Whole room indirect calorimeter: a tool to accurately investigate the role of energy expenditure and substrate oxidation in endocrine and metabolic disorders

Prof. Ferruccio Santini (Principal Investigator)

Prof. Paolo Vitti, Chief Endocrine Unit. Co-investigator

Prof. Alberto Landi (Department of Information Engineering, University of Pisa)

Dr. Paolo Piaggi NIDDK National Institutes of Health (NIH), Phoenix, AZ, USA

Collaborations:

Dr. Clifton Bogardus and **Dr. Jonathan Krakoff,** NIDDK National Institutes of Health (NIH), Phoenix, AZ, USA

Financing: "Ricerca Finalizzata" Ministry of Health 2010

Metabolic chamber: potential use

Assessing the effect on energy expenditure of:

- gene mutations affecting fuel homeostasis pathways
- circulating hormones
- bariatric surgery
- locomotor activity under different circumstances




Potential Involvement of Industry

1. Testing possible effects of novel drugs or nutracetic compounds on energy expenditure

2. Developing sensors to be used inside the chamber in order to monitor physical activity in a sensitive way

3. Developing practical and precise systems for calories counting to be coupled with the chamber

Plant Biofortification: a new tool for fighting micronutrient malnutrition

- **Iodine deficiency is the result of insufficient intake of dietary iodine and as a consequence causes multiple adverse effects.**
- **It has been found that the most effective way to control iodine deficiency is through the universal salt iodization.**

However, salt iodization alone may not be sufficient to assure adequate iodine nutrition, in view of the recommendation of reducing salt intake to prevent CV disease

Prof. Massimo Tonacchera, Dr. Agretti P., Dr. Di Cosmo C., Dr. Dimida A., Dr De Marco G., Dr Ferrarini E. (Department of Clinical and Experimental Medicine, Univerity of Pisa).

Iodine biofortification of Plants: an "alternative" to iodized salt?

A food industry has funded a study to test the efficacy of a **new model of iodine prophylaxis in a group of healthy volunteers through the intake of vegetables (potatoes, cherry tomatoes, carrots, and green salad) fortified with iodine**.

Results: **biofortification of vegetables with iodine provides a mild but significant increase in urinary iodine concentration** and, together with the habitual use of iodized salt, may contribute to improve the iodine nutritional status of the population without risks of iodine excess*.

Biofortification of crops is a valuable industrial program that has its strength in delivering in a simple, natural, healthy way physiological amounts of iodine.



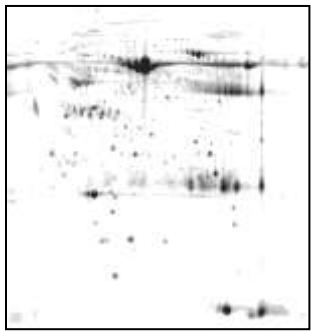
*Iodine fortification of vegetables improves human iodine nutrition: in vivo evidence for a new model of iodine prophylaxis. Tonacchera, et al J Clin Endocrin Metab. March 12, 2013

PROTEOMICS

Research in collaboration with Prof. Lucacchini (*Department of Pharmacy-University of Pisa*)

THYROID

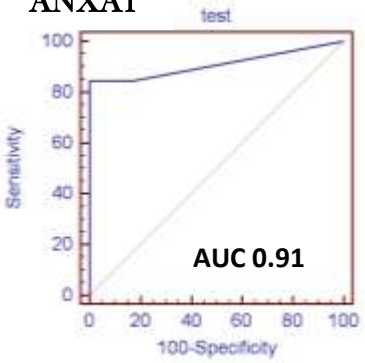
Ricerca Finalizzata Regione Toscana-Progetto Salute



