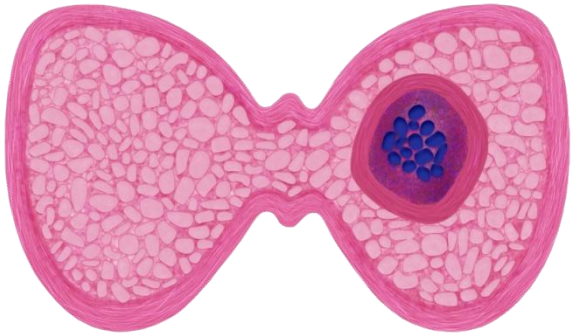
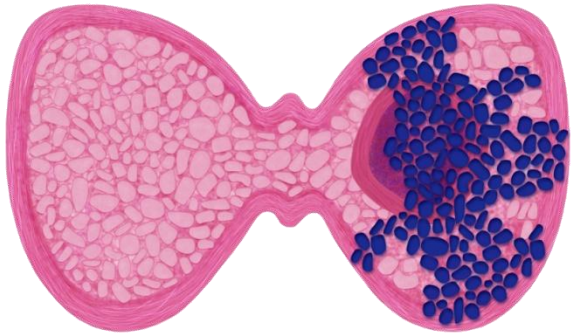
3RD ANNUAL COURSE OF PHARMACOGENETICS AND PERSONALIZED MEDICINE

Emerging pathways in Personalized Medicine: breaking barriers and moving forward





Molecular alteration in thyroid cancers.

F. Basolo

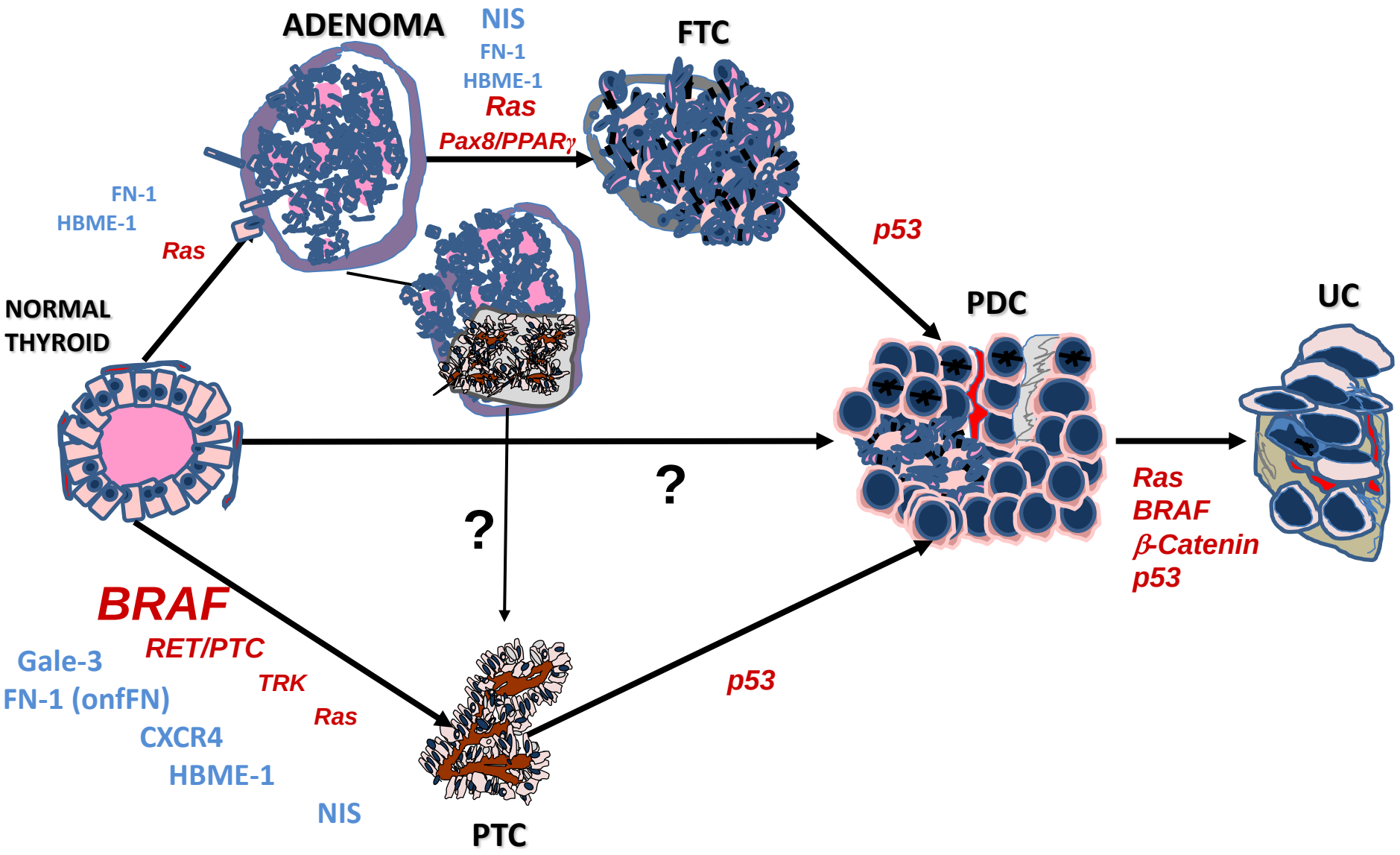
Thursday 9th - Friday 10th February 2012

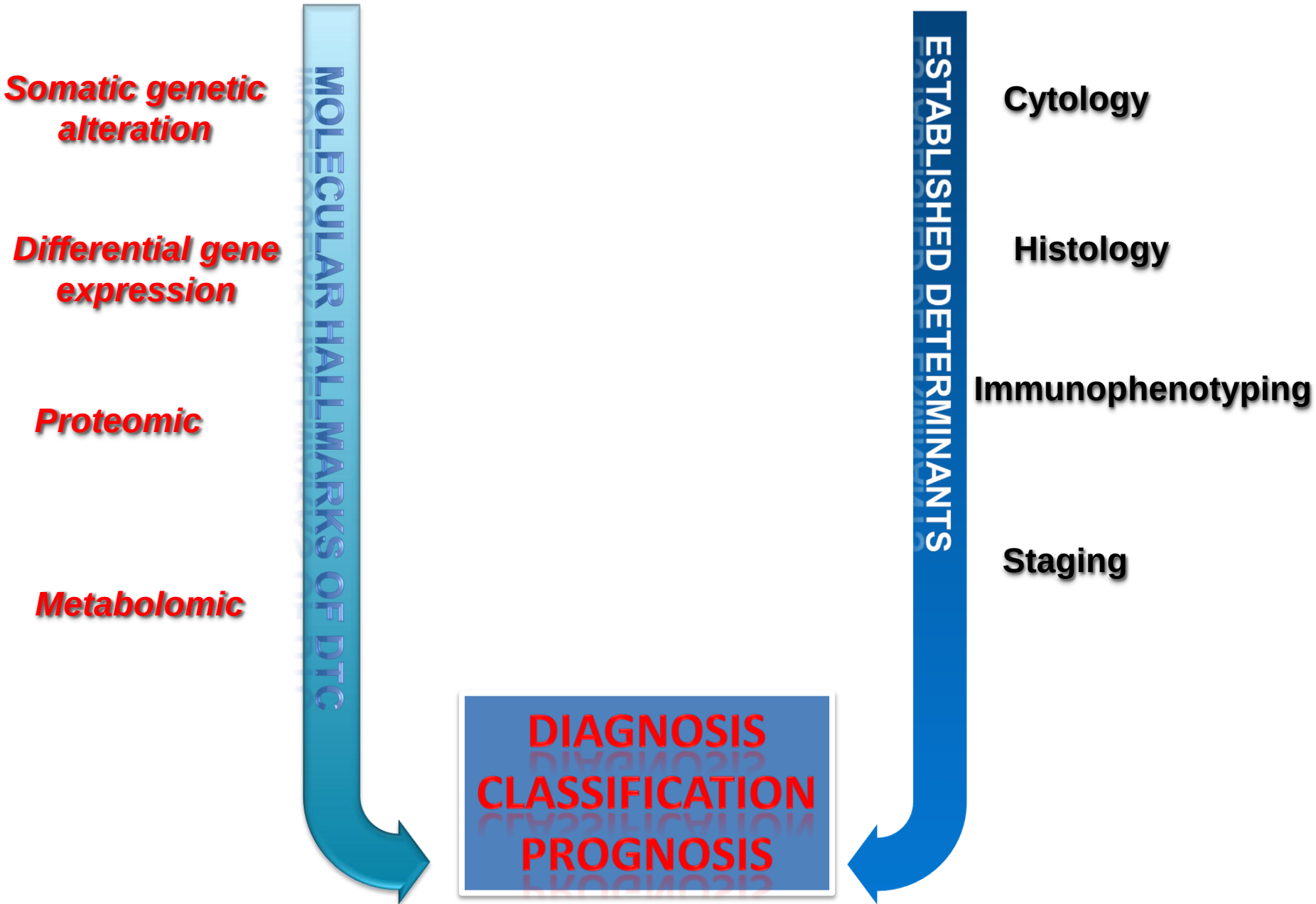
Aula Magna Sapienza University of Roma

MOLECULAR GENETICS OF THYROID CANCERS

SOMATIC GENETIC ALTERATIONS

DIFFERENTIAL GENE EXPRESSION




Somatic genetic alteration
Differential gene expression
Proteomic
Metabolomic
MOLECULAR HALLMARKS OF DTC
ESTABLISHED DETERMINANTS
Cytology
Histology
Immunophenotyping
Staging
DIAGNOSIS
CLASSIFICATION
PROGNOSIS

THYROID-TUMOR MARKERS (TTM)

DIAGNOSIS

Pre-operative differential diagnosis

PROGNOSIS

Pre- and post-operative follow-up

Surgery

Unconventional therapy, tailored drugs

ROLE OF BRAF STATUS

Pisa experience
2012

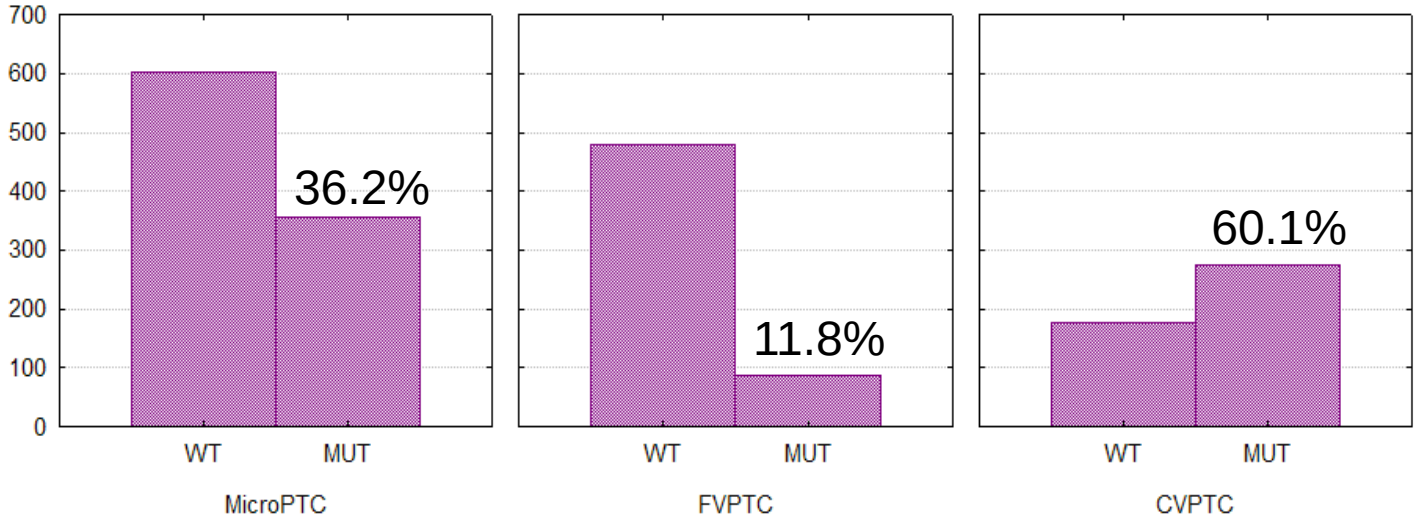
BRAF analysis on **2,192** consecutive PTCs

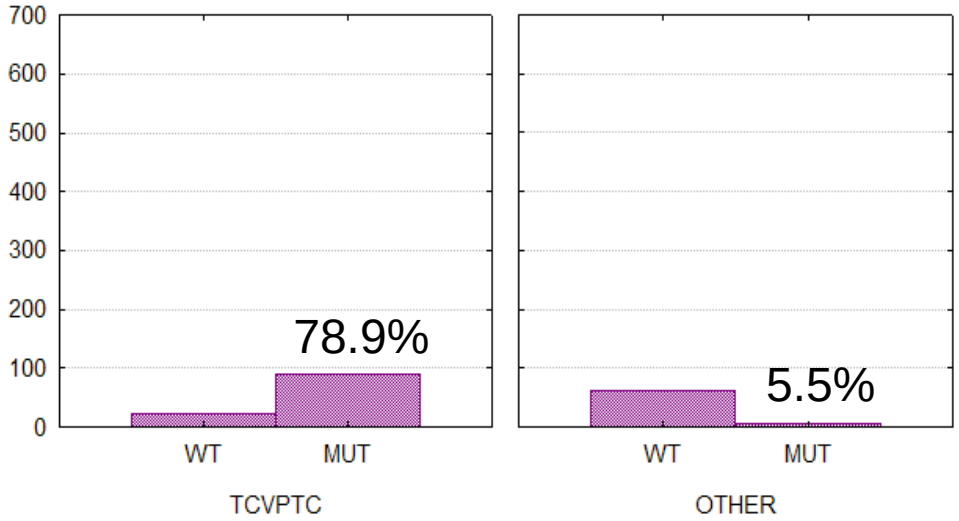
BRAF mutation
823 (37.5%)

