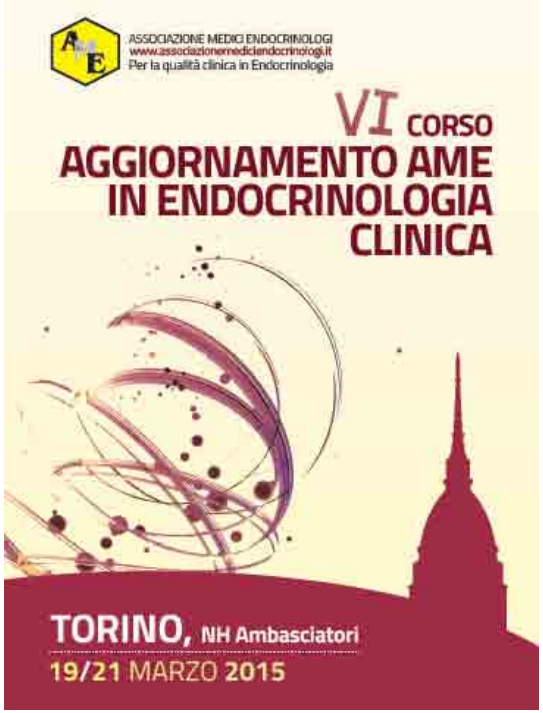

Marcatori genetici in oncologia tiroidea: un' esperienza già consolidata

Simonetta Piana
Anatomia Patologica
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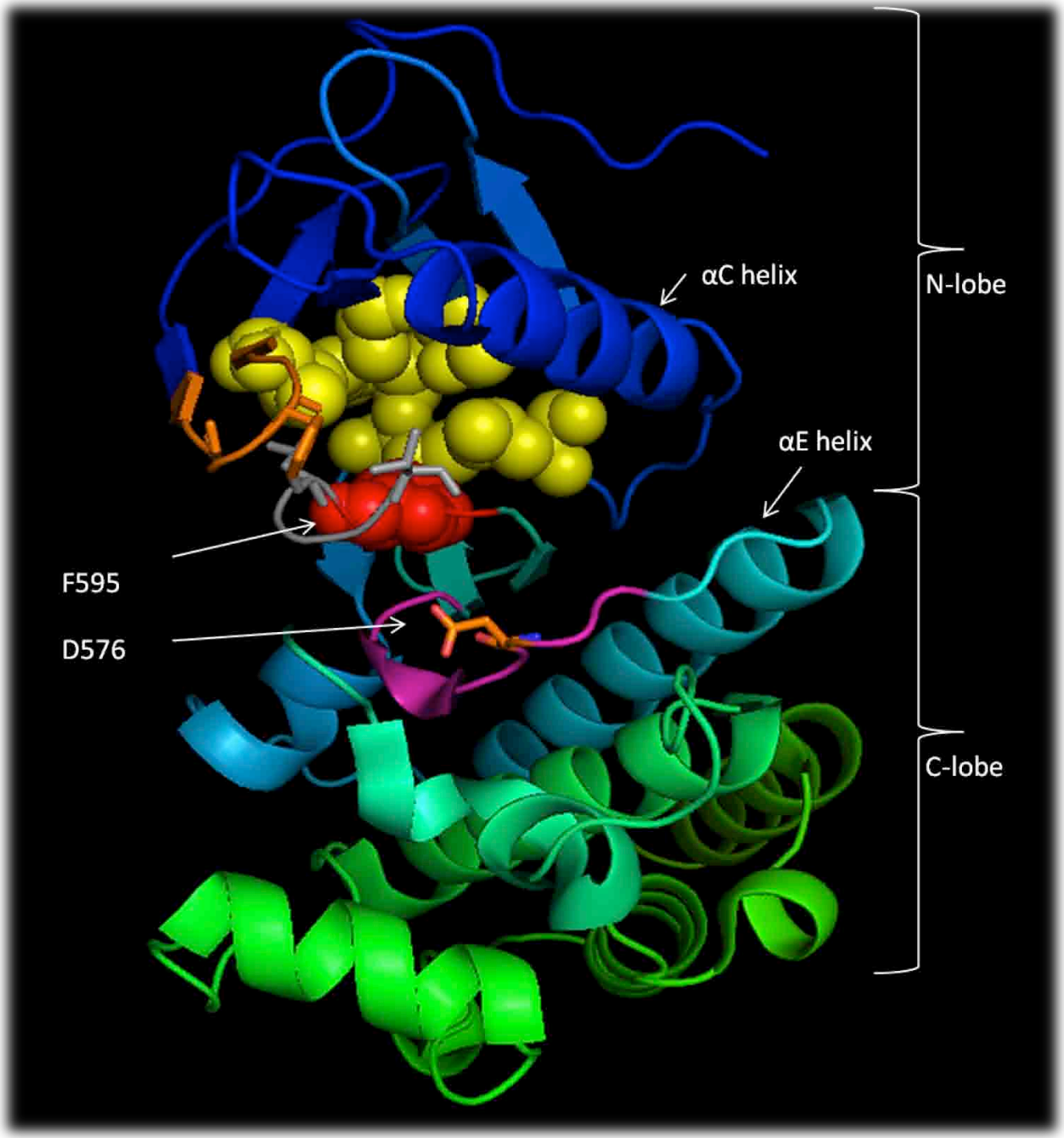
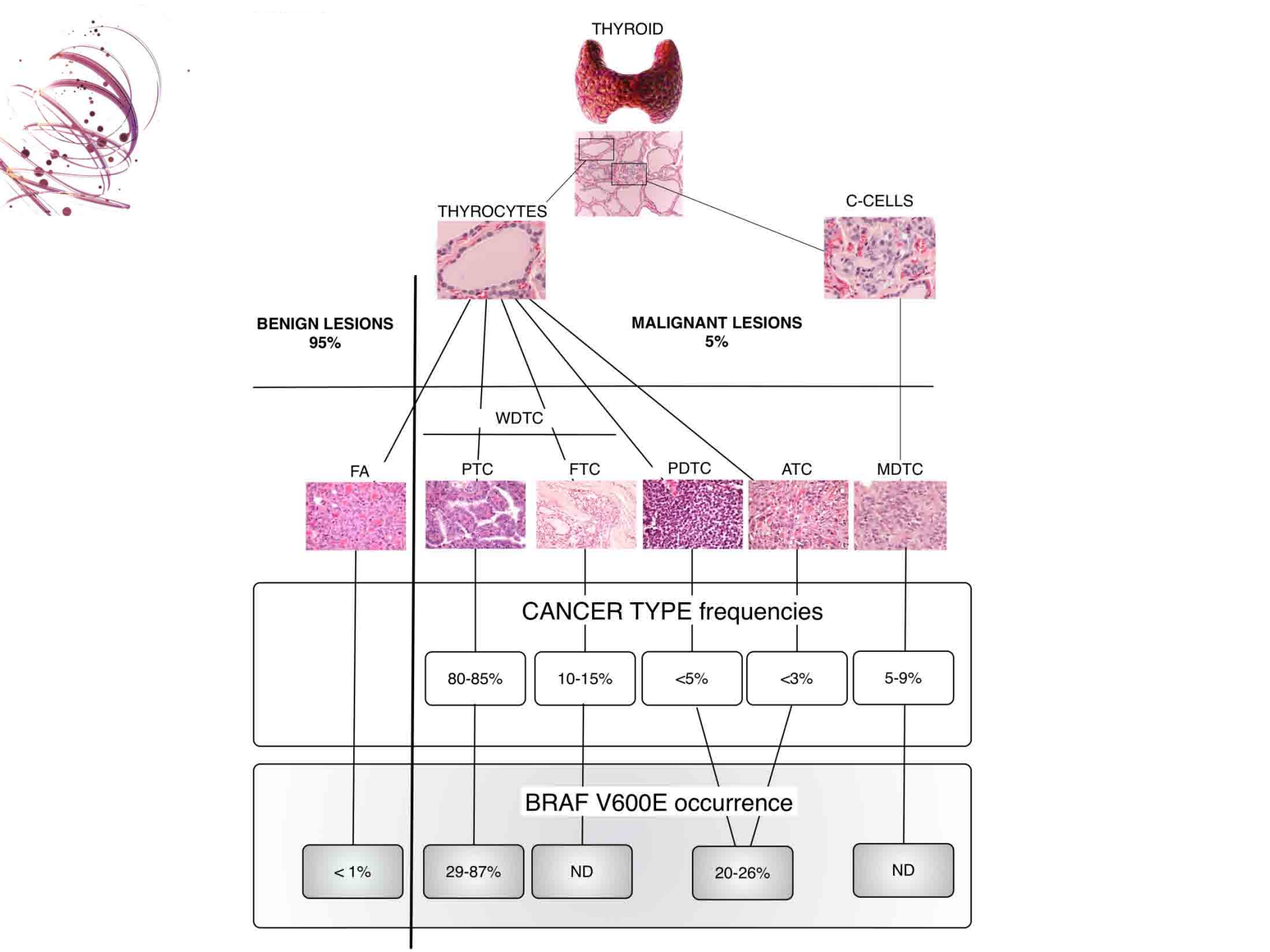
BRAF