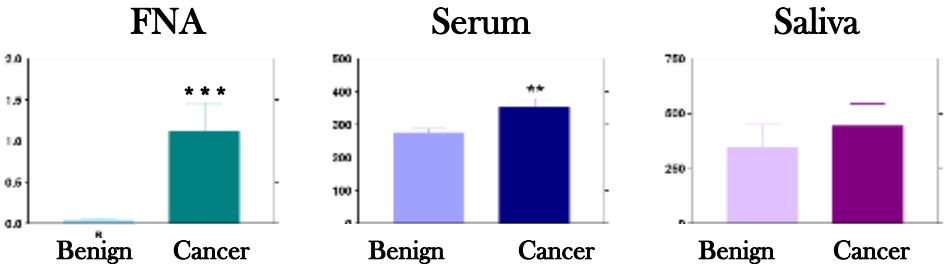
Proteomics analysis of fine-needle aspiration fluids to identify a pattern of potential biomarkers useful to distinguish benign nodules from malignant. Two-dimensional electrophoresis, coupled to mass-spectrometry, found 24 proteins able to differentiate benign from malignant.

The different expression of **annexinA1 (ANXA1), lactate dehydrogenase, moesin, cornulin, malate dehydrogenase and enolase** was confirmed by ELISA assay in FNA.

ANXA1



Tuning of an ELISA kit able to detect ANXA1 in FNA, serum and saliva



POTENTIAL APPLICATION TO THE DIFFERENTIAL DIAGNOSIS OF FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE

Mini-invasive treatment of benign thyroid nodules

Laser ablation is a new treatment for benign thyroid nodules causing pressure symptoms or cosmetic issues in patients who decline surgery or are at surgical risk, that offers the advantage of reducing the size of the thyroid nodule

Preliminary study:

IALT study: Italian Multicentric Laser Ablation treatment study 2010-2013. (n. 2527/ 2007) – Funding Esaote SPA, El.En SPA

Study Group 101 treated patients; 100 controls 36 months after laser ablation:

Results: Nodular volume reduction (*DVN* - 56,02% ± 4.49; p=0.0001).
Reduction >50%: 70% of cases.

Firenze 9 -10 LUGLIO, 2014

TRAP Project

New Integrated Technology for **percutaneous laser ablation therapy** guided by ultrasound imaging. Funding by "Progetti Finalizzati Regione Toscana"

Objective: setting of a new technology for treatment of neoplastic thyroid disease using a mini-invasive approach

Partecipants: Esaote S.p.A., El.En. S.p.A. , Deimos Consulting S.r.l.

Collaborating centers: Dept. Oncology, Dept of Clinical and Experimental Medicine, University of Pisa, Dept. of Critical Area, Surgery, Electron. Engeering, University of Florence, Telecom.

TRAP Study: 2011-2012. (n. 3310/ 2011); Study Group 20 patients

Results: 36 months after laser ablation: Nodular volume reduction (*DVN* - 58,01% ± 4.0; p=0.0001).

Reduction > 50%: 70% of cases

Possible Developments

1. Improvement of the software of the ultrasound systems in order to better define the effects of laser treatment in thyroid nodules:

2. Improvement of innovative technologies that study the elasticity of nodular thyroid tissue

3. Production of new equipment, software, and optical fibers with the aim of improving the performance of Laser treatment

Thyroid cancer is a rare cancer!