BRAF wild type
1369

BRAF MUTATION and PTC variants

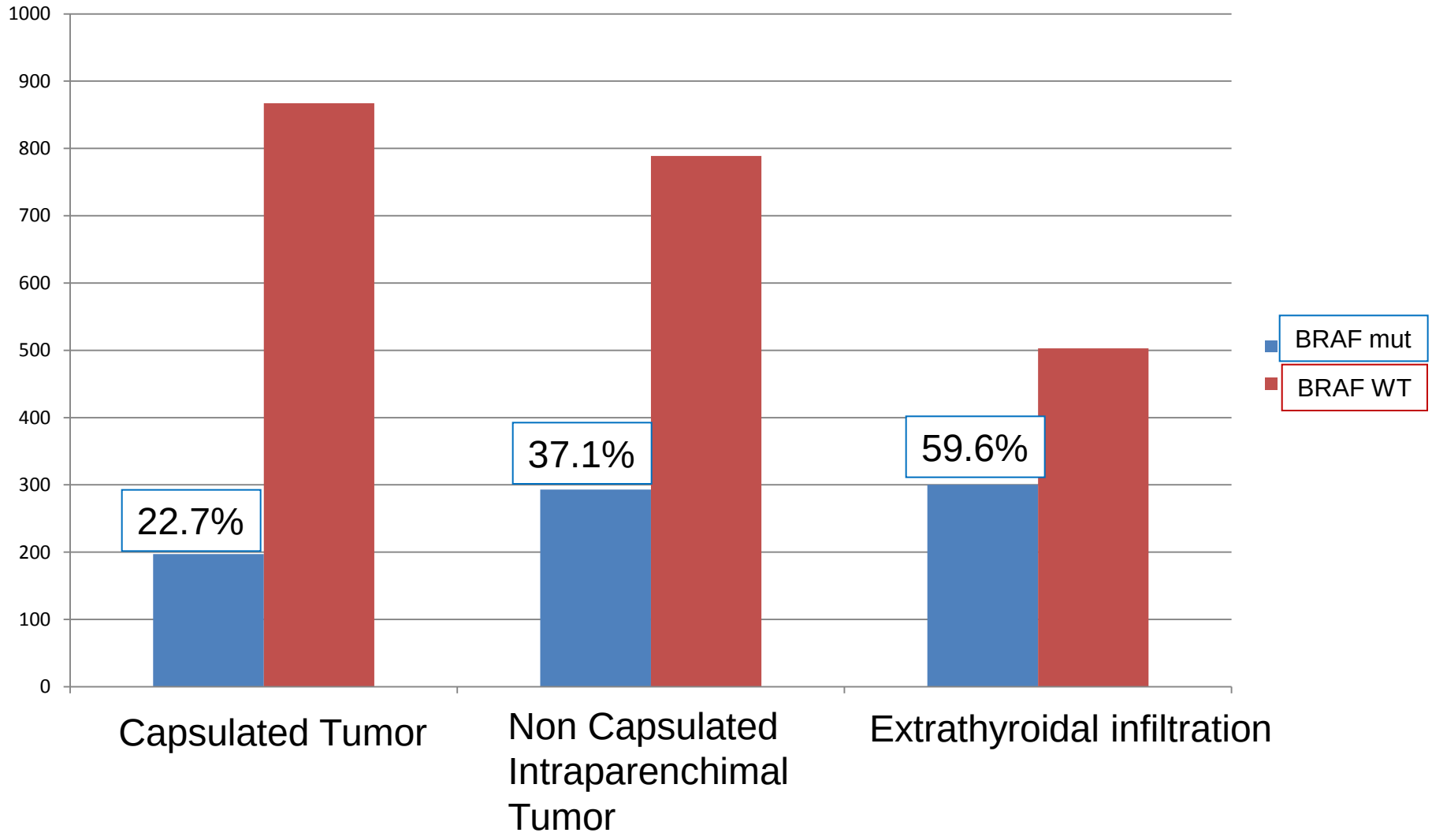
2,192 PTCs



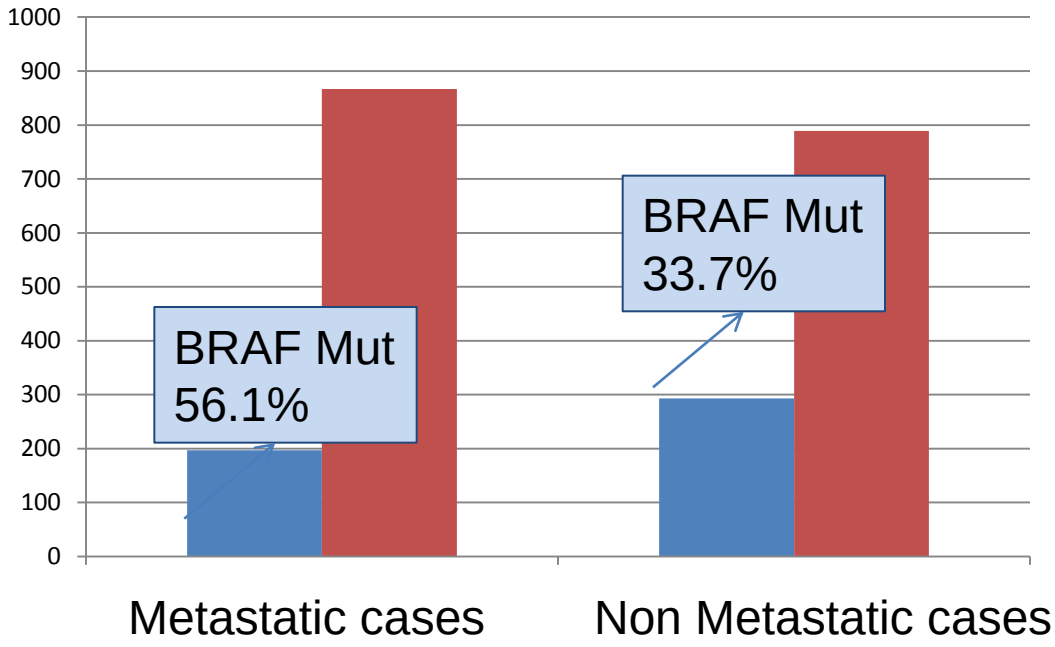


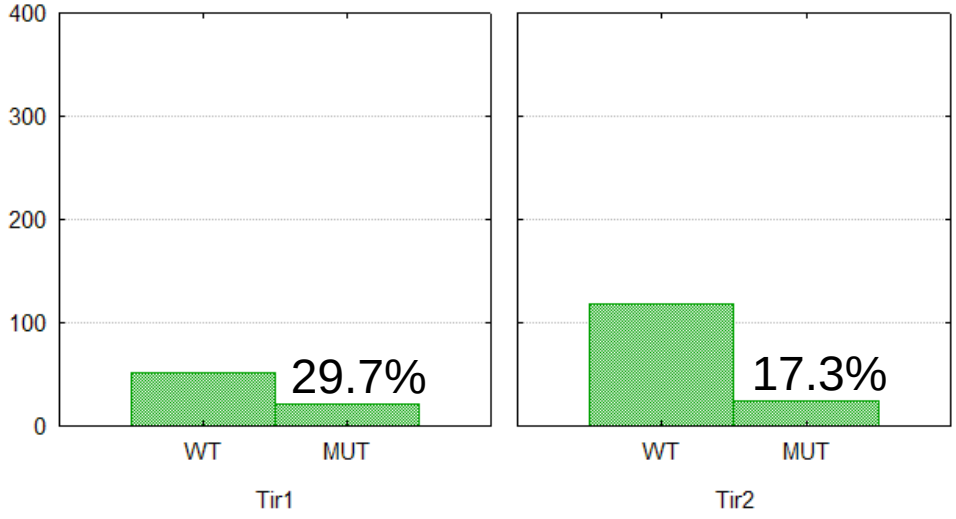
BRAF MUTATION
Mean 39.1% (excluding MicroPTC)
36.2% (in MicroPTC)
Total 38.5%

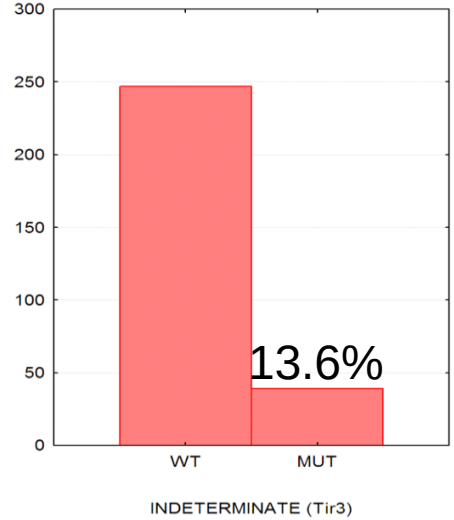
BRAF MUTATION and infiltration

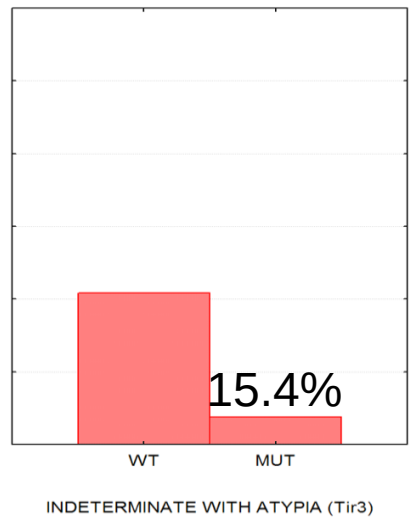


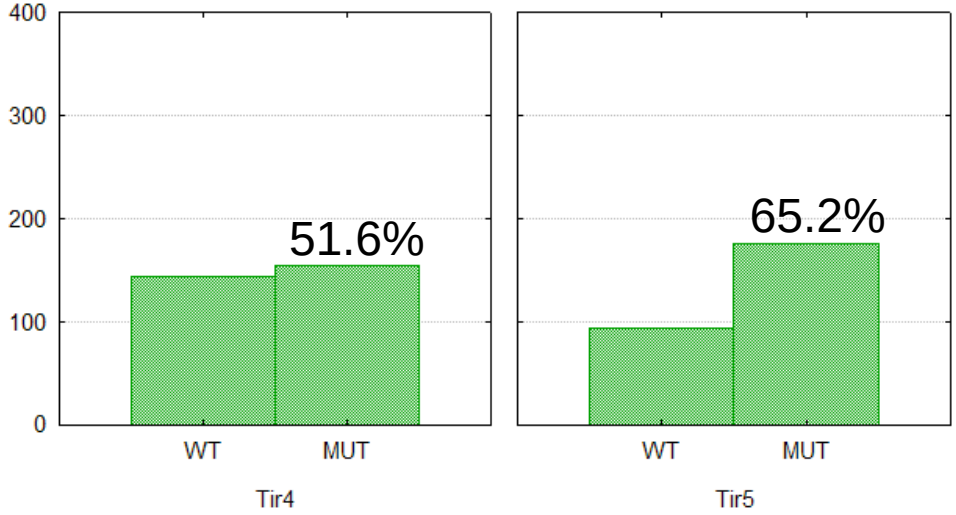
BRAF mutation and lymphnode metastasis











BRAF analyses on 1,195 PTCs grouped using preoperative FNAB classification.

DIAGNOSIS

Possible diagnostic role of BRAF mutation: Its importance in PREOPERATIVE CYTOLOGY

0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(10):5175–5180
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doi: 10.1210/jc.2003-032221

2003

Analysis of BRAF Point Mutation and RET/PTC Rearrangement Refines the Fine-Needle Aspiration Diagnosis of Papillary Thyroid Carcinoma

GIULIANA SALVATORE, RICCARDO GIANNINI, PINUCCIA FAVIANA, ALESSIA CALEO, ILENIA MIGLIACCIO, JAMES A. FAGIN, YURI E. NIKIFOROV, GIANCARLO TRONCONE, LUCIO PALOMBINI, FULVIO BASOLO, AND MASSIMO SANTORO

Istituto di Endocrinologia ed Oncologia Sperimentale del Consiglio Nazionale delle Ricerche and Dipartimento di Biologia e Patologia Cellulare e Molecolare (G.S., M.S.), and Dipartimento di Scienze Biomorfologiche e Funzionali (A.C., I.M., G.T., L.P.), University 'Federico II,' 80131 Napoli, Italy; Dipartimento di Oncologia (R.G., P.F., F.B.), University of Pisa, 56126 Pisa, Italy; and Department of Pathology and Laboratory Medicine and Division of Endocrinology (J.A.F., Y.E.N.), University of Cincinnati, Cincinnati, Ohio 45267

Several studies have been conducted to evaluate the diagnostic applicability of *BRAF* mutation detection on FNAB specimens with a result of inadequate (class1) or follicular neoplasm (class 3) or suspicious for malignancy (class 4).