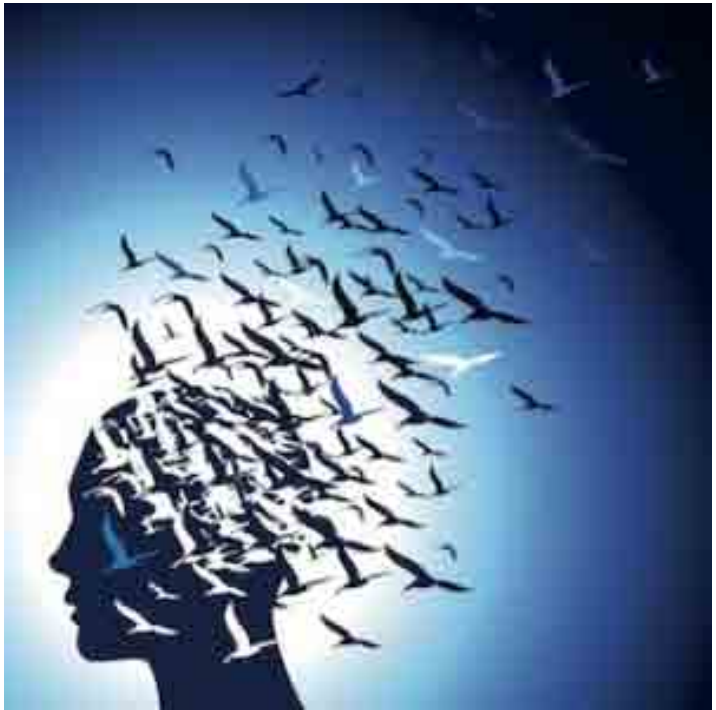
RAS


αC helix
αE helix
F595
D576
N-lobe
C-lobe


THYROID
THYROCYTES
C-CELLS
BENIGN LESIONS
95%
MALIGNANT LESIONS
5%
WDTC
FA
PTC
FTC
PDTC
ATC
MDTC
CANCER TYPE frequencies
80-85%
10-15%
<5%
<3%
5-9%
BRAF V600E occurrence
< 1%
29-87%
ND
20-26%
ND

Decine di papers su BRAF….

con risultati spesso contradditori



Association Between *BRAF* V600E Mutation and Mortality in Patients With Papillary Thyroid Cancer

Mingzhao Xing, MD, PhD
Ali S. Alzahrani, MD
Kathryn A. Carson, ScM
David Viola, MD
Rossella Elisei, MD
Bela Bendlova, PhD
Linwah Yip, MD
Caterina Mian, MD
Federica Vianello, MD
R. Michael Tuttle, MD
Enid Rabinowitz, MD
James A. Fagin, MD
Efisio Puxeddu, MD, PhD
Laura Fugazzola, MD
Agnieszka Czarniecka, MD
Barbara Jarzab, MD, PhD
Christine J. O'Neill, MBBS(Hons), MS
Mark S. Sywak, MD
Alfred K. Lam, MD, PhD
Gerardino Bruno Vetrugno, MD, PhD
Pilar Santisteban, PhD
Hirotaka Nakayama, MD
Ralph P. Tufano, MD
Save U. Pai, M.D, PhD
Martha A. Zeiger, MD
William H. Westra, MD
Douglas P. Clark, MD
Roderick Clifton-Bligh, PhD
David Sidransky, MD
Paul W. Ladenson, MD
Vlasta Sykorova, PhD

Importance *BRAF* V600E is a prominent oncogene in papillary thyroid cancer (PTC), but its role in PTC-related patient mortality has not been established.

Objective To investigate the relationship between *BRAF* V600E mutation and PTC-related mortality.

Design, Setting, and Participants Retrospective study of 1849 patients (1411 women and 438 men) with a median age of 46 years (interquartile range, 34-58 years) and an overall median follow-up time of 33 months (interquartile range, 13-67 months) after initial treatment at 13 centers in 7 countries between 1978 and 2011.

Main Outcomes and Measures Patient deaths specifically caused by PTC.

Results Overall, mortality was 5.3% (45/845; 95% CI, 3.9%-7.1%) vs 1.1% (11/1004; 95% CI, 0.5%-2.0%) ($P<.001$) in *BRAF* V600E–positive vs mutation-negative patients. Deaths per 1000 person-years in the analysis of all PTC were 12.87 (95% CI, 9.61-17.24) vs 2.52 (95% CI, 1.40-4.55) in *BRAF* V600E–positive vs mutation-negative patients; the hazard ratio (HR) was 2.66 (95% CI, 1.30-5.43) after adjustment for age at diagnosis, sex, and medical center. Deaths per 1000 person-years in the analysis of the conventional variant of PTC were 11.80 (95% CI, 8.39-16.60) vs 2.25 (95% CI, 1.01-5.00) in *BRAF* V600E–positive vs mutation-negative patients; the adjusted HR was 3.53 (95% CI, 1.25-9.98). When lymph node metastasis, extrathyroidal invasion, and distant metastasis were also included in the model, the association of *BRAF* V600E with mortality for all PTC was no longer significant (HR, 1.21; 95% CI, 0.53-2.76). A higher *BRAF* V600E–associated patient mortality was also observed in several clinicopathological subcategories, but statistical significance was lost with adjustment for patient age, sex, and medical center. For example, in patients with lymph node metastasis, the deaths per 1000 person-years were 26.26 (95% CI, 19.18-36.94) vs 5.93 (95% CI, 2.96-11.86) in *BRAF* V600E–positive vs mutation-negative patients (unadjusted HR, 4.43 [95% CI, 2.06-9.51]; adjusted HR, 1.46 [95% CI, 0.62-3.47]). In patients with distant tumor metastasis, deaths per 1000 person-years were 87.72 (95% CI, 62.68-122.77) vs 32.28 (95% CI, 16.14-64.56) in *BRAF* V600E–positive vs mutation-negative patients (unadjusted HR, 2.63 [95% CI, 1.21-5.72]; adjusted HR, 0.84 [95% CI, 0.27-2.62]).