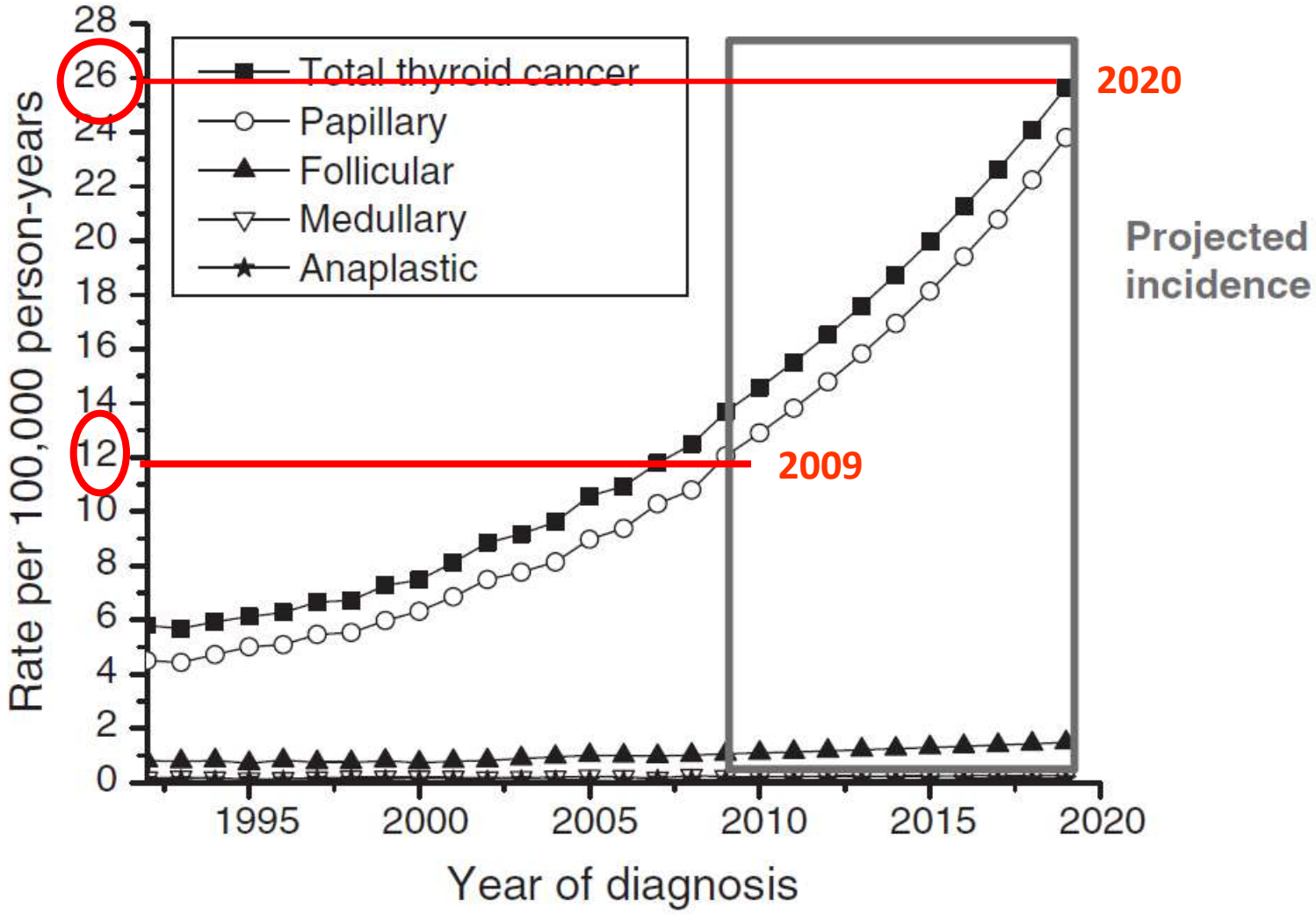
	Common Types of Cancer	Estimated New Cases 2013	Estimated Deaths 2013
1.	Prostate Cancer	238,590	29,720
2.	Breast Cancer	232,340	39,620
3.	Lung and Bronchus Cancer	228,190	159,480
4.	Colon and Rectum Cancer	142,820	50,830
5.	Melanoma of the Skin	76,690	9,480
6.	Bladder Cancer	72,570	15,210
7.	Non-Hodgkin Lymphoma	69,740	19,020
8.	Kidney and Renal Pelvis Cancer	65,150	13,680
9.	**Thyroid Cancer**	**60,220**	**1,850**
10.	Endometrial Cancer	49,560	8,190

Thyroid cancer represents 3.6% of all new cancer cases in the U.S.