Possible diagnostic role of BRAF mutation

THYROID
Volume 19, Number 12, 2009

DOI: 10.1089/thy.2009.0240

FRONTIERS IN THYROID CANCER

Molecular Diagnostics and Predictors in Thyroid Cancer

Marina N. Nikiforova and Yuri E. Nikiforov

TABLE 3. ROLE OF MOLECULAR TESTING OF FINE-NEEDLE ASPIRATION WITH INDETERMINATE CYTOLOGY IN REFINING CANCER PROBABILITY IN THYROID NODULES

Category of indeterminate cytology	*Molecular testing result*	*Cancer probability (%)*
Follicular lesion of indeterminate significance ($n=21$)	Mutation positive ($n=3$)	100
	Mutation negative ($n=18$)	0
Follicular of Hürthle cell neoplasm ($n=23$)	Mutation positive ($n=9$)	100
	Mutation negative ($n=14$)	21
Suspicious for malignancy ($n=7$)	Mutation positive ($n=3$)	100
	Mutation negative ($n=4$)	50
Total ($n=51$)	Mutation positive ($n=15$)	100
	Mutation negative ($n=36$)	14

Based on the data reported by Nikiforov *et al.* (74).

of the 581 *BRAF*-positive nodules tested in various types of FNA samples are papillary carcinomas, with a false-positive rate of 0.2%. Importantly, a significant proportion (15–39%) of *BRAF*-positive FNA samples in many of these studies were indeterminate or nondiagnostic by cytology, demonstrating that testing for *BRAF* is helpful in establishing the definitive diagnosis of cancer in nodules with indeterminate cytology (74,78,81,84,85,89). In addition, several FNA samples with

Impact of Proto-Oncogene Mutation Detection in Cytological Specimens from Thyroid Nodules Improves the Diagnostic Accuracy of Cytology

Silvia Cantara, Marco Capezzone, Stefania Marchisotta, Serena Capuano, Giulia Busonero, Paolo Toti, Andrea Di Santo, Giuseppe Caruso, Anton Ferdinando Carli, Lucia Brilli, Annalisa Montanaro, and Furio Pacini

Department of Internal Medicine, Endocrinology, and Metabolism and Biochemistry, Section of Endocrinology and Metabolism (S.Can., M.C., S.M., S.Cap., G.B., L.B., A.M., F.P.), Department of Human Pathology and Oncology (P.T., A.D.S.), Unit of Otorinolaringoiatry (G.C.), and Department c Surgery and Bioengineering (A.F.C.), Section of Surgery, University of Siena, 53100 Siena, Italy

J Clin Endocrinol Metab, March 2010, 95(3):1365–1369

Cytology (n=235)	Mutation (in cytology)		Histology
Suspicious for Thyroid cancer (n=54)	BRAF	21	PTC 21
	RET/PTC	6	PTC 6
	RAS	10	PTC 10
	None	17	PTC 9 FA 4 Hyperplastic 4
Benign (87)	BRAF	2	PTC 2
	RET/PTC	2	PTC 2
	RAS	5	PTC 2 FA 3
	None	78	PTC 2 FTC 1 FA 10 Hyperplastic 65
Indeterminate (n=41)	BRAF	2	PTC 2
	RET/PTC	2	PTC 2
	RAS	3	PTC 2 FA 1
	None	34	PTC 1 FA 25 Hyperplastic 8
Inadequate (n=53)	BRAF	8	PTC 8
	RET/PTC	1	PTC 1
	RAS	5	PTC 2 HCC 1 FA 2
	None	39	PTC 2 FTC 2 FA 11 Hyperplastic 24

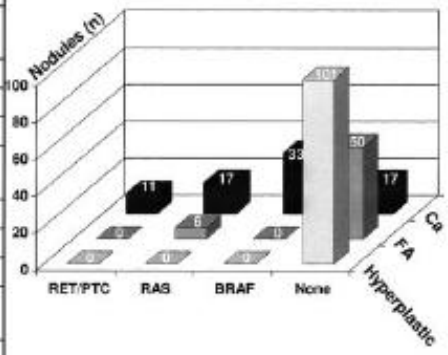

TABLE 1. Diagnostic performance of cytology, molecular analysis, or a combination of both

Diagnostic modality	Sensivity TP/TP+FN (%)	Specificity TN/FP+TN (%)	PPV TP/TP+FP (%)	NPV TN/TN+FN (%)	Accuracy TP+TN/All (%)
Cytology (positive for malignancy)	59.0	94.9	85.2	82.3	83.0
Molecular analysis (mutation in malignancy)[a]	78.2	96.2	91.0	89.9	90.2
Molecular analysis (mutation in malignancy)[b]	79.8	100	100	89.9	92.8
Cytology and molecular analysis[a]	89.7	94.9	89.7	94.9	93.2
Cytology and molecular analysis[b]	90.5	98.7	97.4	94.9	95.7

ATA Guidelines

THYROID
Volume 19, Number 11, 2009

DOI: 10.1089/thy.2009.0110

ORIGINAL STUDIES, REVIEWS, AND SCHOLARLY DIALOG

THYROID CANCER AND NODULES

Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association (ATA) Guidelines Taskforce
on Thyroid Nodules and Differentiated Thyroid Cancer

David S. Cooper, M.D.[1] (Chair)*, Gerard M. Doherty, M.D.,[2] Bryan R. Haugen, M.D.,[3]
Richard T. Kloos, M.D.,[4] Stephanie L. Lee, M.D., Ph.D.,[5] Susan J. Mandel, M.D., M.P.H.,[6]
Ernest L. Mazzaferri, M.D.,[7] Bryan McIver, M.D., Ph.D.,[8] Furio Pacini, M.D.,[9] Martin Schlumberger, M.D.,[10]
Steven I. Sherman, M.D.,[11] David L. Steward, M.D.,[12] and R. Michael Tuttle, M.D.[13]

72). Recent large prospective studies have confirmed the ability of genetic markers (BRAF, Ras, RET/PTC) and protein markers (galectin-3) to improve preoperative diagnostic accuary for patients with indeterminate thyroid nodules (69,73,74). Many of these markers are available for commercial use in reference laboratories but have not yet been widely applied in clinical practice. It is likely that some combination of molecular markers will be used in the future to optimize management of patients with indeterminate cytology on FNA specimens.

NEW METHODS FOR THE IDENTIFICATION OF GENETIC ALTERATIONS

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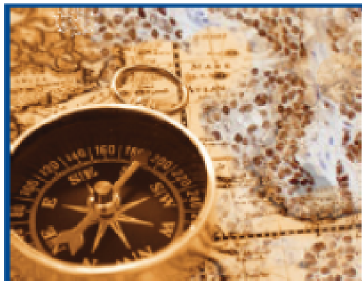

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EGFR	*N-RAS*
ERBB2	*PDGFRα*
FGFR-1	*PIK3CA*
FGFR-3	*RET*
FLT-3	

See back for complete list of mutations.

Disclaimer: OncoCarta™ is for Research Use Only. Not for use in diagnostic procedures.

CCGATGATCGACCAGTATGCGCATGATGATCGAAGTATGCGCATTATGCGCATGAT
GCGCATTATGCGCATGATGATCGAAGCCGATGATCGAC
GCGCATTATGCGCGCATGATGATCGAAGTATCATGATG
GTATCATGATGATCGAAGCCGATGAGTATCATGATGATCGAAGCCGATGATGAT

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Oncogene	Mutations Detected with the OncoCarta Assay Panel v1.0
ABL-1	G250E, Q252H, Y253H, Y253F, E255K, E255V, D276G, F311L, T315I, F317L, M351T, E355G, F359V, H396R
AKT-1	V461L, P388T, L357T, E319G, V167A, Q43X, E17del
AKT-2	S302G, R371H
BRAF	G464R, G464V/E, G466R, F468C, G469S, G469E, G469A, G469V, G469R, G469R, D594V/G, F595L, G596R, L597S, L597R, L597Q, L597V, T599I, V600E, V600K, V600R, V600L, K601N, K601E
CDK-4	R24C, R24H
EGFR	R108K, T263P, A289V, G598V, E709K/H, E709A/G/V, G719S/C, G719A, M766_A767insAI, S768I, V769_D770insASV, V769_D770insCV, D770_N771>AGG/V769_D770insASV/V769_D770insASV, D770_N771insG, N771_P772>SVDNR, P772_H773insV, H773>NPY, H773_V774insNPH/PH/H, V774_C775insHV, T790M, L858R, L861Q, E746_T751del, E746_A750del, E746_T751del, E746_T751del, S752D, L747_E749del, L747_T750del, L747_S752del, L747_T751del, L747_S752del, P753S, A750P, T751A, T751P, T751I, S752I/F, S752_I759del, L747_Q ins, E746_T751del, I ins (combined), E746_A750del, T751A (combined), L747_E749del, A750P (combined), L747_T750del, P ins (combined), L747_S752del, Q ins (combined)
ERBB2	L755P, G776S/LC, G776VC/VC, A775_G776insYVMA, P780_Y781insGSP, P780_Y781insGSP, S779_P780insVGS
FGFR-1	S125L, P252T
FGFR-3	G370C, Y373C, A391E, K650Q/E, K650T/M
FLT-3	I836del, D835H/Y
JAK-2	V617F
KIT	D52N, Y503_F504insAY, W557R/R/G, V559D/A/G, V559I, V560D/G, K550_K558del, K558_V560del, K558_E562del, V559del, V559_V560del, V560del, Y570_L576del, E561K, L576P, P585P, D579del, K642E, D816V, D816H/Y, V825A, E839K, M552L, V568D, F584S, P551_V555del, Y553_Q556del
MET	R970C, T992I, Y1230C, Y1235D, M1250T
PDGFRα	V561D, T674I, F808L, D846Y, N870S, D1071N, D842_H845del, I843_D846del, S566_E571>K, I843_S847>T, D842V
PIK3CA	R88Q, N345K, C420R, P539R, E542K, E545K, Q546K, H701P, H1047R/L, H1047Y, R38H, C901F, M1043I
H-RAS	G12V/D, G13C/R/S, Q61H/H, Q61L/R/P, Q61K
K-RAS	G12C, G12R, G12S, G12V, G12D, G12A, G12F, G13V/D, A59T, Q61E/K, Q61L/R/P, Q61H/H
N-RAS	G12V/A/D, G12C/R/S, G13V/A/D, G13C/R/S, A18T, Q61L/R/P, Q61H, Q61E/K
RET	C634R, C634W, C634Y, E632_L633del, M918T, A664D

CCGATGATCGACCAGTATGCGCATGATGATCGAAGTATGCGCATTATGCGCATGAT
GCGCATTATGCGCATGATGATCGAAGCCGATGATCGACCAGTATGCGCATGATGAT
GCGCATTATGCGCGCATGATGATCGAAGTATCATGATGATCGAAGCCGATGATCGA
GTATCATGATGATCGAAGCCGATGAGTATCATGATGATCGAAGCCGATGATGAT

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THYROIDCARTA???????

PROGNOSIS

2006

THYROID
Volume 17, Number 5, 2007

DOI: 10.1089/thy.2006.0305

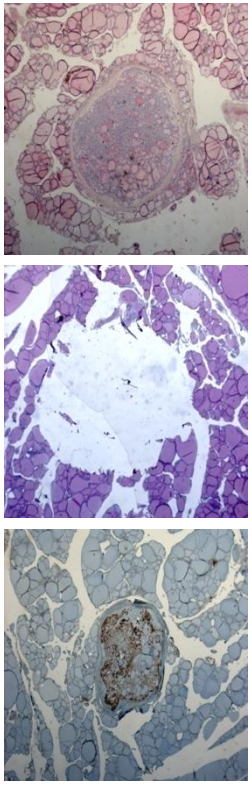
Laboratory Research

Presence of *BRAF* V600E in Very Early Stages of Papillary Thyroid Carcinoma

Clara Ugolini,[1] Riccardo Giannini,[1] Cristiana Lupi,[1] Giuliana Salvatore,[2] Paolo Miccoli,[1] Agnese Proietti,[1] Rossella Elisei,[3] Massimo Santoro,[2] and Fulvio Basolo[1]