Conclusions and Relevance In this retrospective multicenter study, the presence of the *BRAF* V600E mutation was significantly associated with increased cancer-related mortality among patients with PTC. Because overall mortality in PTC is low and the association was not independent of tumor features, how to use *BRAF* V600E to manage mortality risk in patients with PTC is unclear. These findings support further investigation of the prognostic and therapeutic implications of *BRAF* V600E status in PTC.

JAMA. 2013;309(14):1493-1501 www.jama.com

PAPILLARY THYROID CANCER (PTC) is the most common endocrine malignancy and accounts for 80% to 90% of all thyroid cancers.[1,2] There are several variants of PTC, the majority of which are conventional PTC and follicular variant PTC, with the former typically showing papillary structures and the latter follicular structures in addition to the characteristic nuclear features of PTC. The overall 5-year patient survival rate for PTC is 93% to 97%.[3] A major clinical challenge is how to reliably distinguish patients who need aggressive treatment to reduce mortality from those who do not. This represents a widely controversial issue in thyroid cancer medicine, particularly because of the low overall mortality of this cancer. The issue has become even more challenging given the high annual incidence of PTC.[1,4] Several clinicopathological risk factors have been

See also pp 1529 and 1533.

Author Affiliations: [illegible] **Corresponding Author:** Michael Mingzhao Xing, MD, PhD, Division of Endocrinology and Metabolism, Johns Hopkins University School of Medicine, 1830 E Monument St, Ste 333, Baltimore, MD 21287 (mxing1@jhmi.edu).

Design, Setting, and Participants Retrospective study of 1849 patients (1411 women and 438 men) with a median age of 46 years (interquartile range, 34-58 years) and an overall median follow-up time of 33 months (interquartile range, 13-67 months) after initial treatment at 13 centers in 7 countries between 1978 and 2011.

Conclusions and Relevance In this retrospective multicenter study, the presence of the *BRAF* V600E mutation was significantly associated with increased cancer-related mortality among patients with PTC. Because overall mortality in PTC is low and the association was not independent of tumor features, how to use *BRAF* V600E to manage mortality risk in patients with PTC is unclear. These findings support further investigation of the prognostic and therapeutic implications of *BRAF* V600E status in PTC.

JAMA. 2013;309(14):1493-1501 www.jama.com

When the aggressive tumor features of LNM, extrathyroidal invasion, and distant metastasis were also included in the model, the association of *BRAF* V600E with mortality was no longer statistically significant (for all PTC, HR, 1.21 [95% CI, 0.53-2.76]; for conventional PTC, HR, 1.51 [95% CI, 0.50-4.57]).

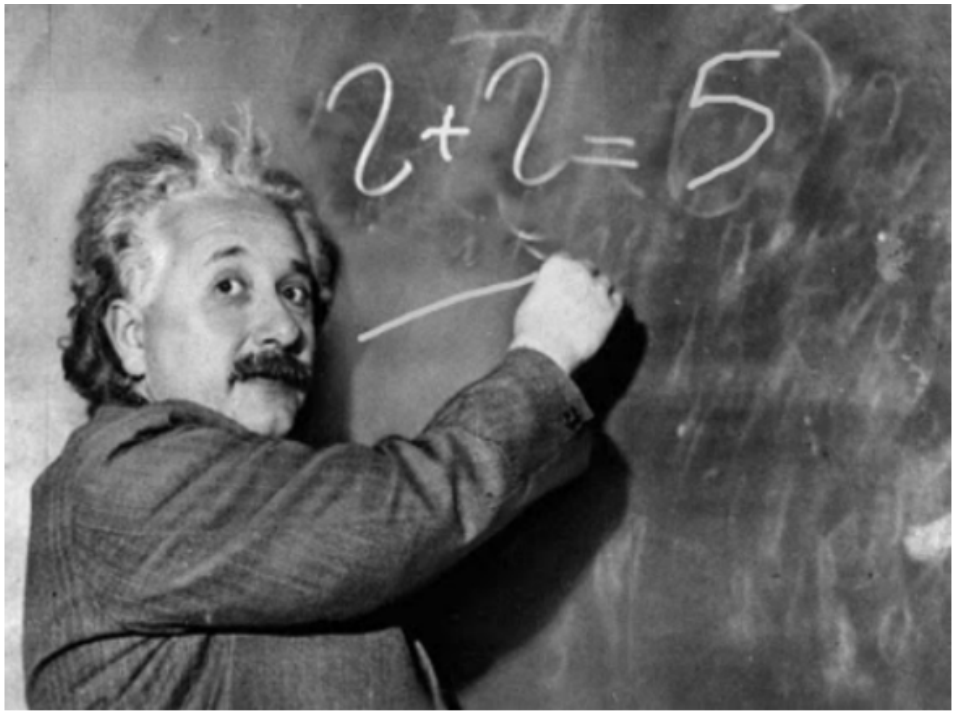
Virchows Arch (2014) 464:333–346
DOI 10.1007/s00428-013-1521-2

INVITED REVIEW

Prognostic biomarkers in thyroid cancer

Paula Soares · Ricardo Celestino · Miguel Melo ·
Elsa Fonseca · Manuel Sobrinho-Simões

The use of *BRAF* mutation per se for PTC prognosis remains controversial mainly due to the fact that *BRAF* V600E mutation is found in about half of PTCs [46], from which less than 10–15 % of the tumours will display aggressive behaviour



Staging is considered the most important prognostic factor in thyroid cancer as in other human cancer models.

CANCER

Small papillary thyroid cancers —is *BRAF* of prognostic value?

Paula Soares and Manuel Sobrinho-Simões

The growing incidence in thyroid cancer results mainly from the detection of small or very small papillary thyroid carcinomas. The management of patients with such small tumors represents a major clinical challenge. Could evaluation of the *BRAF* status of such tumors aid risk stratification and patient management?

Soares, P. & Sobrinho-Simões, M. *Nat. Rev. Endocrinol.* 7, 9–10 (2011); doi:10.1038/nrendo.2010.213

We concur with Basolo *et al.* that the correlation between *BRAF* status and clinicopathological parameters in microPTC remains controversial, but we think one cannot clarify the controversy without integrating histotype together with tumor invasiveness. Furthermore, we think the excellent prognosis of microPTC means that it is unrealistic to suggest, as it has recently been advanced, that patients with *BRAF*-mutated microPTC should be treated more aggressively merely on the basis of *BRAF* status.