3.6%

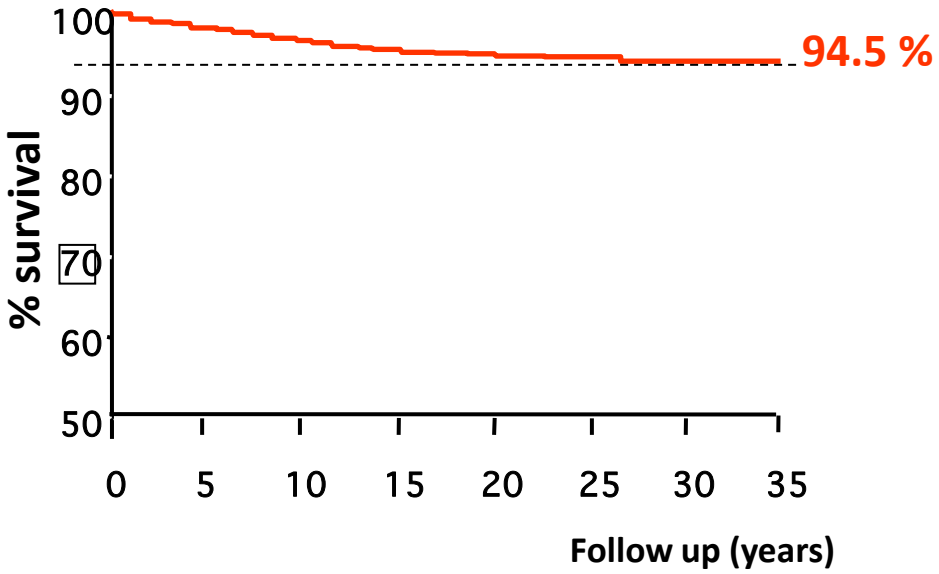
National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.

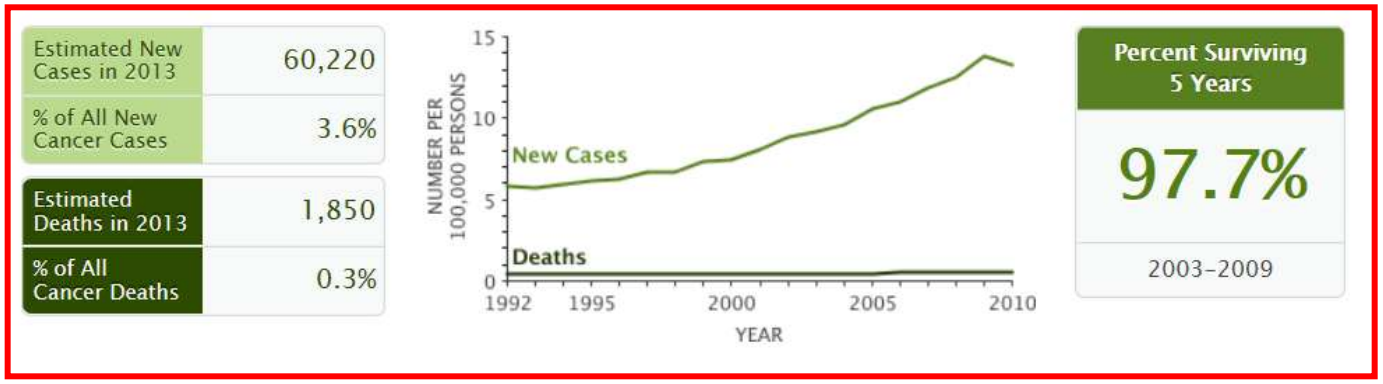
THYROID CANCER INCIDENCE IS STILL GROWING



National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.

4187 DIFFERENTIATED THYROID CANCER (PTC and FTC) OVERALL SURVIVAL AT 35 YEARS FOLLOW UP (Department of Endocrinology, University of Pisa, Italy)





HOW TO FOLLOW UP ALL THESE PATIENTS WITH LOWER COSTS BUT STILL HIGH QUALITY MEDICINE

1) Employing ultrasensitive serum Tg assay to reduce the need of a stimulation test with recombinant TSH produced only by Genzyme:

- **Testing new assays in old collected sera**
- **Comparing results with previous stimulation tests**
- **Measuring the interference of TgAb in the new assays**