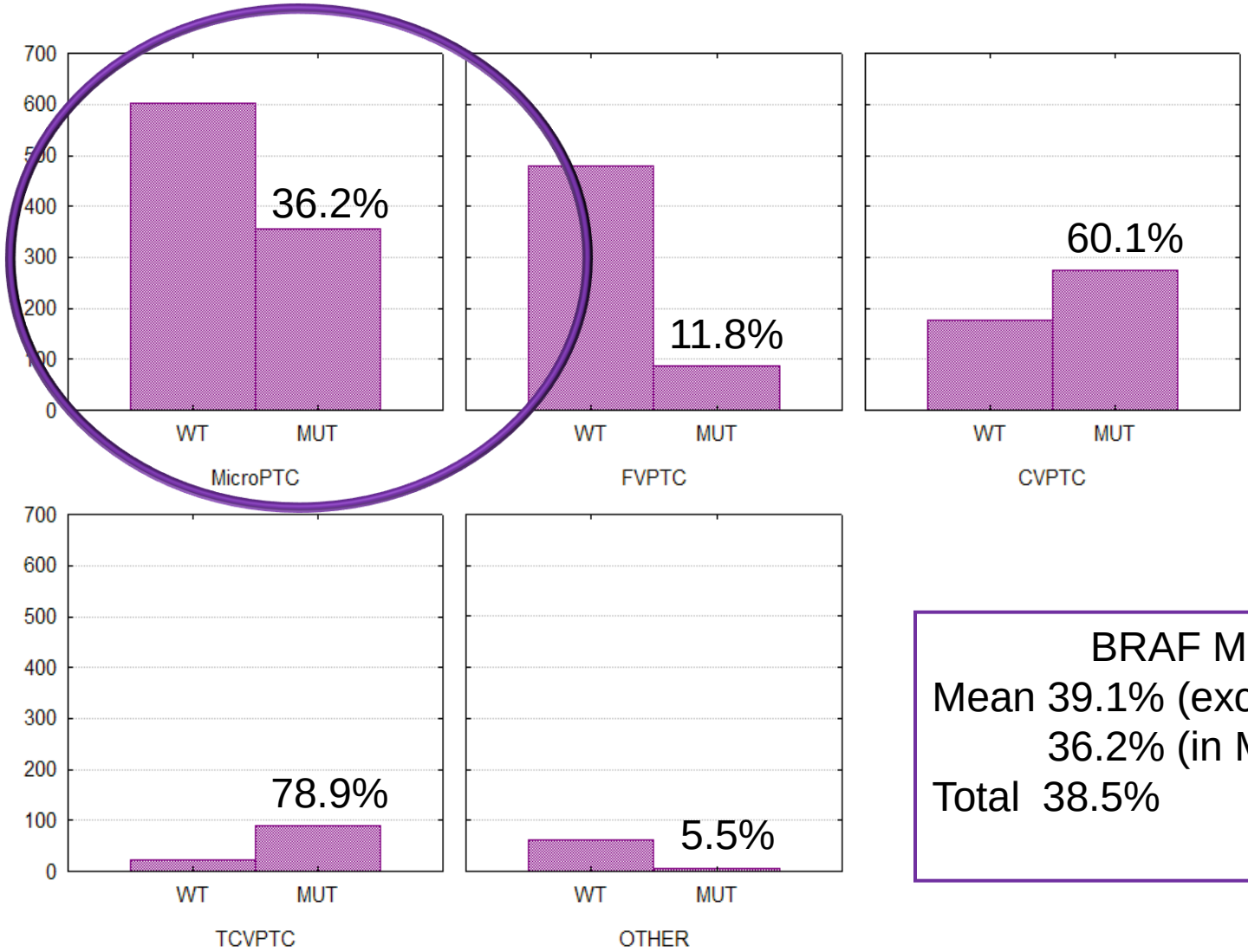
BRAF(V600E) may be found in Incidental Microcarcinoma (IM) despite their extremely small (<1mm) size.

We recognize that this is not a formal demonstration that IM can evolve in clinical PTC, but on the basis of our data and on a practical point of view, patients with BRAF(V600E) IM may need to be managed more carefully than patients affected by a mere benign condition.



BRAF MUTATION and PTC variants

2,192 PTCs



BRAF MUTATION
Mean 39.1% (excluding MicroPTC)
36.2% (in MicroPTC)
Total 38.5%

2007

EXTENSIVE CLINICAL EXPERIENCE

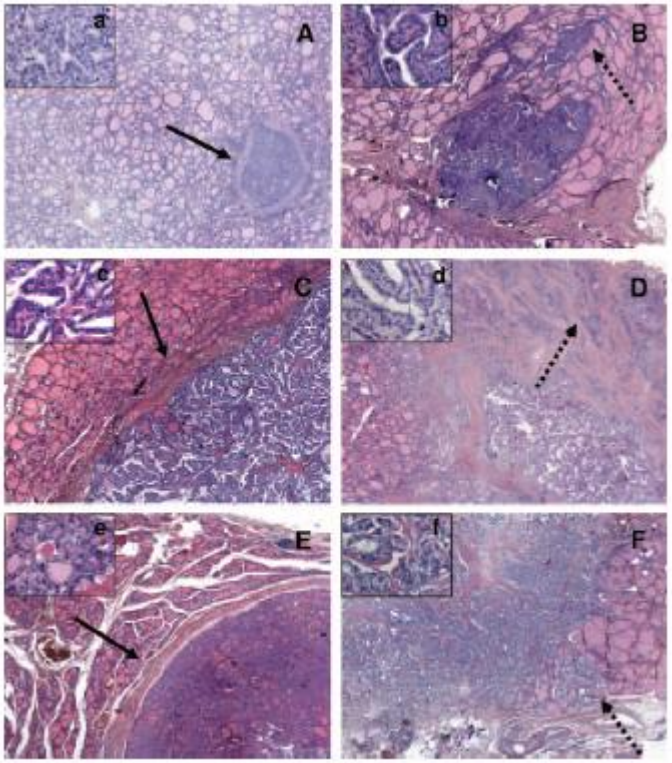
Association of BRAF V600E Mutation with Poor Clinicopathological Outcomes in 500 Consecutive Cases of Papillary Thyroid Carcinoma

Cristiana Lupi, Riccardo Giannini, Clara Ugolini, Agnese Proietti, Piero Berti, Michele Minuto, Gabriele Materazzi, Rossella Elisei, Massimo Santoro, Paolo Miccoli, and Fulvio Basolo

Departments of Surgery (C.L., R.G., C.U., A.P., P.B., M.M., G.M., P.M., F.B.) and Endocrinology (R.E.), University of Pisa, 56126 Pisa, Italy; and Dipartimento di Biologia e Patologia Cellulare e Molecolare (M.S.), Istituto di Endocrinologia ed Oncologia Sperimentale del Consiglio Nazionale delle Ricerche, University Federico II, 80131 Naples, Italy

The Journal of Clinical Endocrinology & Metabolism 92(11):4085–4090

doi: 10.1210/jc.2007-1179



	BRAF V600E-positive cases					
	Total cases		PTC[a]		Micro PTC[b]	
	n (%)	*P*[c]	n (%)	*P*[c]	n (%)	*P*[c]
Age (yr)						
Younger than 45	108/243 (44.4)	>0.5	68/143 (47.5)	>0.5	40/100 (40)	>0.5
45 or older	99/244 (40.6)		52/118 (44)		47/126 (37.3)	
Gender						
Male	57/124 (45.9)	>0.5	30/65 (46,2)	>0.5	27/59 (45.7)	>0.5
Female	157/376 (36.4)		94/205 (45.8)		63/171 (36.8)	
Extrathyroidal invasion						
Yes	82/129 (63.5)	**<0.0001**	52/84 (61.9)	**0.0004**	30/45 (66.7)	**<0.0001**
No	132/371 (35.6)		72/186 (38.7)		60/185 (32.4)	
Multicentricity						
Yes	89/171 (52)	**0.0026**	58/97 (59.8)	**0.0006**	31/74 (41.9)	>0.5
No	125/329 (38)		66/173 (38.2)		59/156 (37.8)	
Nodal metastases						
Yes	34/53 (64.1)	**0.0009**	27/42 (64.3)	**0.0094**	7/11 (63.6)	>0.5
No	180/447 (40.2)		97/228 (42.5)		83/219 (37.9)	
Class[d]						
I	124/357 (34.7)	**<0.00001**	67/177 (37.8)	**0.001**	57/180 (31.7)	**<0.00001**
II	9/15 (60)		6/9 (66.7)		3/6 (50)	
III	81/127 (63.7)		51/83 (61.4)		30/44 (68.2)	
Encapsulated[e]						
Yes	30/138 (21.7)	**<0.0001**	19/81 (23.4)	**<0.0001**	11/57 (19.3)	**0.0004**
No	184/362 (50.8)		105/189 (55.6)		79/173 (45.7)	

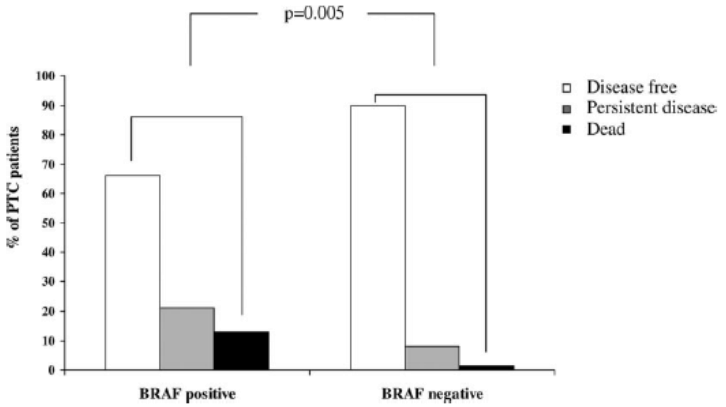
2008

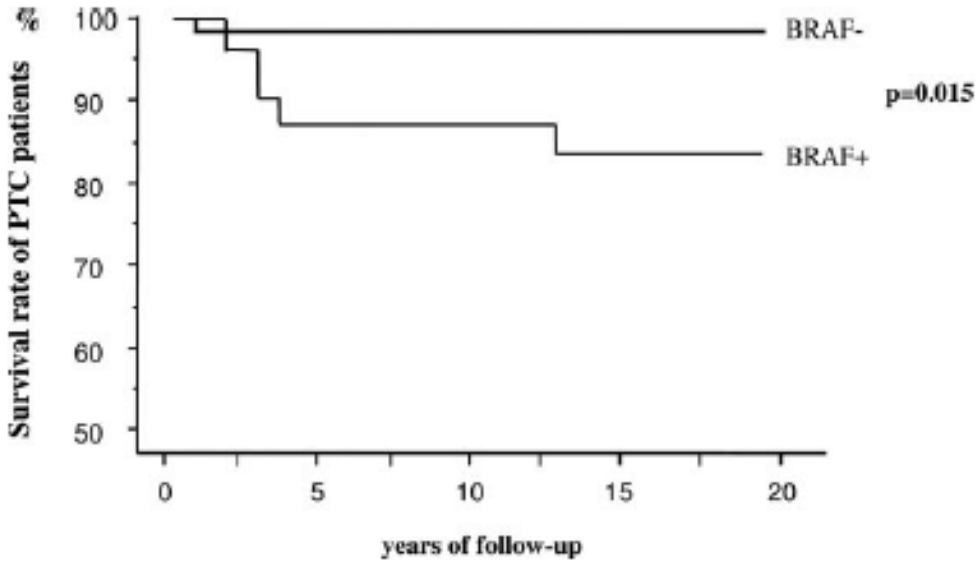
BRAF^{V600E} Mutation and Outcome of Patients with Papillary Thyroid Carcinoma: A 15-Year Median Follow-Up Study

Rossella Elisei, Clara Ugolini, David Viola, Cristiana Lupi, Agnese Biagini, Riccardo Giannini, Cristina Romei, Paolo Miccoli, Aldo Pinchera, and Fulvio Basolo

Departments of Endocrinology and Metabolism (R.E., D.V., A.B., C.R., A.P.), and of Surgery (P.M., C.U., C.L., R.G., F.B.), University Hospital of Pisa, 56100 Pisa, Italy; and AMBISEN Center (A.P.), High Technology Center for the Study of the Environmental Damage of the Endocrine and Nervous Systems, University of Pisa, 56124 Pisa, Italy

J Clin Endocrinol Metab, October 2008, 93(10):3943–3949



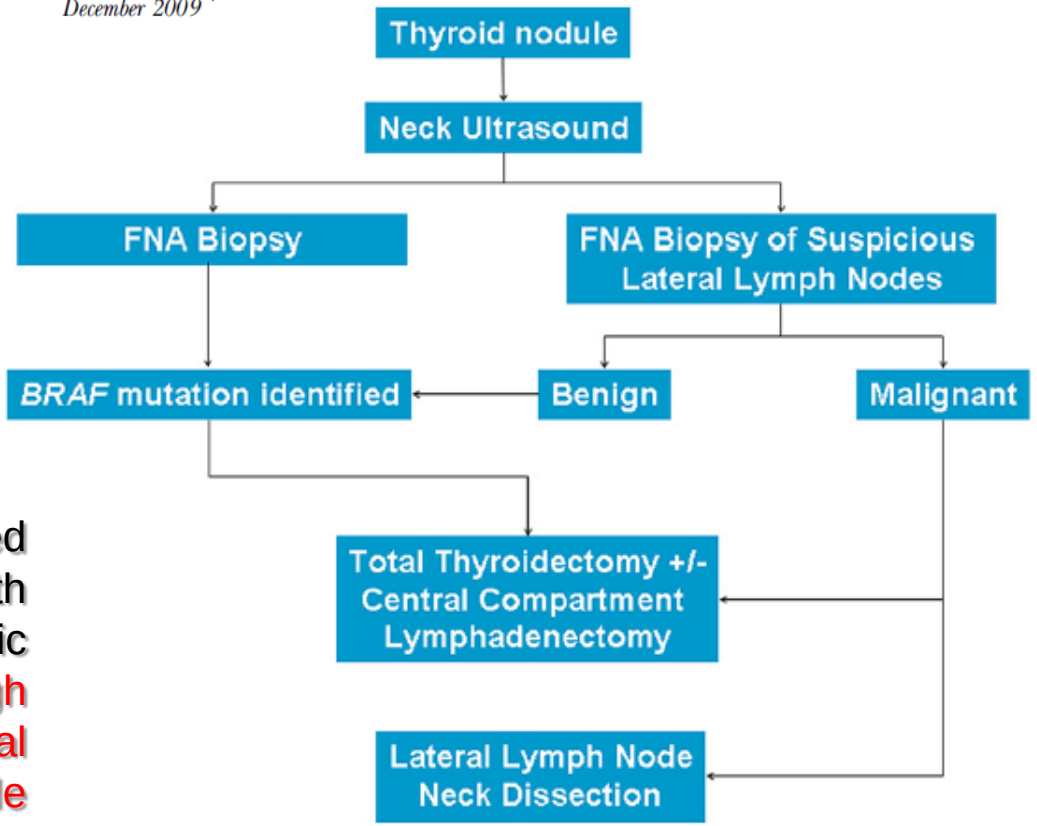


Optimizing surgical treatment of papillary thyroid carcinoma associated with BRAF mutation

Linwah Yip, MD,[a] Marina N. Nikiforova, MD,[b] Sally E. Carty, MD,[a] John H. Yim, MD,[a] Michael T. Stang, MD,[a] Mitchell J. Tublin, MD,[c] Shane O. LeBeau, MD,[d] Steven P. Hodak, MD,[d] Jennifer B. Ogilvie, MD,[a] *and* Yuri E. Nikiforov, MD,[b] *Pittsburgh, PA*

Surgery
December 2009

2009



In PTC, BRAF mutations are associated with cervical recurrence and with reoperation. Pre-operative cytologic identification of BRAF mutation has high specificity and may guide the initial extent of thyroidectomy and node dissection.

