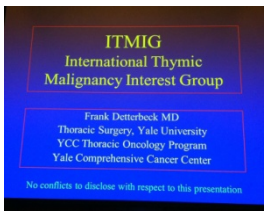
Report of 3rd International Thymic Malignancy Interest Group (ITMIG) Annual Meeting Fukuoka, Japan

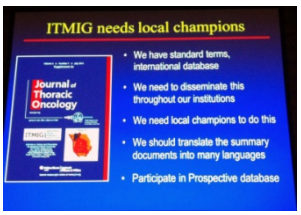
In a superlative venue, the Hilton Sea Hawk Hotel in Fukuoka, Japan, the 3rd ITMIG Annual Meeting took place in conjunction with the 5th APLCC Congress, between November 25 and November 26, 2012. More than 100 physicians (Oncologists, Pathologists, Radiotherapists and Thoracic Surgeons) attended this ITMIG Meeting, which has been superbly organized by Meinoshin Okumura and Kazuya Kondo.

Dr. Meinoshin Okumura and the Hilton Sea Hawk Hotel in Fukuoka

Scientific works were planned as follows: in the first Meeting day, updates, symposiums, lectures and Pro-Con debates were scheduled, in the second, oral abstract presentations and poster discussions.

On Sunday, November 25, at the end of the ITMIG Business Meeting chaired by Frank Detterbeck (see the below pictures) ,

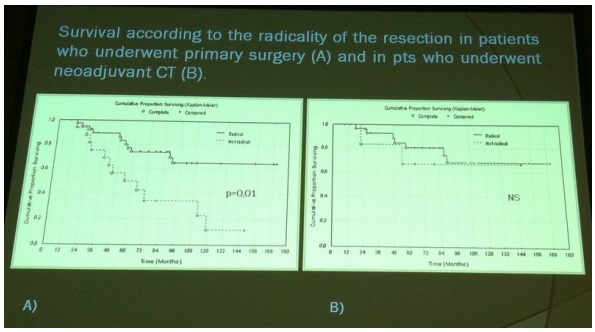


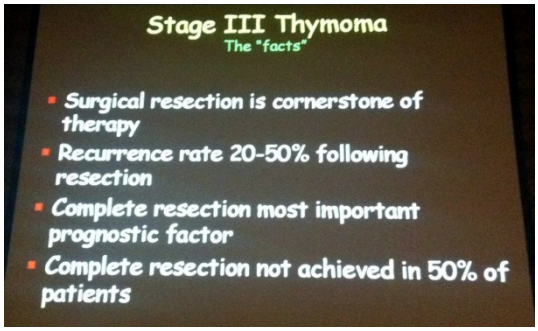


Nicolas Girard (Lyon, France) focused his lecture on the molecular characterization of Thymoma and Thymic Carcinoma, which recently led to identify potentially druggable targets: EGF receptors (EGFR), KIT/mast/stem-cell growth factor receptor and the IGF-1-receptor pathways. Futher efforts should be oriented to evaluate the possible effects of neoangiogenesis, as activation of the Vascular Endothelial Growth Factor (VEGF) receptor pathway, which has been correlated with a more aggressive tumor biological behavior.

A “Pro-and Con” debate concerning Stage III Thymoma management, followed. Marco Lucchi from Pisa (Italy), who has got a personal large experience on multimodal management of advanced Stage Thymomas,

showed the advantage of an induction chemotherapy when the tumor demonstrate to be locally invasive at the time of their presentation.





Lucchi observed how patients receiving induction platinum-based chemotherapy had a greater chance to achieve a radical tumor resection (R0), and survived longer than those in whom surgery was upfront offered.

Motoki Yano (Nagoya, Japan) highlighted the importance of a R0 resection of both Thymoma and the involved organs. Radiotherapy can be offered as adjuvant local treatment whenever an incomplete resection is done. According to Yano, the efficacy of adjuvant CT-RT is controversial, and should be assessed by further randomized controlled clinical trials. Surgery or chemotherapy might be offered to patients who develop tumor recurrence in form of pleural spreads.