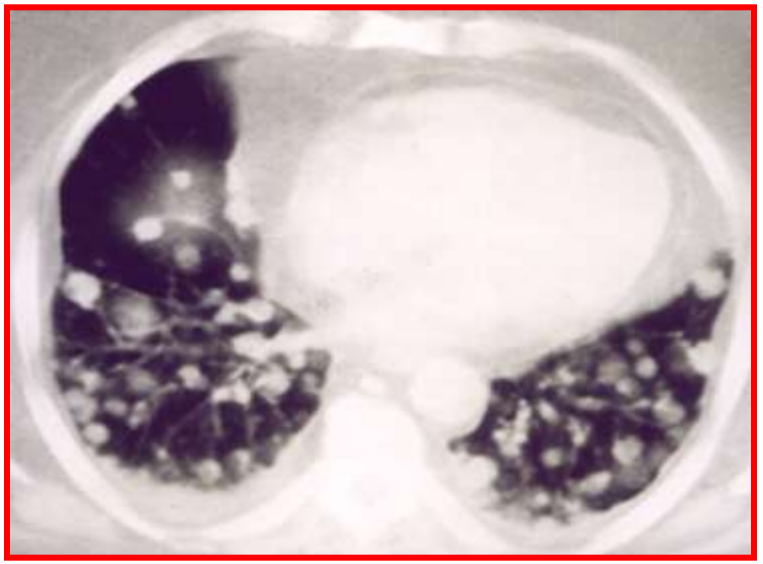
GREAT COLLABORATION WITH GENZYME AND SEVERAL COMPANIES PRODUCING TG ASSAYS!!!

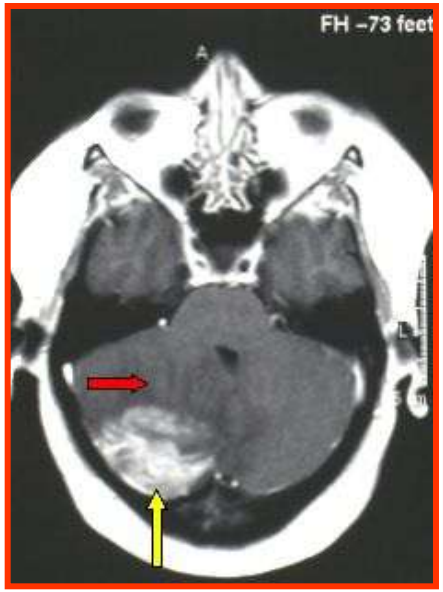
HOW TO FOLLOW UP ALL THESE PATIENTS WITH LOWER COSTS BUT STILL HIGH QUALITY MEDICINE

2) Reducing the hospitalization of patients who have to be treated with 131-I for remnant ablation and improving their QoL:

- **Only 30 mCi instead of 100 mCi for remnant ablation: less exposure to radiation of both patients and community**
- **Only 1 night of hospitalization other than 2 or 3**
- **Use of rhTSH instead of LT4 withdrawal thus avoiding all the side effects of hypothyroidism including a longer retention time of 131-I in the body**