Correlation between the *BRAF* V600E Mutation and Tumor Invasiveness in Papillary Thyroid Carcinomas Smaller than 20 Millimeters: Analysis of 1060 Cases

2010

Fulvio Basolo, Liborio Torregrossa, Riccardo Giannini, Mario Miccoli, Cristiana Lupi, Elisa Sensi, Piero Berti, Rossella Elisei, Paolo Vitti, Angelo Baggiani, and Paolo Miccoli

Departments of Surgery (F.B., L.T., R.G., C.L., E.S., P.B., P.M.), Experimental Pathology B.M.I.E., Biostatistics Research Unit (M.M., A.B.), and Endocrinology (R.E., P.V.), University of Pisa, 56126 Pisa, Italy

J Clin Endocrinol Metab, September 2010, 95(9):4197–4205

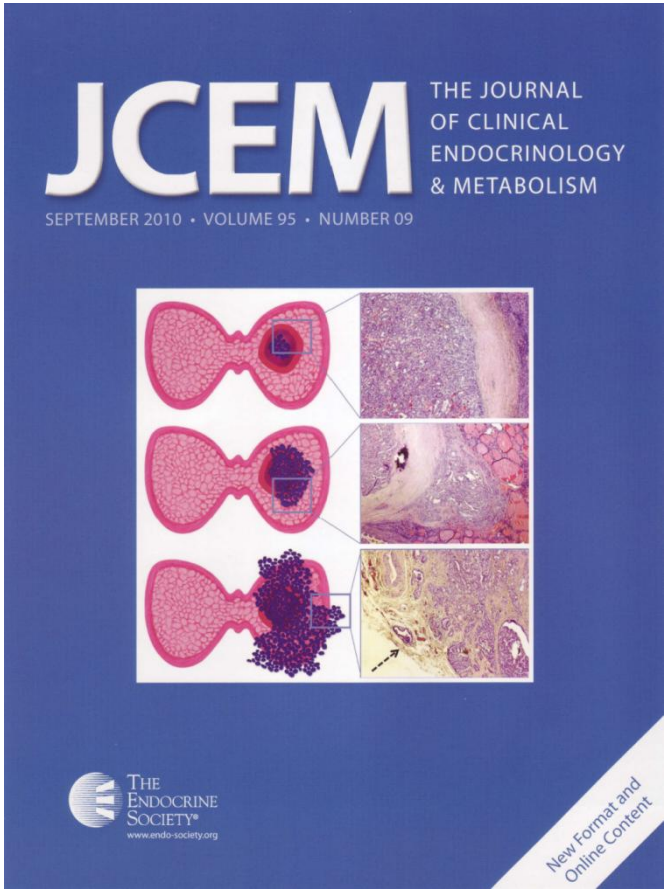


TABLE 2. Correlation between *BRAF* V600E mutation and clinical-pathological features in 1047 cases of PTCs 20 mm or smaller

Clinical-pathological features	*BRAF* V600E positive, n (%)	*P* value	OR (95% CI)	Statistical power (1−β)
Age at diagnosis[a]				
Patients <45 yr (n = 544)	269 (49.4)	0.006	0.71 (0.55 to 0.90)	>0.95
Patients ≥45 yr (n = 497)	203 (40.8)			
Gender				
Male (n = 252)	121 (48.0)	>0.05	1.16 (0.88 to 1.54)	<0.7
Female (n = 795)	352 (44.3)			
Tumor size				
≤10 mm (n = 578)	229 (39.6)	0.0001	1.65 (1.29 to 2.11)	0.99
11–20 mm (n = 469)	244 (52.0)			
Multifocality[b]				
Yes (n = 400)	210 (52.5)	<0.0001	1.61 (1.26 to 2.07)	0.99
No (n = 647)	263 (40.6)			
Presence of tumor capsule				
Yes (n = 324)	94 (29.0)	<0.0001	2.70 (2.04 to 3.57)	0.99
No (n = 723)	379 (52.4)			
Extrathyroidal extension/pT				
Yes/pT3 (n = 311)	210 (67.5)	<0.0001	3.74 (2.82 to 4.95)	0.99
No/pT1 (n = 736)	263 (40.6)			
Lymph node metastasis				
Yes (n = 186)	127 (68.3)	<0.0001	3.20 (2.29 to 4.49)	0.99
No (n = 861)	346 (40.2)			
AJCC stages[a]				
I (n = 905)	376 (41.5)	<0.0001	3.38 (2.28 to 5.00)	0.99
II/IV (n = 142)	96 (67.6)			

CI, Confidence interval.

[a] In six cases, age at diagnosis was unknown.

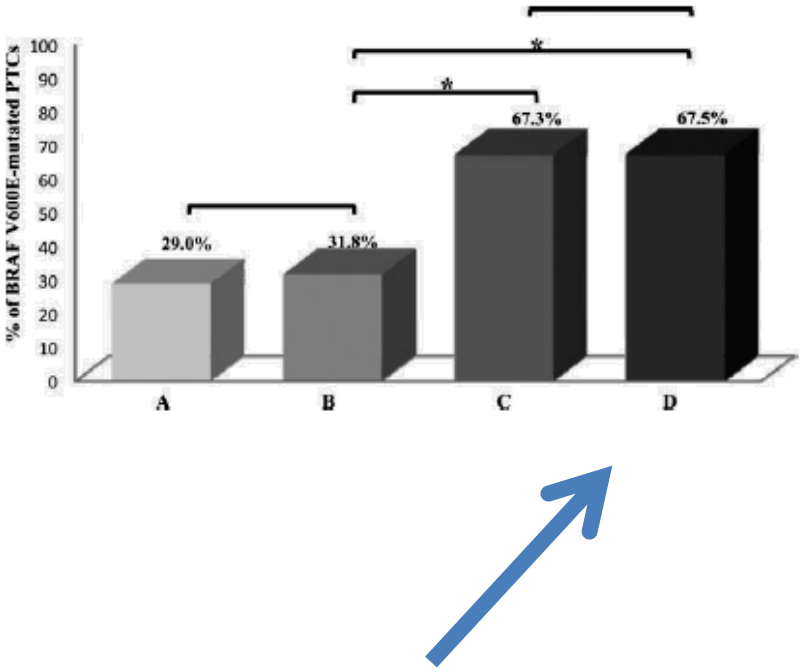
[b] The neoplasm with the greatest size or the highest pT status has always been analyzed in the presence of multifocality.

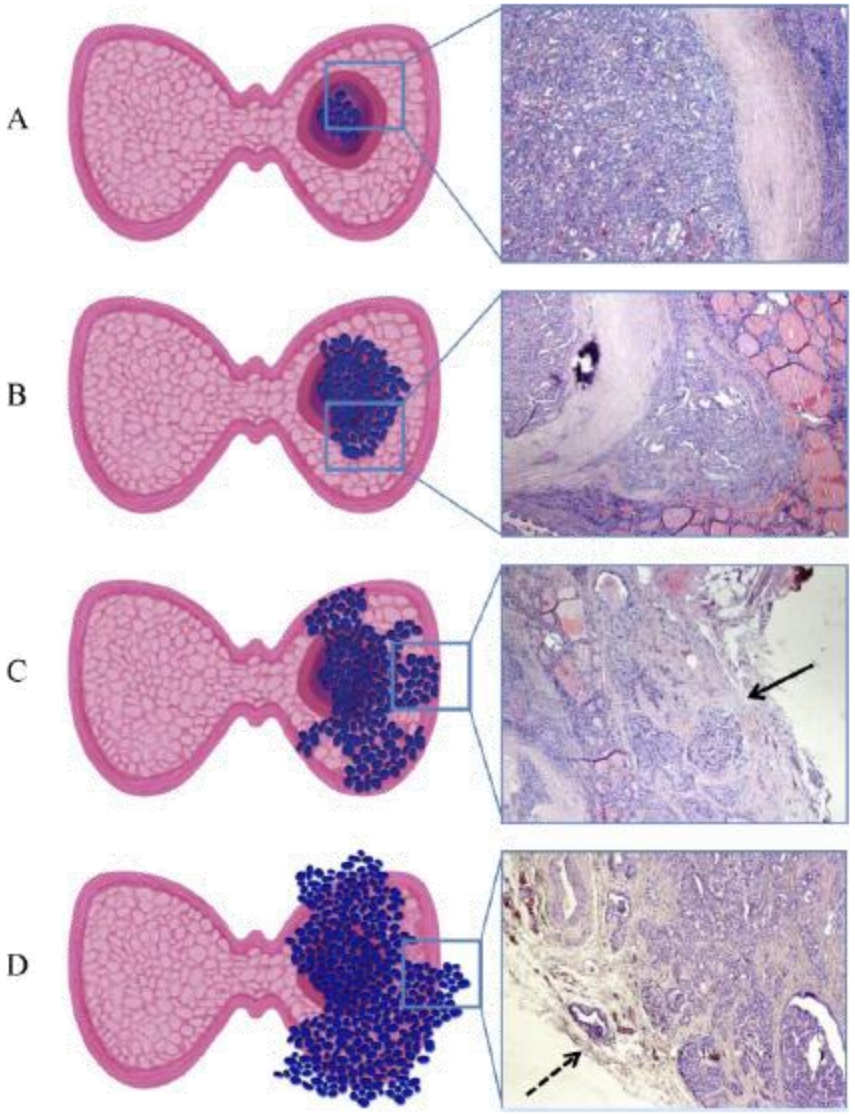
Correlation between the *BRAF* V600E Mutation and Tumor Invasiveness in Papillary Thyroid Carcinomas Smaller than 20 Millimeters: Analysis of 1060 Cases

Fulvio Basolo, Liborio Torregrossa, Riccardo Giannini, Mario Miccoli, Cristiana Lupi, Elisa Sensi, Piero Berti, Rossella Elisei, Paolo Vitti, Angelo Baggiani, and Paolo Miccoli

Departments of Surgery (F.B., L.T., R.G., C.L., E.S., P.B., P.M.), Experimental Pathology B.M.I.E., Biostatistics Research Unit (M.M., A.B.), and Endocrinology (R.E., P.V.), University of Pisa, 56126 Pisa, Italy

J Clin Endocrinol Metab, September 2010, 95(9):4197–4205



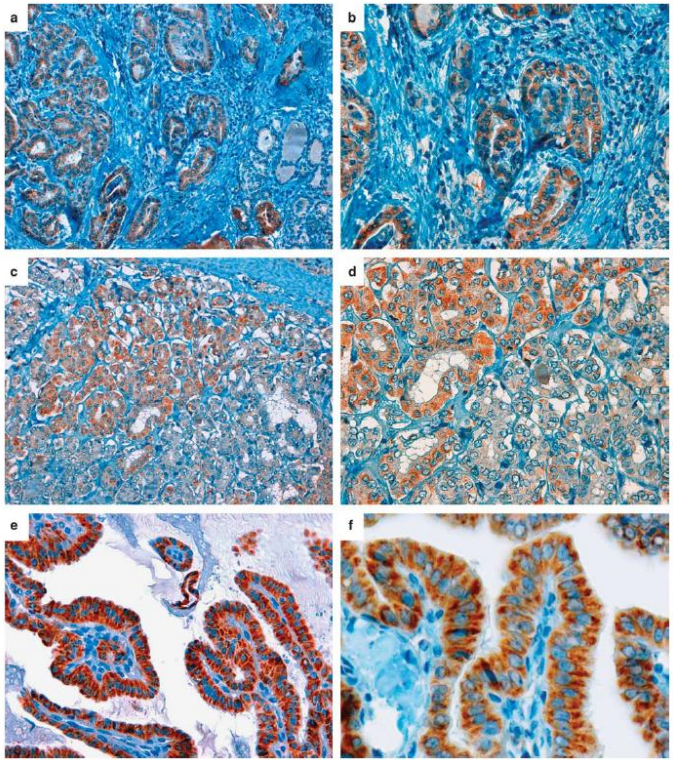


MODERN PATHOLOGY (2011), 1–10

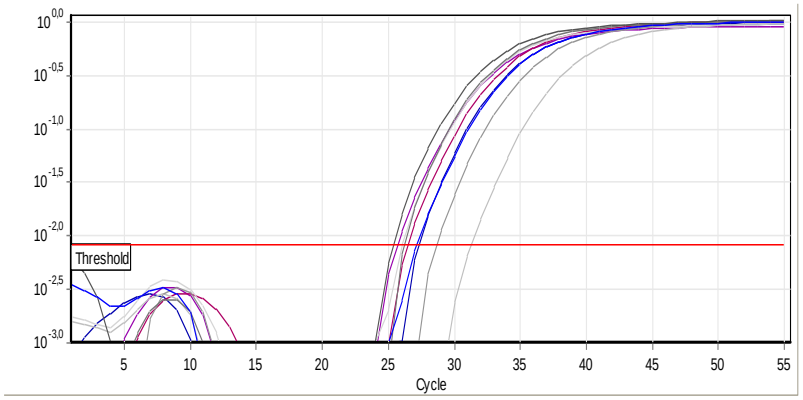
CXCR4 expression correlates with the degree of tumor infiltration and *BRAF* status in papillary thyroid carcinomas