Heather Wakelee (Stanford, USA) treated in her Lecture the rationale for a primary chemotherapy in Thymoma and Thymic Carcinoma patients. According to ITMIG standards, she remarked, Primary Chemotherapy (PC) is "a chemotherapy delivered as first treatment in case of locally advanced non-metastatic thymic tumor (Masaoka-Koga Stage III or IVA) which main objective is to make feasible subsequent R0 resection". Wakelee observed how presently there is no one standard approach to locally invasive thymic neoplasms, and also chemotherapic regimens might differ from Institutions. The most commonly used are platinum-based regimens, consisting of a combination of cisplatin with anthracycline, with other agents such as cyclophosphamide, vincristine, isophamide and etoposide. ADOC (cisplatin, doxorubicin, vincristine, and cyclophosphamide) and PAC (cisplatin, doxorubicin, and cyclophosphamide) are the 2 mainly proposed schedules. The possible use of corticosteroids (CS) in association with drugs is still controversial, but many Authors believe that CS may reduce tumor size due to its lympholitic activity in those patients in which the thymic tumor shows lymphocytic predominant characteristics. Wakelee reminded that there is an ongoing phase II clinical trial of cetuximab with cisplatin, doxorubicin and cyclophosphamide in patients with locally invasive Thymoma in the USA (NCT01025089), and she also wished that future trials will follow.

Robert Korst (New Jersey, USA) then discussed about the rationale to add radiotherapy to induction CT for Stage III Thymomas. He highlighted how thymic epithelial neoplasms are radiosensitive tumors and he also mentioned that older clinical small series of advanced Thymomas definitively treated with external beam radiotherapy (40-60 Gy in total) demonstrated radiological partial and complete response rates ranging from 50% to about 100%. Some recent reports show how a preoperative low radiation dose (18-20 Gy) achieved a significant reduction in tumor size (measured by CT scan), enhancing tumor resectability in Stage III Thymomas. By observing that clinical trials for chemoradiotherapy in an induction setting for esophageal and lung carcinomas are presently available, proving their effectiveness in enhancing tumor resectability rates, and given that Thymoma patients are usually younger than lung/esophageal cancer ones

and that thymoma recurrences usually develop distant from the postoperative radiation field, Korst concluded that the rationale for a preoperative chemo-radiotherapy actually does exist. A phase II multi-institutional clinical trial evaluating the efficacy of an induction chemoradiotherapy (cisplatin + etoposide concurrent with 40-45 Gy RT) for patients with high risk unresectable Thymoma confined to the mediastinum is, in fact ongoing; initial results from this trial are expected to be available in 2013.

A mini-symposium concerning Thymic Carcinoma (TC) biological characterization followed. In the first lecture Philipp Strobel (Gottingen, Germany) pointed out the recent advances in TC classification. If Thymoma is a rare disease, TC is an heterogeneous group of tumor 10 times rarer than Thymoma. It includes Squamous Cell, Clear Cell, Mucoepidermoid and Neuroendocrine Carcinomas. Histology is not different from similar tumors in other organs, although the clinical background (e.g.: the possible and frequent association of Neuroendocrine Tumor and MEN-1 syndrome) may differ. Some "grey zones" between B3 Thymoma and Squamous Cell carcinoma presently do exist, concerning tumor histology and biology, even if immunohistochemical and molecular appearances (e.g.: FOXN1 receptor expression) may help to characterize TC.

Very exhaustive was Meinoshin Okumura's lecture by concerning the clinical and biological differences between Thymomas and TCs. On microscopic evaluation, Thymomas maintain the organotypical appearance, suggesting the thymic origin, whilst TCs do not. Thymomas (especially WHO type B1) possess $CD4^+$ $CD8^+$ double positive T cells, usually expressed in the normal thymic cortex, while TCs do not. These observation might explain why Thymomas are frequently associated with autoimmune disorders, and TCs are not. TCs frequently present in advanced Stage at the time of diagnosis, oftentimes with lymph nodal involvement; due to their more aggressive biology, PET scan is generally positive in TCs, and high SUV values (> 6) are commonly observed. Tumor death occur even after 10 years after resection in Thymomas, while after 5-8 years in TCs.

Concerning the topic of TCs oncological treatment, Ritsuko Komaki (Houston, USA) updated the role of radiotherapy (RT). RT has an important role either as postoperative treatment, to reduce the risk of mediastinal recurrences, or as a part of multimodal treatment for those patients who cannot undergo surgery, for locally invasive tumors or for those who remain unresectable after induction treatment. After R0 resection, postoperative RT should be offered in case of increased risk to develop recurrences, with a minimum accepted 50 Gy in 5 weeks. In R1-R2 tumors (R1: microscopic positive margins; R2: macroscopic positive margins) ITMIG guidelines require delivery of 54-64 Gy in standard fractions of 1.8- 2.0 Gy. Since TC is considered a chemosensitive tumor, a combination of CT and RT is considered more effective to control incompletely resected tumors. Komaki also recommended the use of advanced radiation therapy technologies, such as IMRT, proton beam, 4D imaging, reducing the risk of radiation adverse effects on heart and lung.