THYROID CANCER
IS NOT ALWAYS A GOOD TUMOR





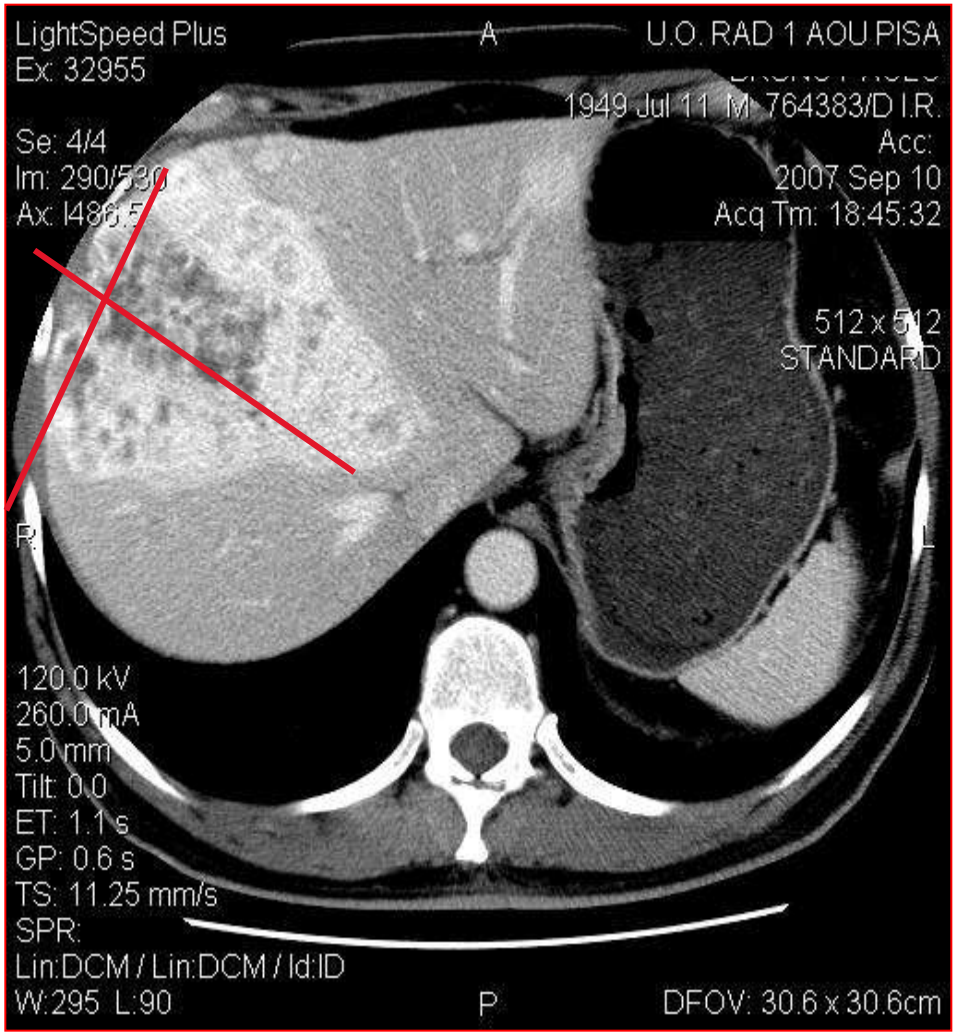
ANAPLASTIC THYROID CANCER TREATED WITH SORAFENIB

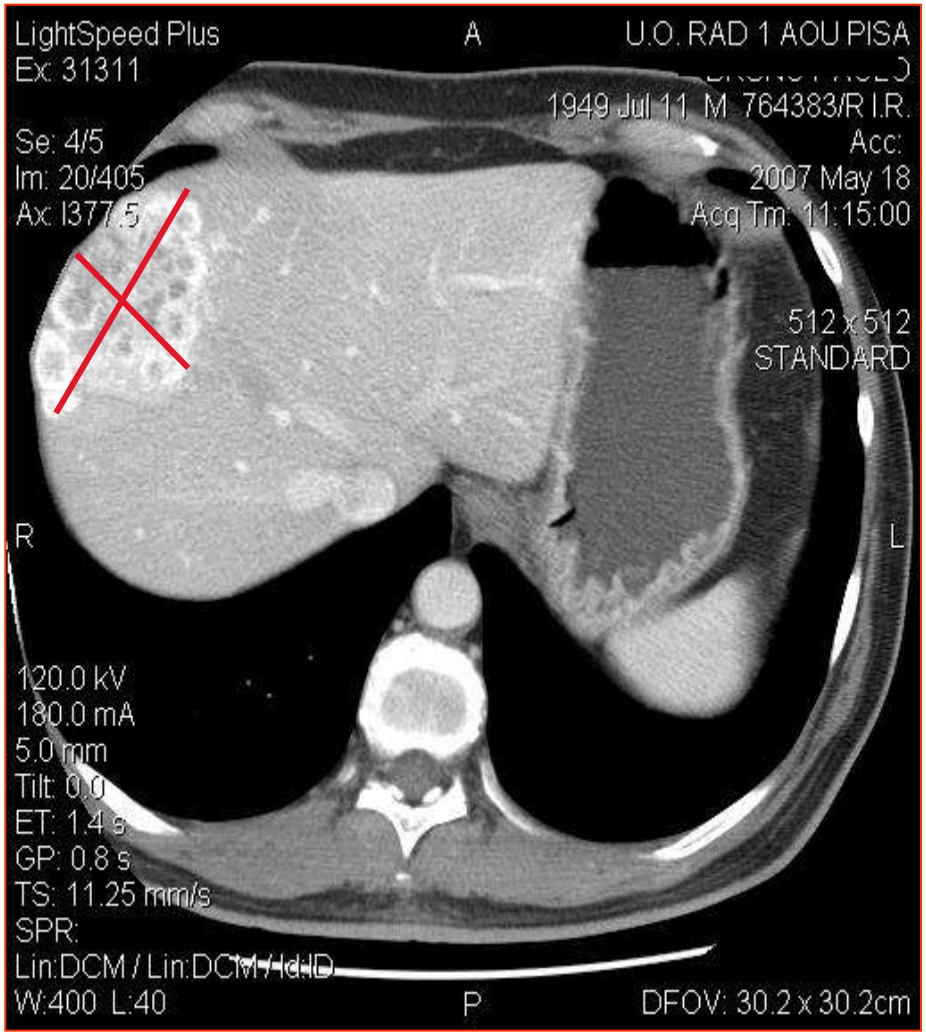
Before therapy

After 10 days

After 20 days

Patient n 018: 2 months of Vandetanib





May 2007

September 2007

PARTECIPATION IN ALL STUDY PROTOCOLS OF TARGET THERAPIES IN THYROID CANCER

Target drug	Company	Tumor type
Motesanib	AMGEN	MTC/PDTC
Axitinib	PFIZER	MTC/PDTC
Vandetanib	ASTRA ZENECA	MTC/PDTC
Cabozantinb	EXELIXIS	MTC
Sorafenib	BAYER	PDTC/ATC
Vemurafenib	LA ROCHE	PDTC Braf+
Lenvatinib	EISAI	PDTC

GREAT COLLABORATION TO FIND THE BEST PROTOCOL WITH THE LOWEST SIDE EFFECTS

Filomena Cetani, MD PhD, Claudio Marcocci, MD

Parathyroid Carcinoma
Background/state of art

- Improvement in PC diagnosis have been attempted by molecular analysis of the the main gene involved ***CDC73***

- Immunohistochemistry of the corresponding protein, **parafibromin**, has also been associated to the genetic screening in order to improve the diagnostic definition

- These strategies have not definitely demonstrated to effectively fulfill the need of an unequivocal diagnosis for a prompt patient management

Aims (1)

Proteomic studies

Research in collaboration with Prof. Lucacchini (*Department of Pharmacy-University of Pisa*)