Liborio Torregrossa[1,4], Riccardo Giannini[1,4], Nicla Borrelli[1], Elisa Sensi[1], Rosa Marina Melillo[2], Pietro Leocata[3], Gabriele Materazzi[1], Paolo Miccoli[1], Massimo Santoro[2] and Fulvio Basolo[1]

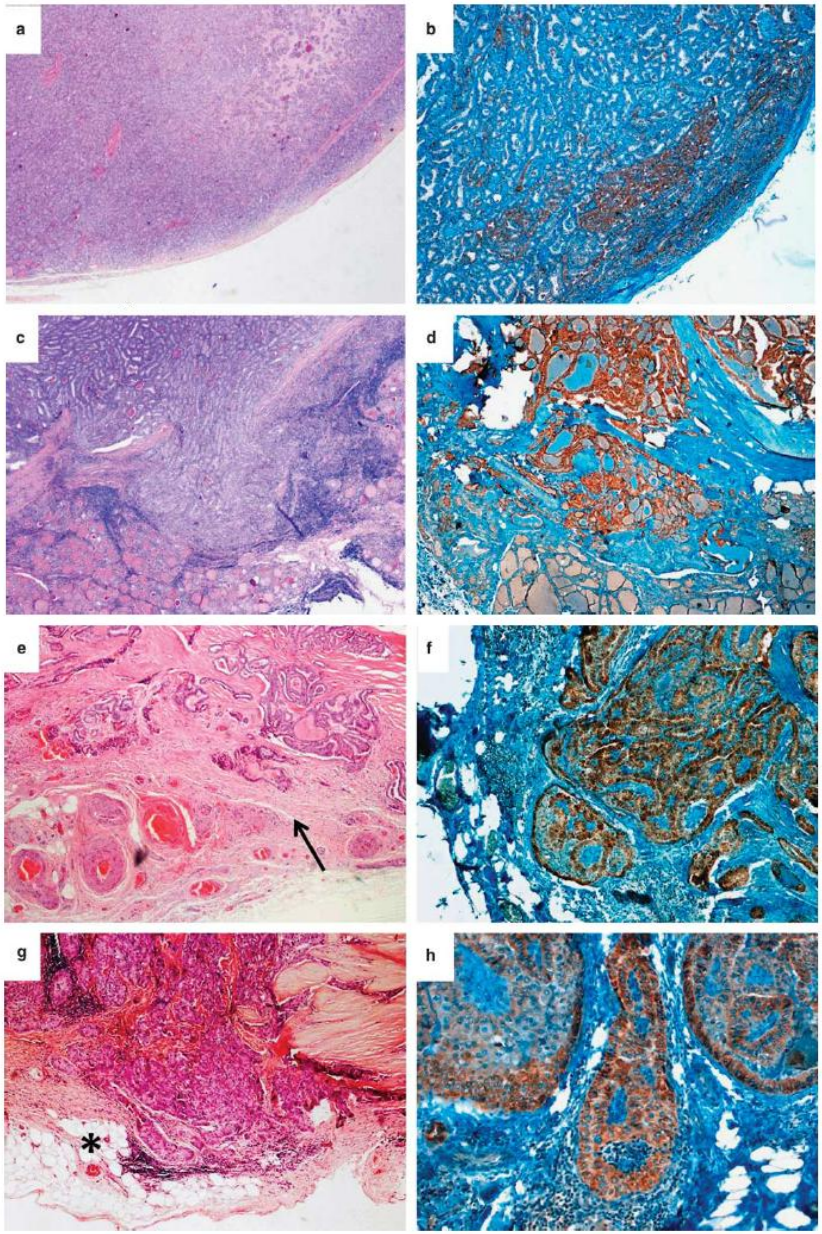
[1]*Dipartimento di Chirurgia, Università di Pisa, Pisa, Italy;* [2]*Dipartimento di Biologia e Patologia Cellulare e Molecolare, Università di Napoli Federico II, Napoli, Italy and* [3]*Dipartimento di Scienze della Salute, Università dell'Aquila, L'Aquila, Italy*



CXCR4 expression was evaluated by immunohistochemical staining and semi quantitative real time RT-PCR together with BRAF mutational status in a consecutive series of 200 papillary thyroid carcinomas.



Modern Pathology (2011), 1–10



CXCR4 expression correlates with the degree of tumor infiltration and *BRAF* status in papillary thyroid carcinomas

Liborio Torregrossa[1,4], Riccardo Giannini[1,4], Nicla Borrelli[1], Elisa Sensi[1], Rosa Marina Melillo[2], Pietro Leocata[3], Gabriele Materazzi[1], Paolo Miccoli[1], Massimo Santoro[2] and Fulvio Basolo[1]

[1]*Dipartimento di Chirurgia, Università di Pisa, Pisa, Italy;* [2]*Dipartimento di Biologia e Patologia Cellulare e Molecolare, Università di Napoli Federico II, Napoli, Italy and* [3]*Dipartimento di Scienze della Salute, Università dell'Aquila, L'Aquila, Italy*

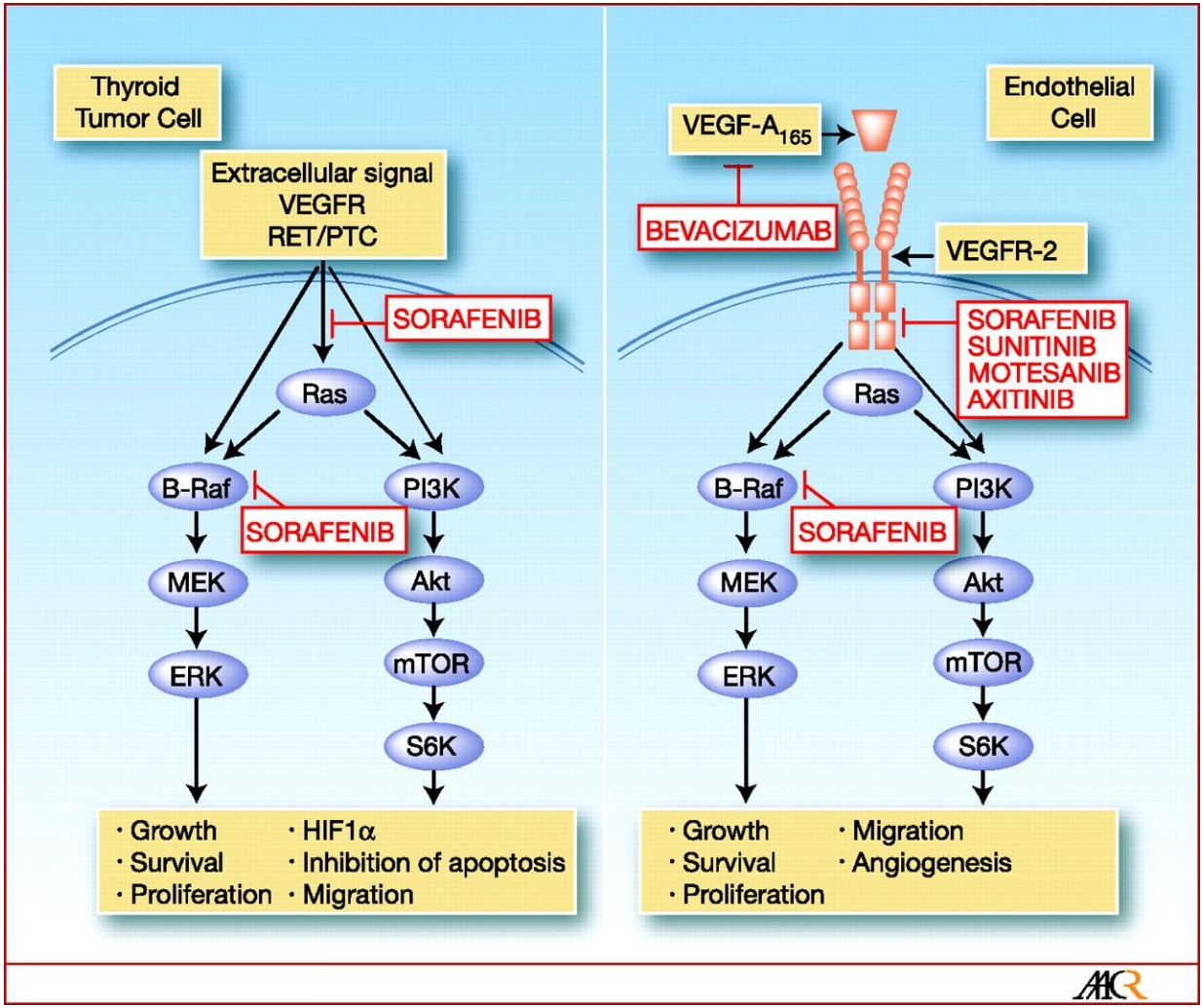
Clinical–pathological features	*CXCR4 FSS (P value)*	*CXCR4 z score (P value)*
PTC variants	0.0181	NS
Lymph node metastasis	0.0310	[a]
Degree of neoplastic infiltration	0.0015	0.0173
AJCC stages	NS	[a]
Lymphocytic thyroiditis	NS	NS
BRAF status	0.0000	0.0002

Abbreviations: AJCC, American Joint Commission on Cancer; FSS, final staining score; NS, not significant; PTC, papillary thyroid carcinoma.

[a]Not significant in univariate analysis.

CXCR4 expression and BRAF mutation status could cooperatively induce and promote a more aggressive phenotype in papillary thyroid carcinoma via several pathways and specifically increase the tumors' spread outside of the thyroid gland.

UNCONVENTIONAL THERAPY
(tailored drugs)



In thyroid cancer drugs such as bevacizumab, sorafenib , sunitinib, axitinib , and motesanib (MOT) have activity **<u>as single agents.</u>**

BRAF Is a Therapeutic Target in Aggressive Thyroid Carcinoma

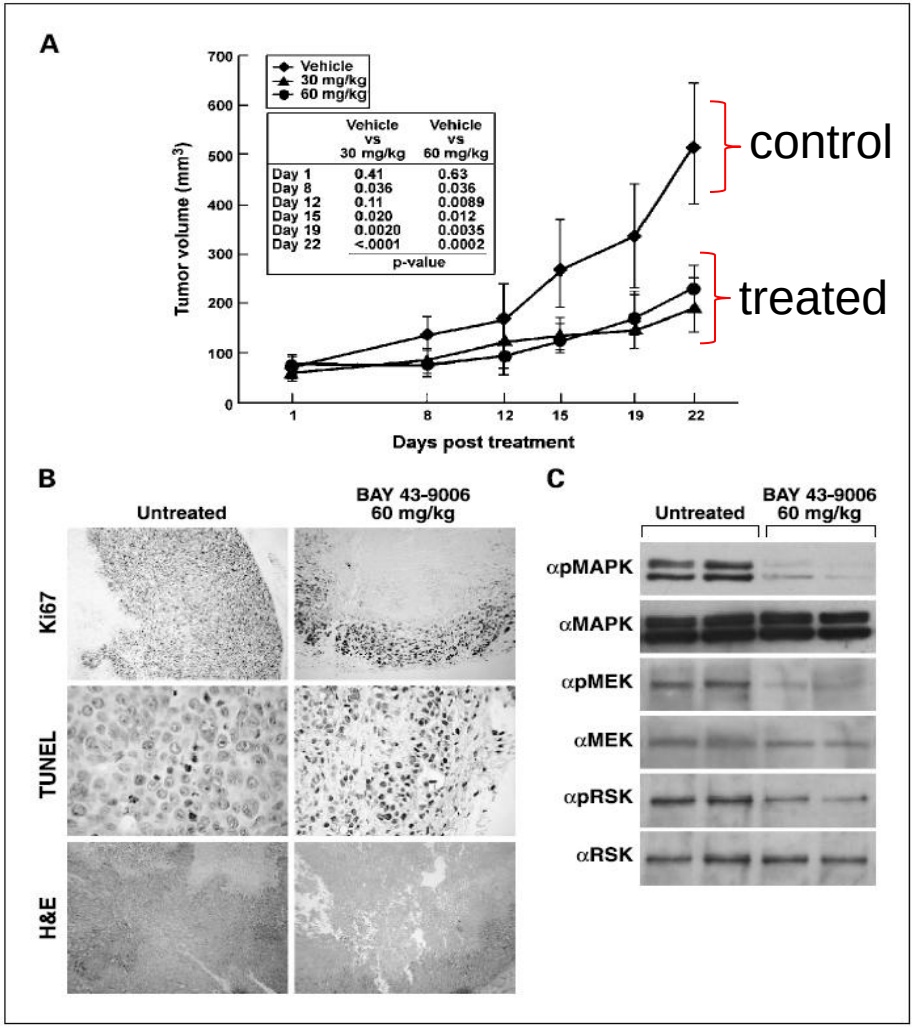
Giuliana Salvatore,[1] Valentina De Falco,[1] Paolo Salerno,[1] Tito Claudio Nappi,[1] Stefano Pepe,[2] Giancarlo Troncone,[3] Francesca Carlomagno,[1] Rosa Marina Melillo,[1] Scott M. Wilhelm,[4] and Massimo Santoro[1]