Cancer Medicine

Open Access

ORIGINAL RESEARCH

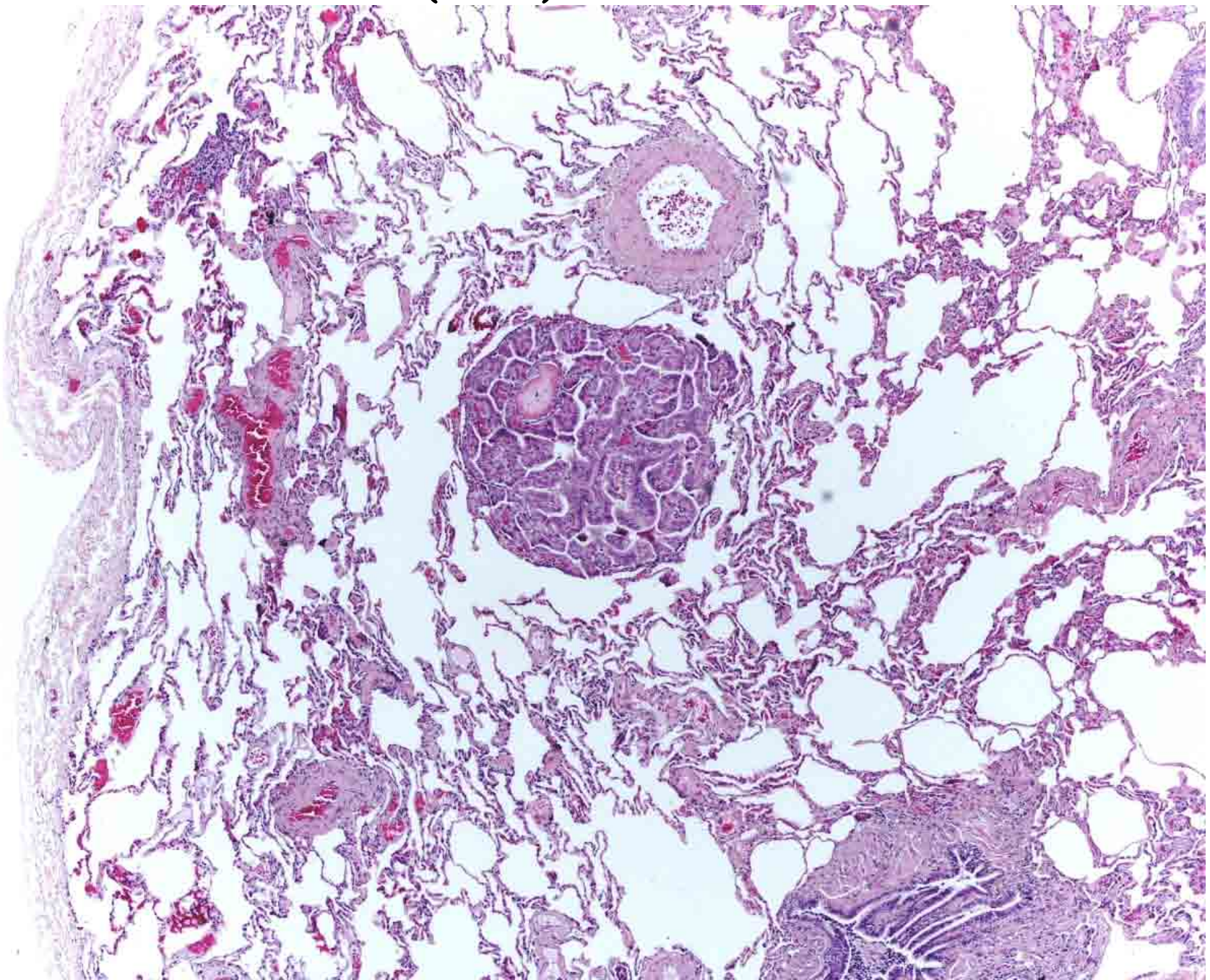
BRAF mutation is not predictive of long-term outcome in papillary thyroid carcinoma

Lauren E. Henke[1], John D. Pfeifer[2], Changquing Ma[2], Stephanie M. Perkins[1], Todd DeWees[1], Samir El-Mofty[2], Jeffrey F. Moley[3], Brian Nussenbaum[4], Bruce H. Haughey[4], Thomas J. Baranski[5], Julie K. Schwarz[1] & Perry W. Grigsby[1,6]

[1]Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri
[2]Department of Pathology, Washington University School of Medicine, St. Louis, Missouri
[3]Section of Endocrine and Oncologic Surgery, Department of General Surgery, Washington University School of Medicine, St. Louis, Missouri
[4]Department of Otolaryngology, Washington University School of Medicine, St. Louis, Missouri
[5]Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, Washington University School of Medicine, Saint Louis, Missouri
[6]Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University School of Medicine, Saint Louis, Missouri

This is the most extensive study to date in the United States to demonstrate that *BRAF* mutation is of no predictive value for recurrence or survival in PTC. We found correlations of *BRAF* status and several clinicopathologic characteristics of high-risk disease, but limited evidence that the mutation correlates with more extensive or aggressive disease. This analysis suggests that *BRAF* is minimally prognostic in PTC. However, prevalence of the *BRAF* mutation is 70% in the general population, providing the opportunity for targeted therapy.

AGGRESSIVITA' (VERA) = METASTASI A DISTANZA



JCEM ONLINE

Advances in Genetics—Endocrine Care

BRAFV600E Mutation Does Not Mean Distant Metastasis in Thyroid Papillary Carcinomas

Valentina Sancisi,* Davide Nicoli,* Moira Ragazzi, Simonetta Piana, and Alessia Ciarrocchi

Laboratory of Molecular Biology (V.S., D.N., A.C.), Department of Oncology, and Pathology Unit (M.R., S.P.), Department of Oncology, Arcispedale Santa Maria Nuova, Istituto di Ricovero e Cura a Carattere Scientifico, 42123 Reggio Emilia, Italy

Distribution of BRAFV600E mutation in distantly metastatic and control PTC

	Total	PTC with distant metastasis	Wild type	BRAFV600E	BRAF V600E (%)
Control PTC	75	0	42	33	44.0
PTC without extrathyroidal invasion and lymph node metastases (pT1-T2, N0)	31	0	15	16	51.7
Distantly metastatic PTC	47	47	33	14	29.8
MicroPTC	5	5	5	0	0
Dead of thyroid carcinoma	26	26	18	8	30.8
Distant metastasis of V600E PTC	5		2	3	60.0

JCEM ONLINE

Advances in Genetics—Endocrine Care

Allele Percentage of the *BRAF* V600E Mutation in Papillary Thyroid Carcinomas and Corresponding Lymph Node Metastases: No Evidence for a Role in Tumor Progression

Greta Gandolfi, Valentina Sancisi, Federica Torricelli, Moira Ragazzi, Andrea Frasoldati, Simonetta Piana, and Alessia Ciarrocchi

Laboratory of Molecular Biology (G.G., V.S., F.T., A.C.), Department of Oncology, Pathology Unit (M.R., S.P.), Department of Oncology, and Endocrinology Unit (A.F.), Department of Surgery, Arcispedale S. Maria Nuova-Istituto di Ricovero e Cura a Carattere Scientifico, 42123 Reggio Emilia, Italy

Occurrence of *BRAF* V600E Mutation in Primary PTC LNMs

	n	BRAF V600E (Frequency)	BRAF Wild Type (Frequency)
Total PTCs	132	58 (0.44)	74 (0.56)
Nonmetastatic PTCs	37	18 (0.49)	19 (0.51)
Metastatic PTCs	95	40 (0.42)	55 (0.58)
PTCs with distant metastases	45	15 (0.33)	30 (0.67)
PTCs without distant metastases	50	25 (0.50)	25 (0.50)
LNMs from V600E-positive primary PTCs	28	23 (0.82)	5 (0.18)
LNMs from wild-type primary PTCs	12	1 (0.08)	11 (0.92)

ORIGINAL ARTICLE

Endocrine Research

HIGH SENSITIVITY BRAF MUTATION ANALYSIS: BRAF V600E IS ACQUIRED EARLY DURING TUMOR DEVELOPMENT BUT IS HETEROGENEOUSLY DISTRIBUTED IN A SUBSET OF PAPILLARY THYROID CARCINOMAS

Dario de Biase[1], Valentina Cesari[1,2], Michela Visani[2], Gian Piero Casadei[3], Nadia Cremonini[4], Greta Gandolfi[5], Valentina Sancisi[5], Moira Ragazzi[6], Annalisa Pession[2], Alessia Ciarrocchi[5*], Giovanni Tallini[1*]

[1] Department of Medicine (DIMES) – Anatomic Pathology Unit, Ospedale Bellaria, University of Bologna, 40139 Bologna, Italy; [2] Department of Pharmacology and Biotechnology (FaBiT), University of Bologna, 40100 Bologna, Italy; [3] Anatomic Pathology Unit, Ospedale Maggiore, 40133 Bologna, Italy; [4] Endocrinology Unit, Ospedale Maggiore, 40133 Bologna, Italy; [5] Molecular Biology Laboratory, IRCCS-Arcispedale Santa Maria Nuova, 42123 Reggio Emilia, Italy; [6] Anatomic Pathology Unit, IRCCS-Arcispedale Santa Maria Nuova, 42123 Reggio Emilia, Italy

Che ruolo ha BRAF nella nostra routine?