1. **To identify a differentially expressed panel of disease-related proteins** in benign and malignant parathyroid tumor tissues obtained by a proteomic approach, in order to find key proteins or networks associated with PC.

2. **To establish primary parathyroid cell culture and carry out the secretome analysis as an *in vitro* model for the study of parathyroid tumorigenesis,** by combining the techniques with the highest resolving power (2-DE and nano-LC/LTQ-Orbitrap MS) with quantitative SILAC (stable isotope labeling with amino-acids in cell culture) to find potential biomarker in PC and/or AA vs PA

3. **To develop assays for measuring potential serum and urinary biomarkers, identified by proteomic studies, useful for an early diagnosis of PC**, to classify equivocal tumors, design the patients follow up, introduce early intervention, and lay the foundation for new pharmacological agents.

Aims (2)

Molecular studies

- ***CDC73* gene analysis** of PC and AA samples by automatic sequencing of the coding region and splice sites of the gene
- **Detection of large deletions of *CDC73* gene in patients negative to sequencing analysis,** by MLPA ((Multiplex Ligation-dependent Probe Amplification) assay using self-designed probes specific for *CDC73* gene.
- **Testing of presymtomatic relatives** of mutation carriers
- **Molecular studies of *CDC73* mutation-negative PC** (cofactors of *CDC73* ie. Paf1 etc; mitocondrial DNA)