Clin Cancer Res 2006

2006

Antitumorigenic effects of

BAY 43-9006 (Sorafenib)



BRAF mutation-selective inhibition of thyroid cancer cells by the novel MEK inhibitor RDEA119 and genetic-potentiated synergism with the mTOR inhibitor temsirolimus

Dingxie Liu[1], Joanna Xing[2], Barry Trink[2] and Mingzhao Xing[1]

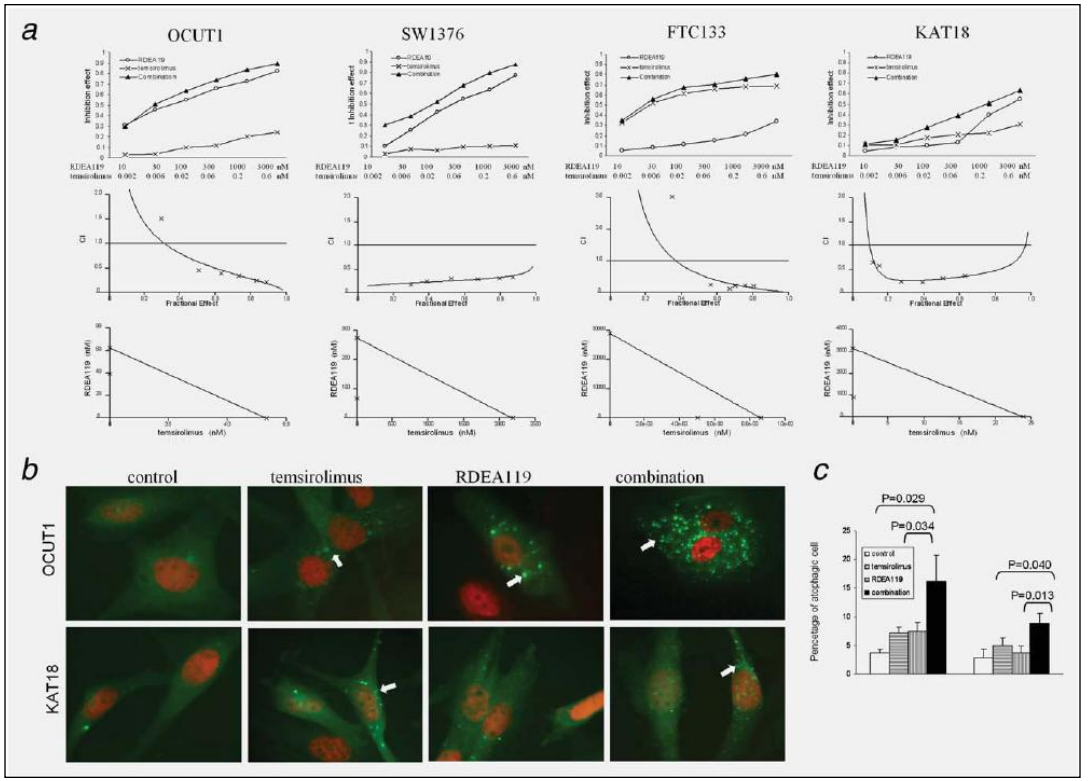
[1] Laboratory for Cellular and Molecular Thyroid Research, Division of Endocrinology and Metabolism, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD

[2] Division of Head and Neck Cancer Research, Department of Otolaryngology and Head & Neck Surgery, The Johns Hopkins University School of Medicine, Baltimore. MD

Int. J. Cancer: **127**, 2965–2973 (2010)

RDEA119 and temsirolimus

synergistically inhibited cell proliferation and induced cell autophagy in thyroid cancer cells.



Proteomic and metabolomic analysis

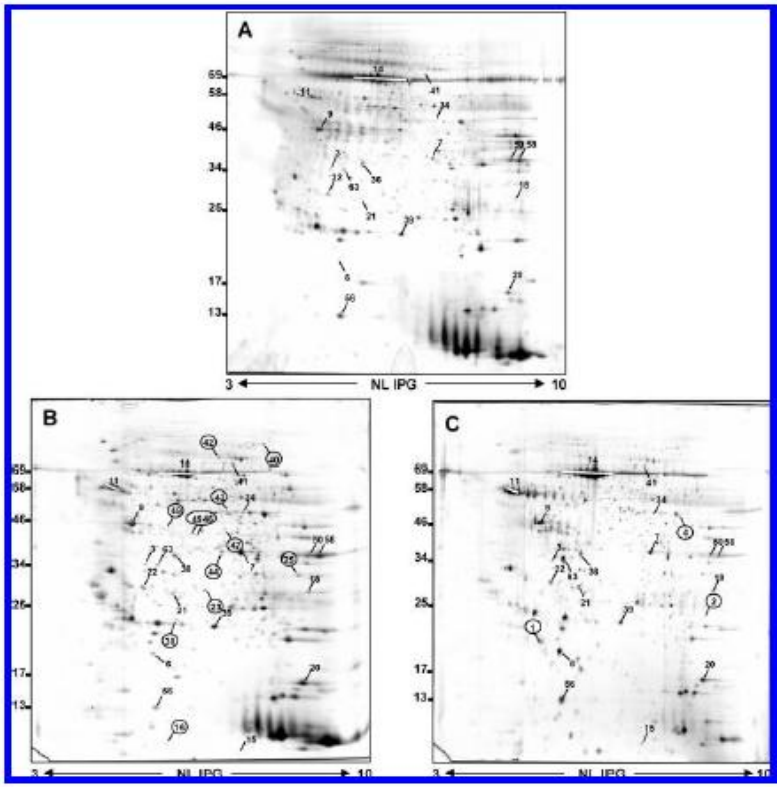
Proteomic

Fine-Needle Aspiration of Thyroid Nodules: Proteomic Analysis To Identify Cancer Biomarkers

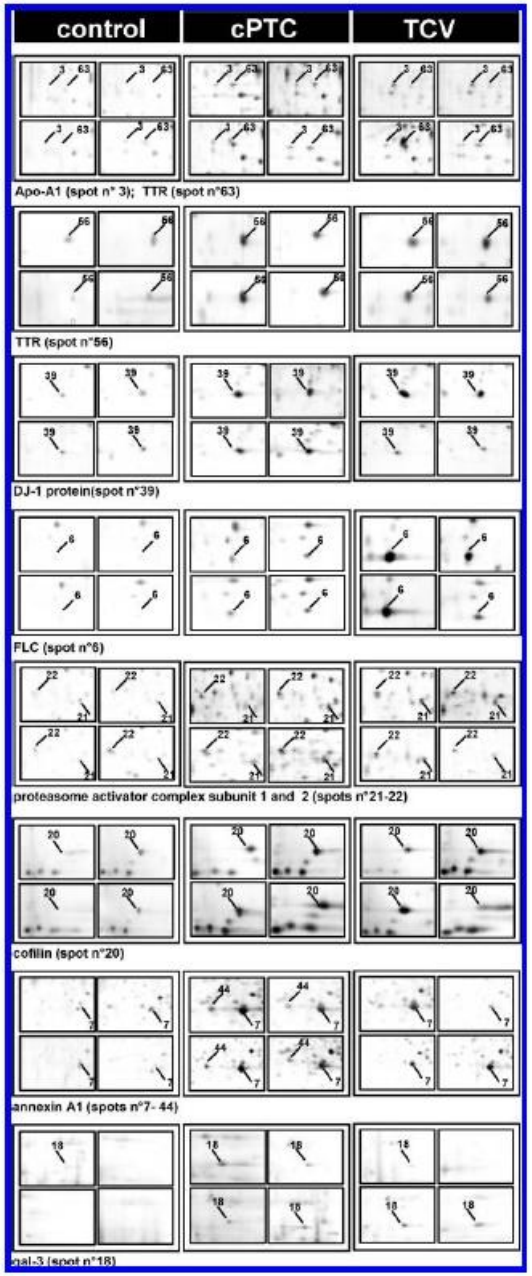
Laura Giusti,[#] Pietro Iacconi,[§] Federica Ciregia,[#] Gino Giannaccini,[#] Gian Luca Donatini,[§] Fulvio Basolo,[§] Paolo Miccoli,[§] Aldo Pinchera,[†] and Antonio Lucacchini*[,#]

Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, Department of Surgery, Department of Endocrinology and Metabolism, Environment and Endocrine and Nervous Systems High Technology Center for the Study of the Effects of Harmful Agents, University of Pisa, Pisa, Italy

Journal of Proteome Research *2008, 7, 4079–4088* **4079**
Published on Web 07/30/2008

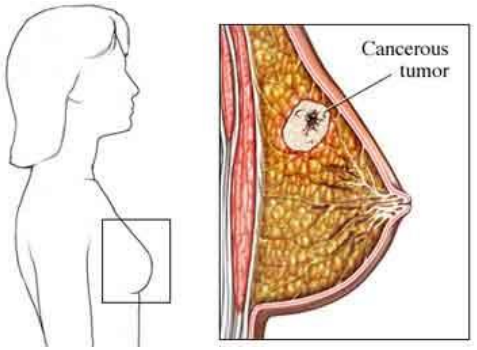


A B C



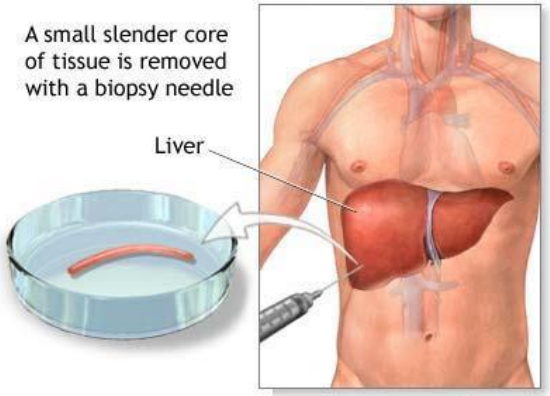
METABOLOMICS IN CANCER

Previous studies have demonstrated that metabolomic analysis can distinguish between cancer and non-cancer tissues



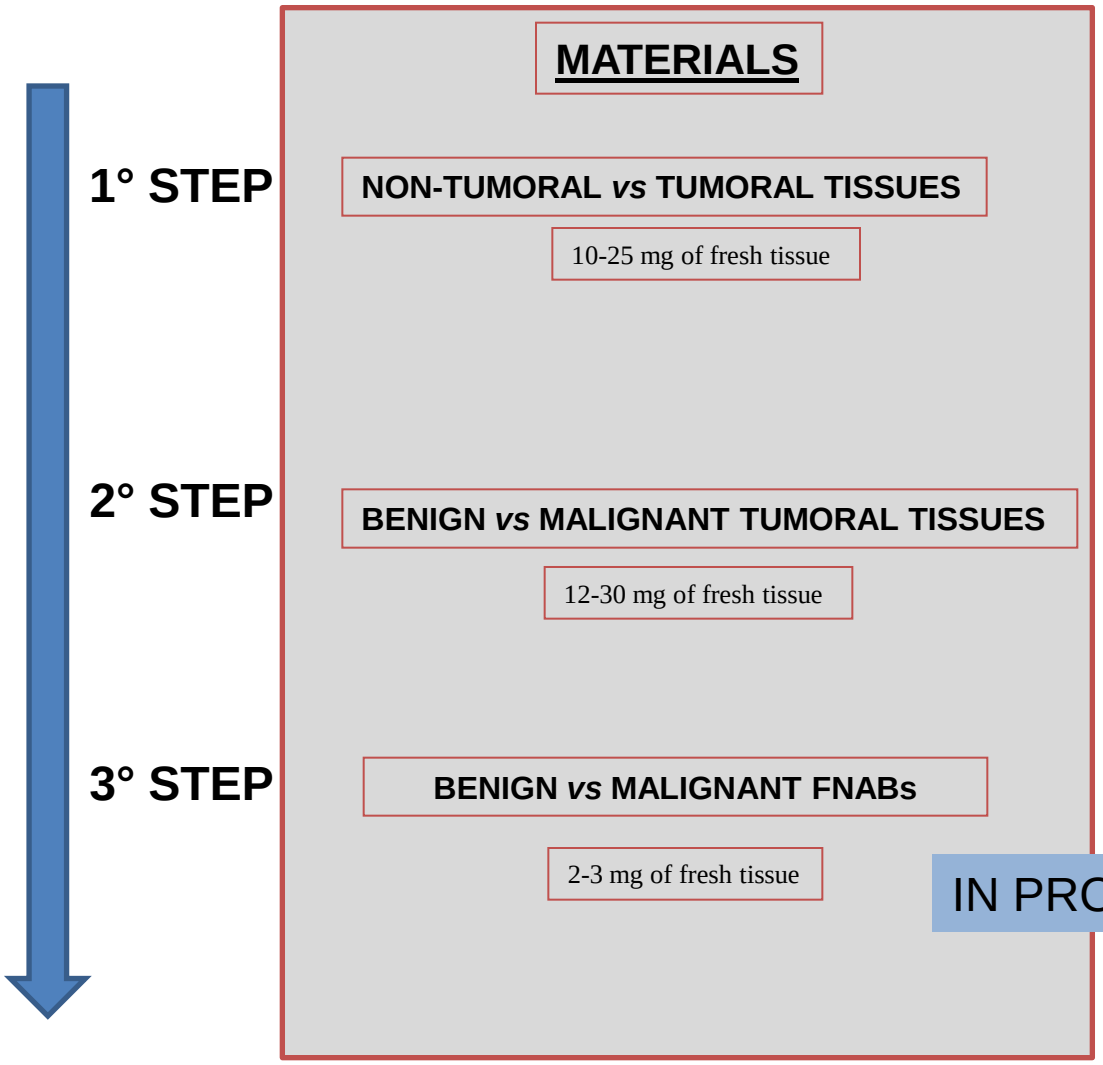
breast

prostate



liver

METABOLOMICS IN THYROID CANCER



METHODS

HRMAS NMR

(high resolution magic angle spinning nuclear magnetic resonance)

