1983-2012. Retrospective analyses using electronic patient records and Mosaiq radiotherapy database were performed to assess demographic data, clinical presentation and treatment. Descriptive statistics were used to report demographic data. Time to event analyses and correlation of outcomes with demographic and treatment variables are planned.

Results: Details on 104 patients treated with post-operative radiotherapy from 1983-2012 were available. The mean age was 52, range 29-73. Of patients assessed, 55/104 were male. Masaoka-Koga stage was assessed: 6% of patients were stage I, 31% IIA, 21% IIB, 27% III, 10% IV and 6% unknown. The most common WHO grade was B2 (37%) followed by B1 (16%). Complete surgical resection (R0) was obtained in 72% patients, R1 in 21%, R2 in 2% and 5% unknown. Radiotherapy doses ranged from 40 Gy – 66 Gy delivered in daily 2 Gy fractions; 57% patients were deemed low risk (typically R0 resection and WHO grade B2 or lower) and received 40Gy while 36% received between 45-66Gy. Neoadjuvant or adjuvant chemotherapy was delivered to 13% of all patients. The mean follow up period was 9.4 years, range 0.5-25.5 years, during which 22% patients experienced relapse. Of these, 43% experienced regional recurrence, defined as an intrathoracic relapse in an area not-contiguous with the thymic bed or original tumour; 39% local (intrathoracic relapse contiguous with original disease or thymic bed), and 17% distant recurrence defined as extrathoracic or intraparenchymal pulmonary nodules. For patients that experienced relapse, the median time to relapse was 8.7 years (range 1.3-18.3 years). Of the 59 patients who received 40 Gy/20 fractions, 8 developed local relapse (13.5%). Overall survival and multivariable analyses will be reported as will assessment of long term toxicities.

Conclusion: Risk-adapted RT prescription for patients with resected thymoma appears efficacious, and may result in an improved therapeutic ratio for these patients. Long-term,

randomized controlled trials are required to further identify patients that are best suited to this approach.

Keywords: radiotherapy, thymic carcinoma, thymoma