The lack of randomized clinical trials, due to TC rarity, is translated on the absence of dedicated CT regimens, as reported by Kiyotaka Yoh (Chiba, Japan). The common oncological practice includes platinum and anthracyclines schedules, similar to those used for Thymoma. First-line platinum based CT has been reported to achieve 22-75% response rates, even if in small series of patients. Imatinib has recently been proposed in prospective trials in advanced TCs, but results are still lacking.

A "Pro and Con" debate concerning the role of robotic surgery in Thymomas, followed.

Jens Rueckert (Berlin, Germany) stated how the minimally-invasive thoracic surgery, after some doubts and criticisms has been approved and widely accepted in the Thoracic Surgeons community.

Nowadays, the robot-assisted thoracoscopic surgery (RATS) has infiltrated also the thoracic field, and the great advantage of robotic surgery is evident in the accurate tissue manipulation by articulated robotic forceps (which offer 7 degrees of freedom), under three-dimensional vision, in a narrow space like the mediastinum as Hiroshige Nakamura (Yonago, Japan) observed. Therefore, an increased dexterity in specific complex procedures (e.g.: to dissect lymph-nodes along specific nerves, without injury to them, as reported by Dae Joon Kim, Seoul, Korea) is enhanced by the robot. The indications for a RATS approach to the mediastinal diseases are: surgical treatment of Myasthenia Gravis (MG), Thymoma, Thymic Cysts and Teratoma resection. An impressive reduction of intraoperative bleeding using RATS, was pointed out by Nakamura, along with low complication rates in his series (1 chylothorax, only, which occurred after an invasive Thymoma resection). As Rueckert observed, RATS approach may enhance the radical resection of all visible and potential ectopic thymic tissue, which is the basis for a correct surgical treatment of MG. A surgical exploration of the space between thyroid gland and diaphragm and between both phrenic nerves, respectively is made easier by the robotic technology, especially when these margins have to be extended to the aorto-pulmonary window or to the aorto-caval groove.

Marlies Keijzers (Maastricht, The Netherlands), one of the *"ITMIG Travel Awards for outside Asia"* winner, reporting the Maastricht University

Dr. Marlies Keijzers (Maastricht, The Netherlands) *ITMIG Travel Award for outside Asia"* winner

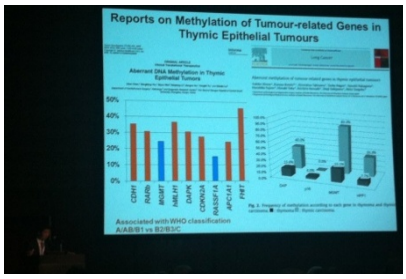
Medical center experience on 37 consecutive Thymoma patients operated between 2004 and 2012 concluded that RATS approach may be feasible also in case of advanced stage Thymoma, to visualize areas of possible tumor invasion, facilitating a subsequent thoracotomy/sternotomy.

To close this symposium, Kim Dae Joon discussed RATS disadvantages for thymic surgery. Three were his questions: 1) is RATS even necessary for thymoma resection?; 2) can it provide a better surgical outcome than VATS thymectomy?; 3) can the current health system accept RATS as standard treatment for Thymoma? According to Kim, RATS approach was disappointing since Stages I-II Thymoma can be easily resected by VATS, whilst Stages III-IVA need an open approach. Furthermore, in RATS surgery there is the possibility of disruption or tumor spillage during manipulation, since robotic system cannot provide a tactile

feedback; so a minimum 10-years survival is needed to assess the oncological outcome of patients receiving such operation. Furthermore, living in an historical period of economic crisis, a health system cannot ethically pay more for a procedure which is not widely recognized to be more effective than others.

Two biological lectures followed: the first concerning the T cell repertoire formation in Thymus by Yousuke Takahama (Tokushima, Japan), who explained the positive and negative selection phenomenon in the light of the most recent development of thymic biology.

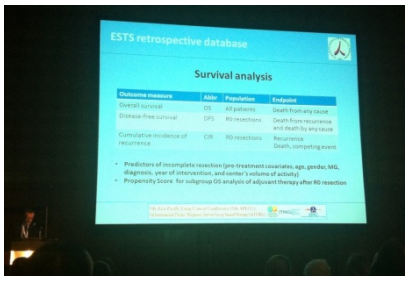
The second concerning the Epigenetic alteration in tumor, pre-tumorous stages and their origin.



Prof. T. Ushijima during his talk

Toshikazu Ushijima (Tokyo, Japan) itemized that the epigenetic alterations consist of DNA methylation alterations and histone modifications. Using two different biological situations as example (DNA methylation in normal appearing gastric mucosa of people with *Helicobacter pylori* infection with the risk to develop gastric cancer and the role of chronic inflammation in inducing histone modifications; DNA methylation effects on Neuroblastoma outcome) Prof. Ushijima indicated that epigenetic alterations are now on of the central players in translational cancer research.