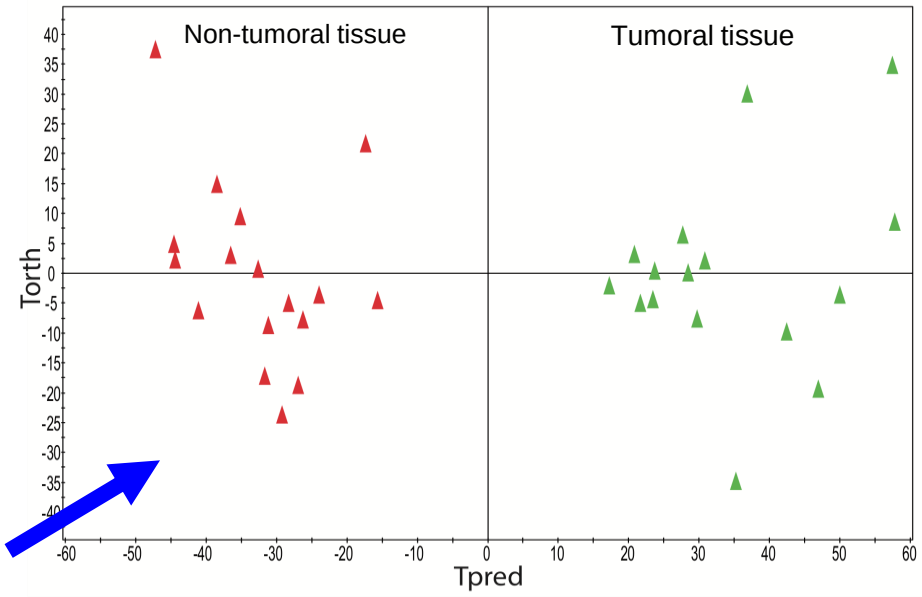
1° STEP

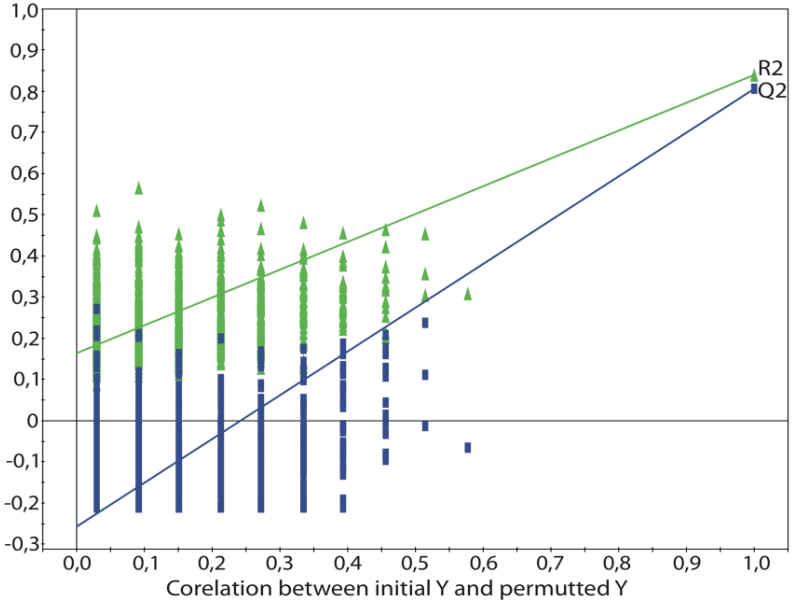
PRELIMINARY DATA

NON-TUMORAL *vs* TUMORAL TISSUES

Methods: **34 samples** were analysed by HRMAS NMR (between 10-25 mg of fresh tissue) (high resolution magic angle spining nuclear magnetic resonance). An OPLS Discriminant Analysis (OPLSDA) was performed on the correlation matrix.

Results: A 1 predictive+1orthogonal OPLSDA component model with Q^2 = 0.80 enabled us to clearly **discriminate all tumors from the non-tumoral tissues** as shown on the OPLS score plot.





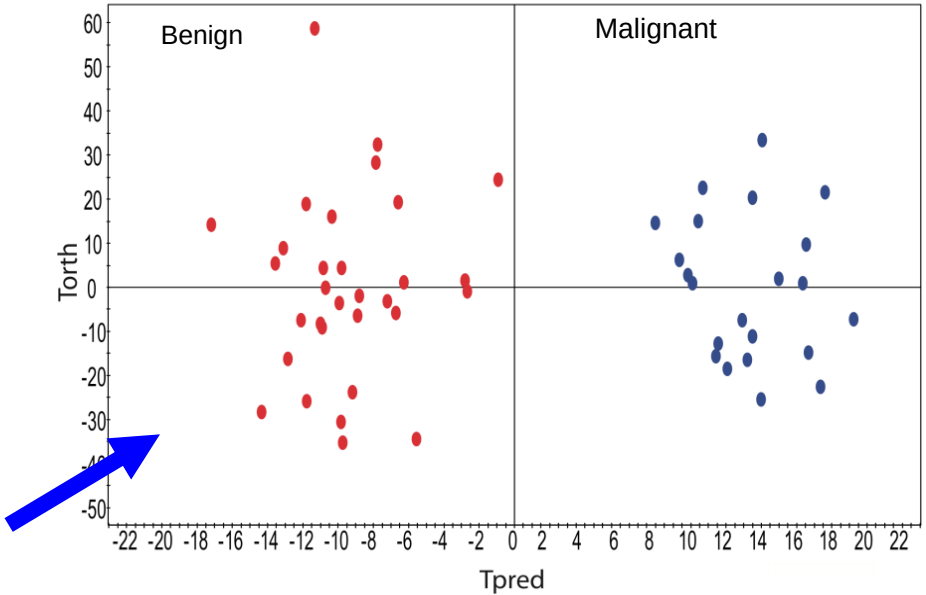
2° STEP

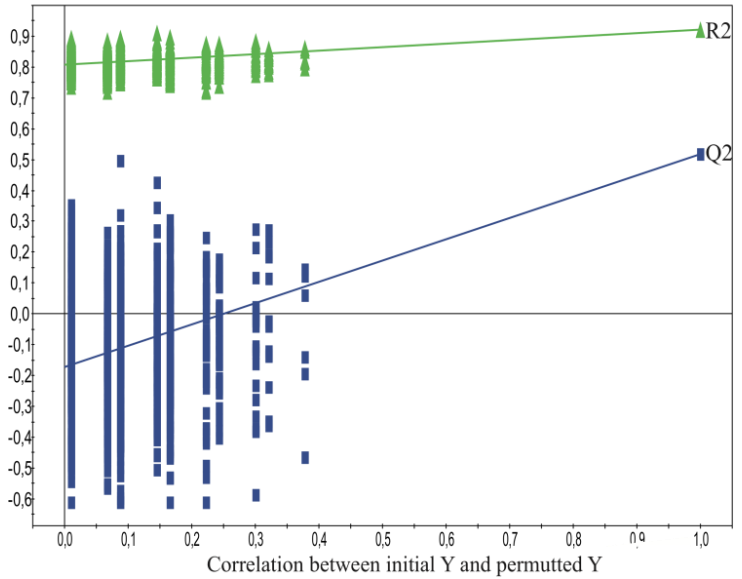
PRELIMINARY DATA

BENIGN vs MALIGNANT TUMORAL TISSUES

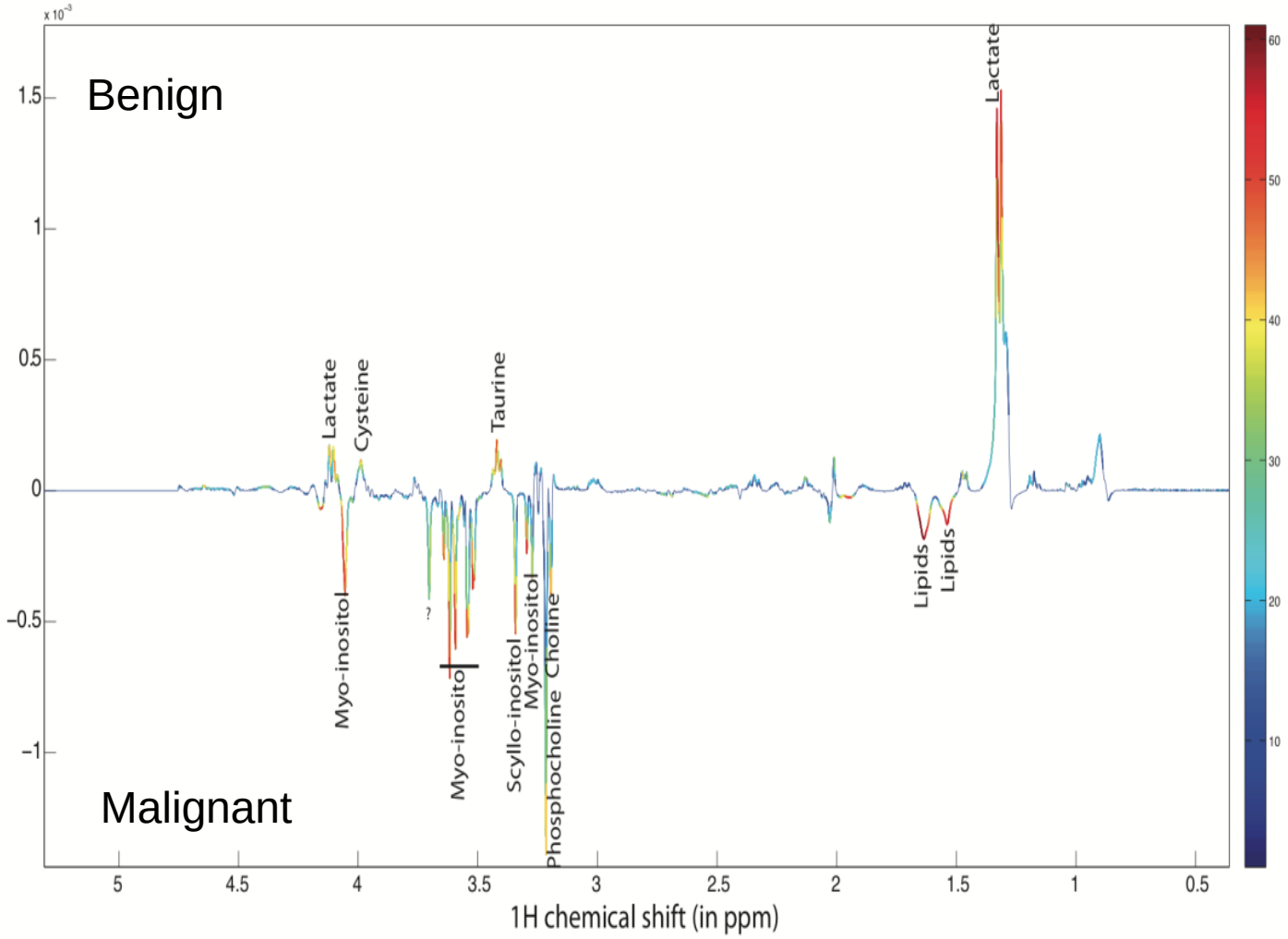
Methods: **52 samples** from 2 different batches (16+36 biopsies) were analysed by HRMAS NMR.

Results: A 1 predictive + 4 orthogonal OPLSDA component model with Q^2 =0.61 enabled us to **clearly discriminate all the benign from the malignant tumors** as shown on the OPLS score plot.





Very specific profile of methabolites



OncoCarta™ v1.0	235 Mutations in 19 Genes
OncoCarta™ v2.0	152 Mutations in 18 Genes
OncoCarta™ v3.0	157 Mutations in 26 Genes
MelaCarta™ v1.0	72 Mutations in 20 Genes

535 Mutations in 51 Oncogenes & Tumor Suppressor Genes

For lung, colon, skin, breast

THYROIDCARTA???????

METABOLICARTA???????

CONCLUSIONS

- BRAF IMPORTANCE:

Prognostic

Diagnostic - associated with other IHC or molecular markers

- NEW OPPORTUNITIES

Metabolomic analysis

THANK YOU