- Solo significato diagnostico
- Mai significato prognostico
- Solo su materiale citologico
- Solo su TIR3 o TIR4

Non c'è alcuna evidenza definitiva che un risultato biomolecolare sia migliore di quello fornito da un patologo esperto e dedicato.

Nella Thyroid Cancer Unit di Reggio Emilia, la percentuale di indeterminati è del 6% circa (TIR 3=4.6% + TIR 4=1,4%), una percentuale nettamente inferiore a quanto atteso, secondo i dati di letteratura.

Cosa si intende per «facciamo il BRAF su citologico»?


Anat. Patologica
A.S.M.N. Reggio E.
00098
4/8
PAP 15
Anat. Patologica
A.S.M.N. Reggio E.
00098
3/8
PAP 15
Anat. Patologica
A.S.M.N. Reggio E.
00098
5/8
MGG 15
Anat. Patologica
A.S.M.N. Reggio E.
00097
B 13/13
MGG 15
Anat. Patologica
A.S.M.N. Reggio E.
00098
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6/8
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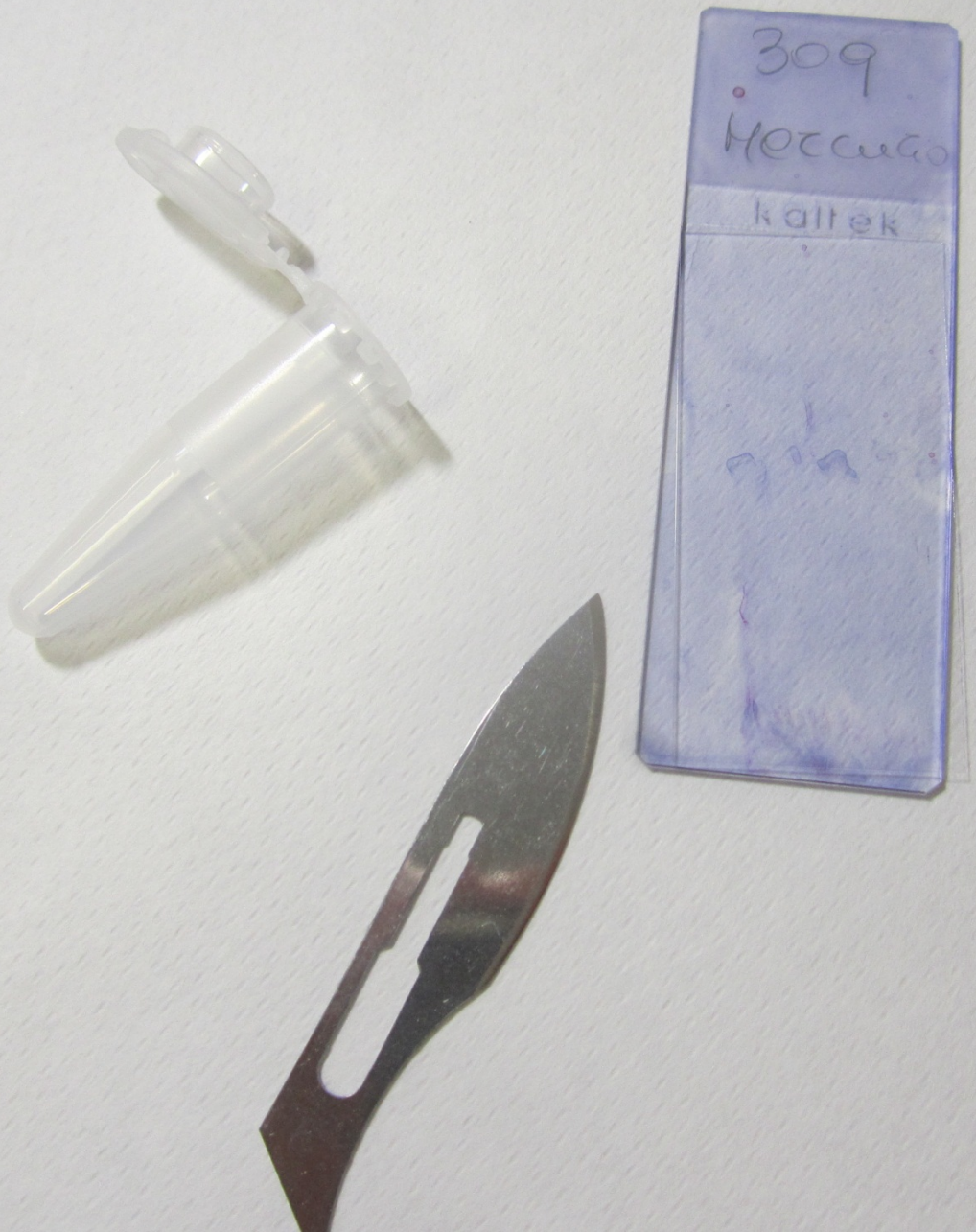
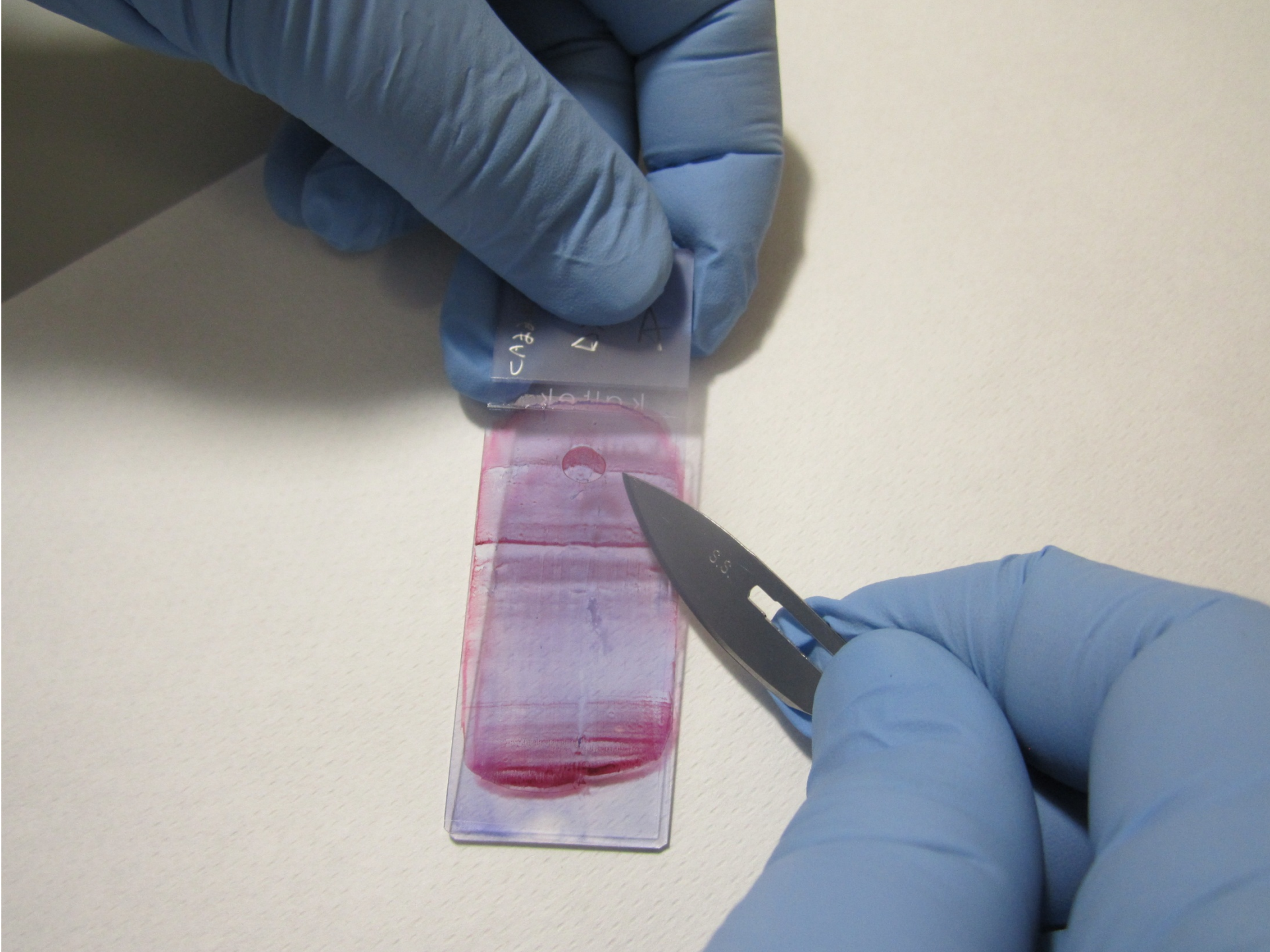
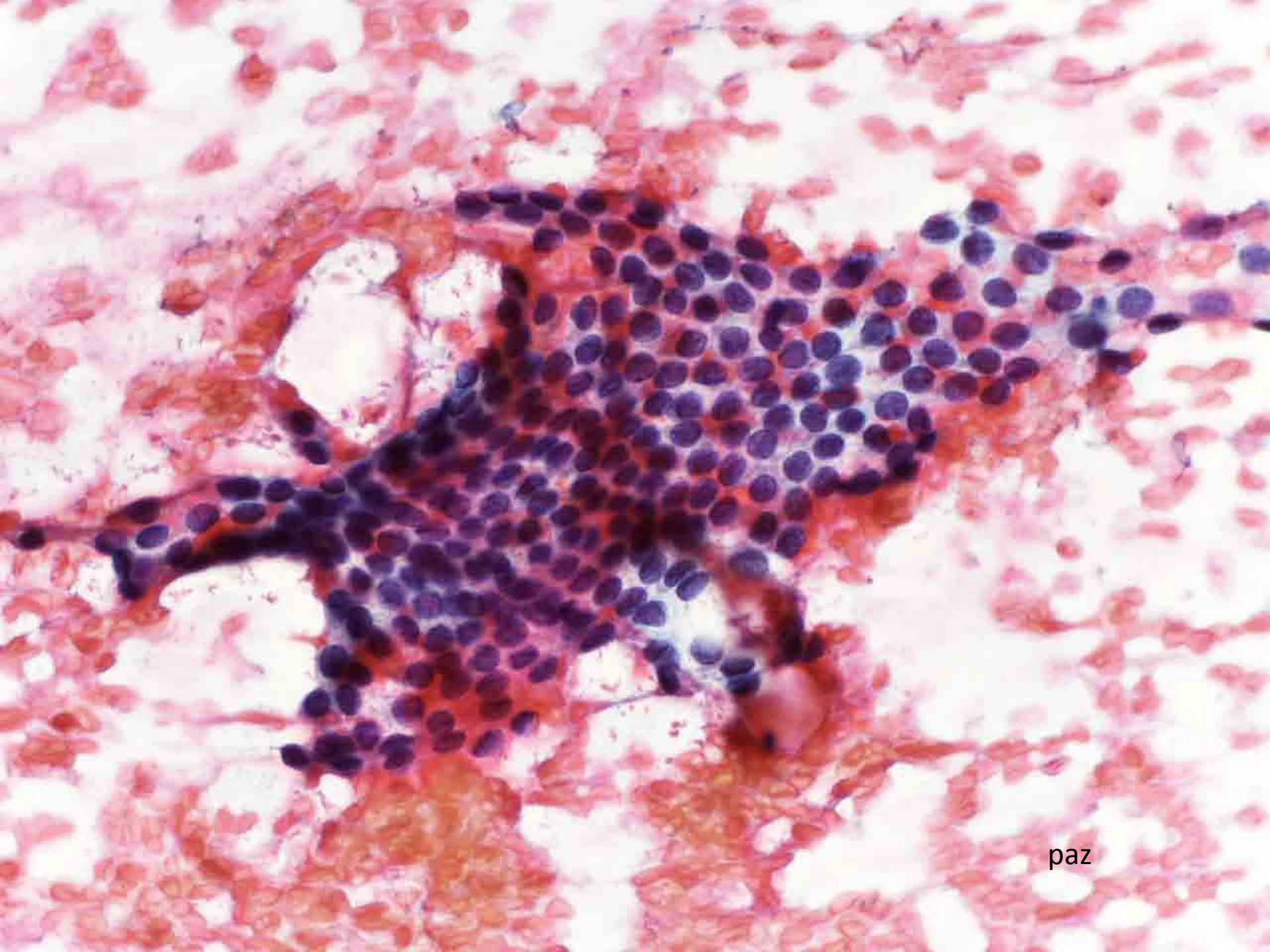
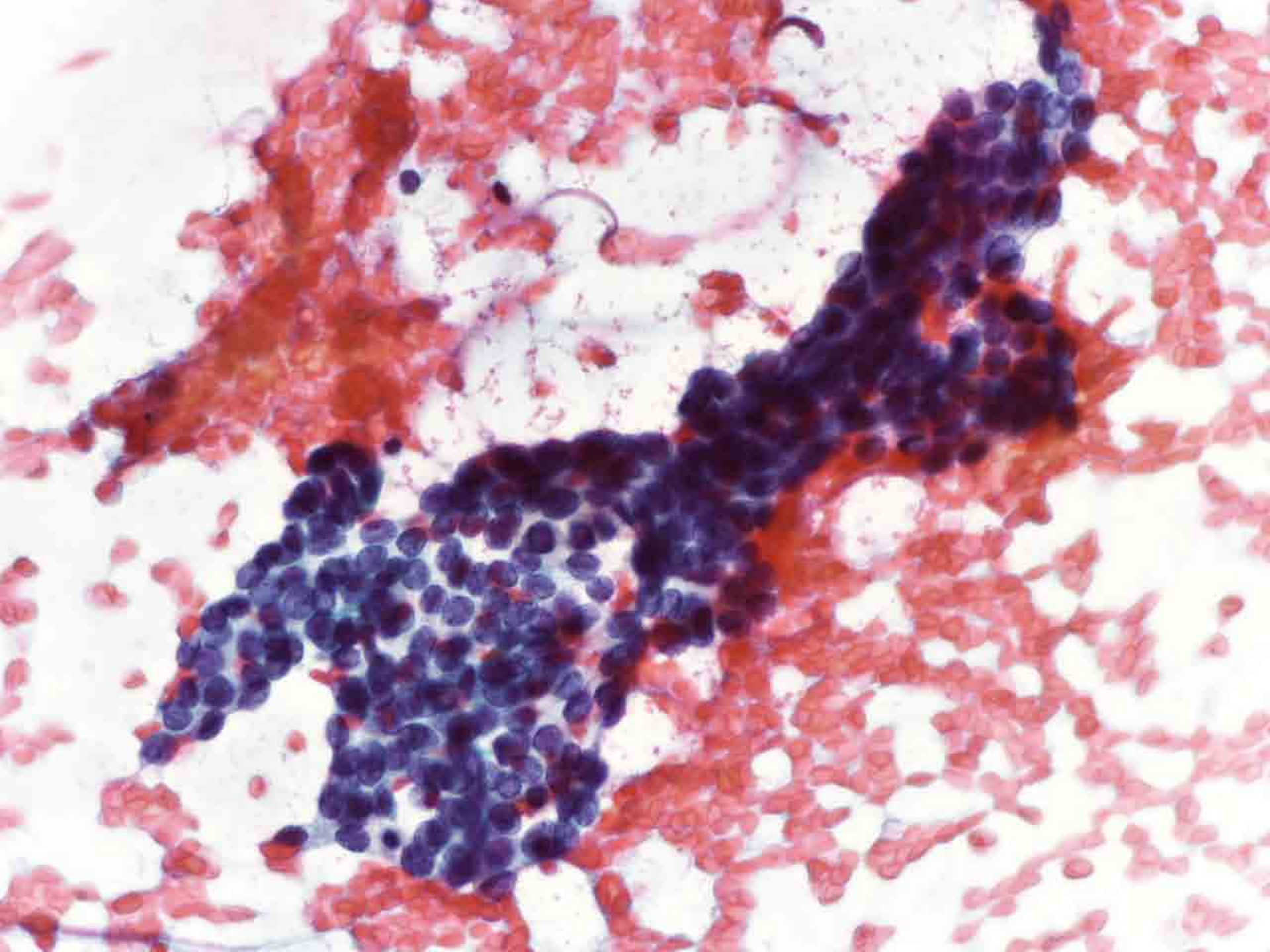