Enrico Ruffini (Torino, Italy, ITMIG Secretary), Kazuya Kondo (Tokushima, Japan) and James Huang (New York, USA, ITMIG Treasurer) outlined the "state of the art" of ITMIG database around the world.

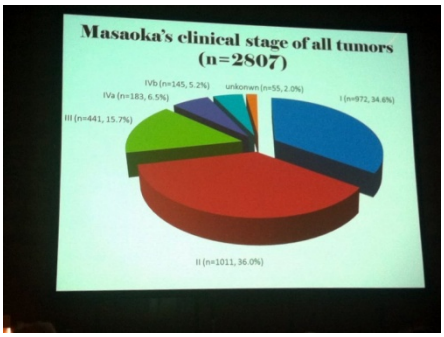


Dr. E. Ruffini during his talk

Data concerning ITMIG database are available in the December 2012 ITMIG Newsletter, by Frank Detterbeck and Pam Bruce.

Enrico Ruffini reported the results of the ESTS (European Society of Thoracic Surgeons) Thymic retrospective database, who collected an overall of 2151 patients covering a 20-year period, from 1990 to 2010. In particular there were 1904 Thymomas, 204 Thymic Carcinomas and 43 Thymic Neuroendocrine Tumors. Outcome measures were employed according to ITMIG's recommendations (J.Thorac. Oncol. 2011;6:S1691-S1697) and results will be available in the next year.

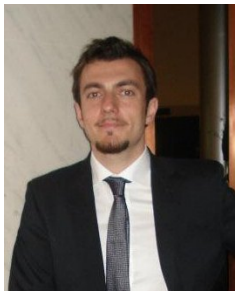
Kazuya Kondo reported the results of the JART (the Japanese Association for Research of the Thymus) database through which an overall of more than 2800 Thymic Epithelial Neoplasms were collected in Japan.



Graphs reported were very impressive and data will probably be the matters of future scientific publications as previously occurred with a similar database through which 1320 patients with Thymic Epithelial Neoplasms were collected in Japan by JACS (the Japanese Association of Chest Surgery) in 2000.

During the second Meeting day, oral and poster presentations were done.

Filippo Lococo (Rome, Italy) was the winner of the prestigious "*Masaoka Award*" for best oral abstract with his presentation: "Single Center results of redo-operation for recurrent Thymoma"(IT-005).



Dr. Filippo Lococo, "*Masaoka Award*" winner

The Catholic University in Rome (Italy) has got a large experience in the treatment of Thymoma, even in advanced stages and also through a multimodal setting. Out of 320 patients who underwent a tumor radical resection between 1970 and 2008, at the above mentioned Institution, 44 relapsed. Of these 30 were deemed suitable for a redo-intervention, whilst the others received radio-chemotherapy, only. Twenty-two experienced a recurrence after radical resection. Patients receiving surgery survived longer than the others, and incomplete relapse resection was associated with a poor survival.

Following are indicated the other winners of ITMIG Grants for Resident, Fellows and Trainees.

Rosai Award (for best poster):

- Yukari Miki (Okayama, Japan): *"The immunohistochemical studies on the Type AB Thymoma"* (ITP-001)

Neibauer Award (best thymic carcinoma paper):

- Wentao Fang (Shangai, China): *"Primary Thymic Carcinoid Tumors: clinicopathologic study in 36 patients"* (IT-014)

Travel Awards for outside Asia:

- Ronny Ben Avi (Ramat Gan, Israel): *"Re-resection following resection and heated pleural chemoperfusion for Thymoma with pleural spread: evaluating the challenge"* (IT-006)
- Stijn R.G. Heyman (Antwerp, Belgium): *"Short and long-term follow-up of patients with Thymoma after surgical resection: a single Institution experience"* (ITP-033)

Travel Awards for Japan and South Korea:

- Atsushi Hayashi (Okayama, Japan): *"The immunohistochemical distinction of Thymic Carcinoma from Lung Squamous Cell Carcinoma and Type B3 Thymoma"* (ITP-002)
- Hyo Yeong Ahn (Pusan, Korea): *"Clinical outcomes of Video-Assisted Thoracoscopic bilateral extended thymectomy for Myasthenia Gravis"* (ITP-037).

Finally, let me thank Frank Detterbeck and Pam Bruce for their fantastic ITMIG organization, and Meinoshin Okumura and Kazuya Kondo for their remarkable job and effectiveness in organizing this Meeting in Fukuoka, and also for the dinner in a typical Japanese restaurant.

A special thank you to Pier Luigi Filosso for writing this excellent meeting summary!