309
kaltek

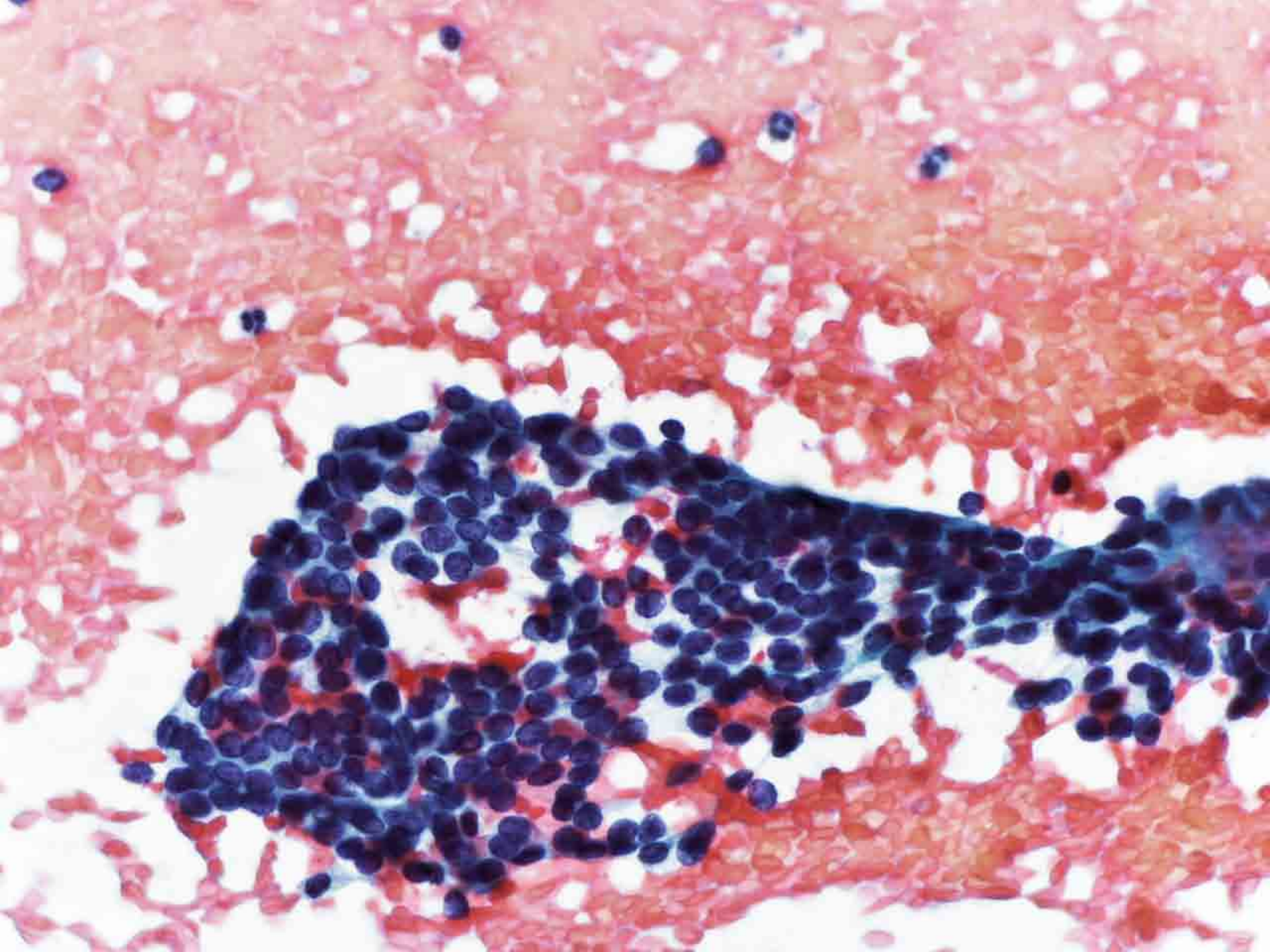

S.S.

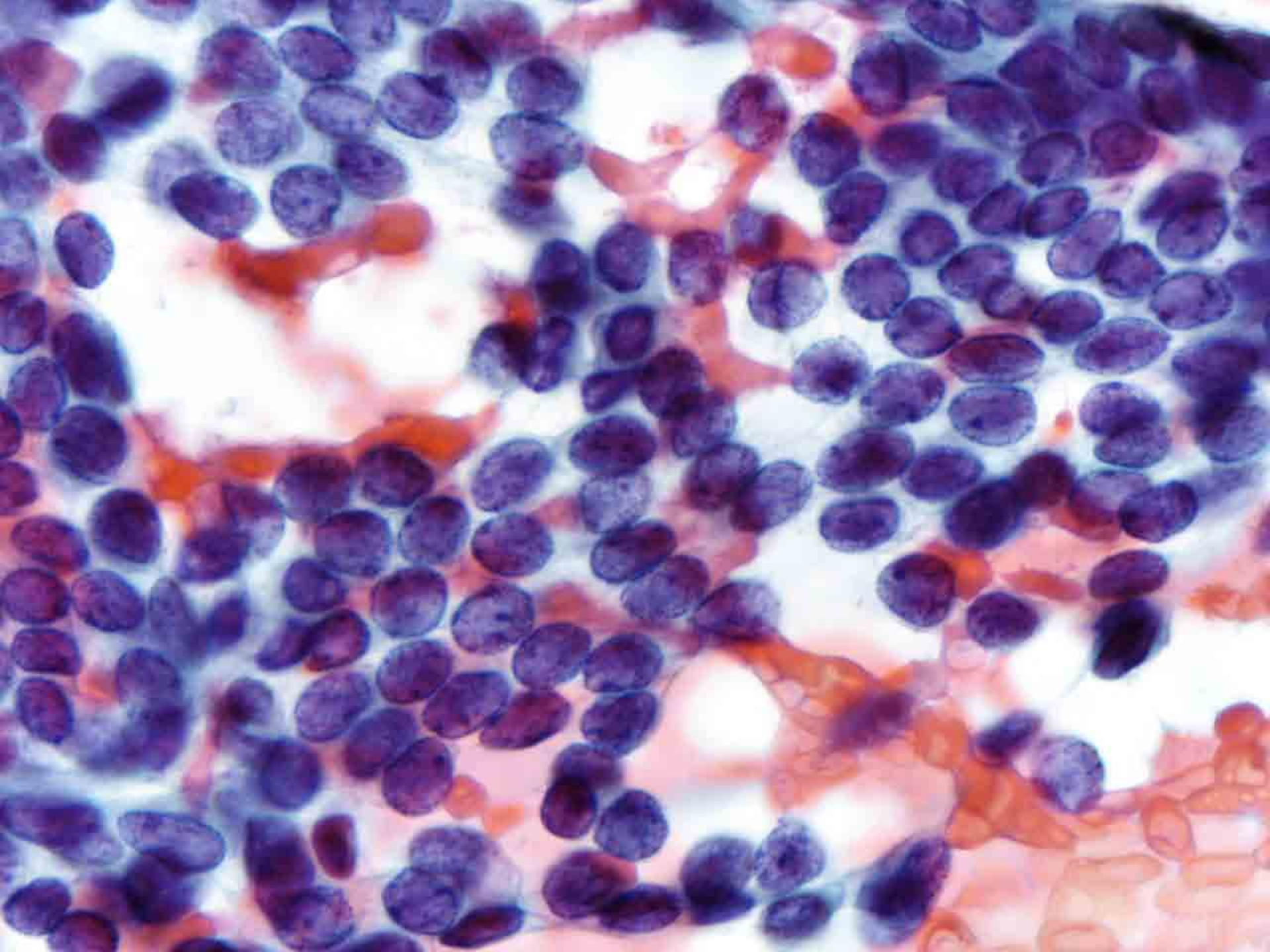
FEMMINA, 31 ANNI,

NODULO DI 0,5 cm
DEL LOBO DESTRO


paz

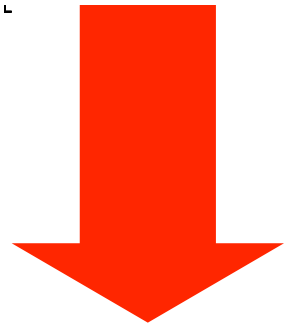






DIAGNOSI CITOLOGICA TIR 3

BRAFV600 mutata



PTC

75 casi di FNAB tiroidea

sottoposti a ricerca biomolecolare di mutazione BRAF V 600E presso il laboratorio di biologia molecolare dal 2011 al 2014

	WILD TYPE	BRAF MUTATI
iperplasia	3	
adenoma	11	
HTT	1	
PTC	11	31
Non operati	13	5
Tot.	39	36

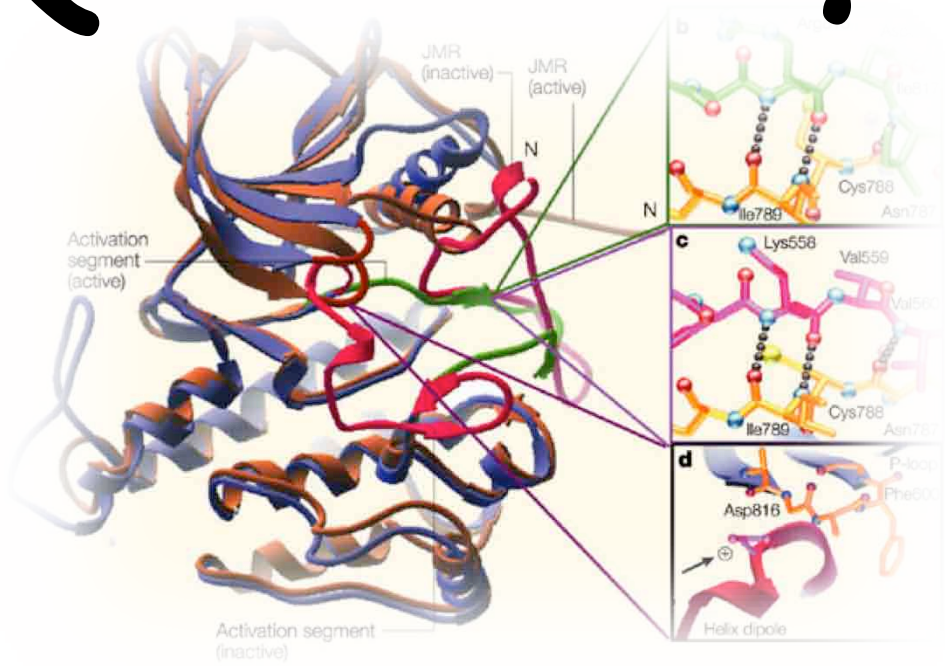
	WILD TYPE	BRAF MUTATI
TIR3 (rossi !!)		
iperplasia	2	
adenoma	10	
HTT	1	
PTC	6	12
non operati	13	4
tot.	32	16
TIR4		
iperplasia		
adenoma	1	
PTC	6	19
non operati		1
tot	7	20

	WILD TYPE	BRAF MUTATI
PTC	11 (26%)	31 (74%)

QUALE RUOLO PER BRAF?

RUOLO DIAGNOSTICO **RUOLO PROGNOSTICO**

OK ?



C'è ancora qualche spazio per BRAF prognostico?

	BRAF mut	BRAF wt	P-value
Total mPTC (n=200)	132 (0.66)	68 (0.44)	
Tumor size (mm)	7.62 ± 1.17	6.88 ± 1.88	0.004
pT			0.005
T1a	77 (0.58)	53 (0.79)	
T3	55 (0.42)	14 (0.21)	

NON EVIDENZA DI ASSOCIAZIONE CON MORTALITA' O METASTASI A DISTANZA

MA

NULLA VIETA CHE SI ASSOCI CON UNA MAGGIORE AGGRESSIVITA' LOCALE!

E RAS?

SCARSA ESPERIENZA ma..

IMPRESSIONE CHE QUALCHE ASSOCIAZIONE CON LE LESIONI FOLLICOLARI MALIGNE ESISTA

Thyroid Nodules With *KRAS* Mutations Are Different From Nodules With *NRAS* and *HRAS* Mutations With Regard to Cytopathologic and Histopathologic Outcome Characteristics

Lisa A. Radkay, MD[1]; Simion I. Chiosea, MD[1]; Raja R. Seethala, MD[1]; Steven P. Hodak, MD[2]; Shane O. LeBeau, MD[2]; Linwah Yip, MD[3]; Kelly L. McCoy, MD[3]; Sally E. Carty, MD[3]; Karen E. Schoedel, MD[1]; Marina N. Nikiforova, MD[1]; Yuri E. Nikiforov, MDPhD[1]; and N. Paul Ohori, MD[1]

NRAS Codon 61 Mutation Is Associated with Distant Metastasis in Patients with Follicular Thyroid Carcinoma

Eun Kyung Jang,[1] Dong Eun Song,[2] So Young Sim,[3] Hyemi Kwon,[1] Yun Mi Choi,[1] Min Ji Jeon,[1] Ji Min Han,[1] Won Gu Kim,[1] Tae Yong Kim,[1] Young Kee Shong,[1] and Won Bae Kim[1]

THYROID
Volume 25, Number 4, 2015

DOI: 10.1089/thy.2014.0362

Molecular Testing of Thyroid Fine-Needle Aspirations Improves Presurgical Diagnosis and Supports the Histologic Identification of Minimally Invasive Follicular Thyroid Carcinomas

Markus Eszlinger,[1] Simonetta Piana,[2] Anja Moll,[1] Eileen Bösenberg,[1] Alessandra Bisagni,[2] Alessia Ciarrocchi,[3] Moira Ragazzi,[2] and Ralf Paschke[1]

3/10 CASI DI ADENOMI FOLLICOLARI RAS-MUTATI SONO STATI RIVISTI E RISULTATI CARCINOMI FOLLICOLARI MINIMAMENTE INVASIVI

C'E' ANCORA MOLTO DA FARE!!

GRAZIE