Che ruolo ha BRAF nella nostra routine e perchè

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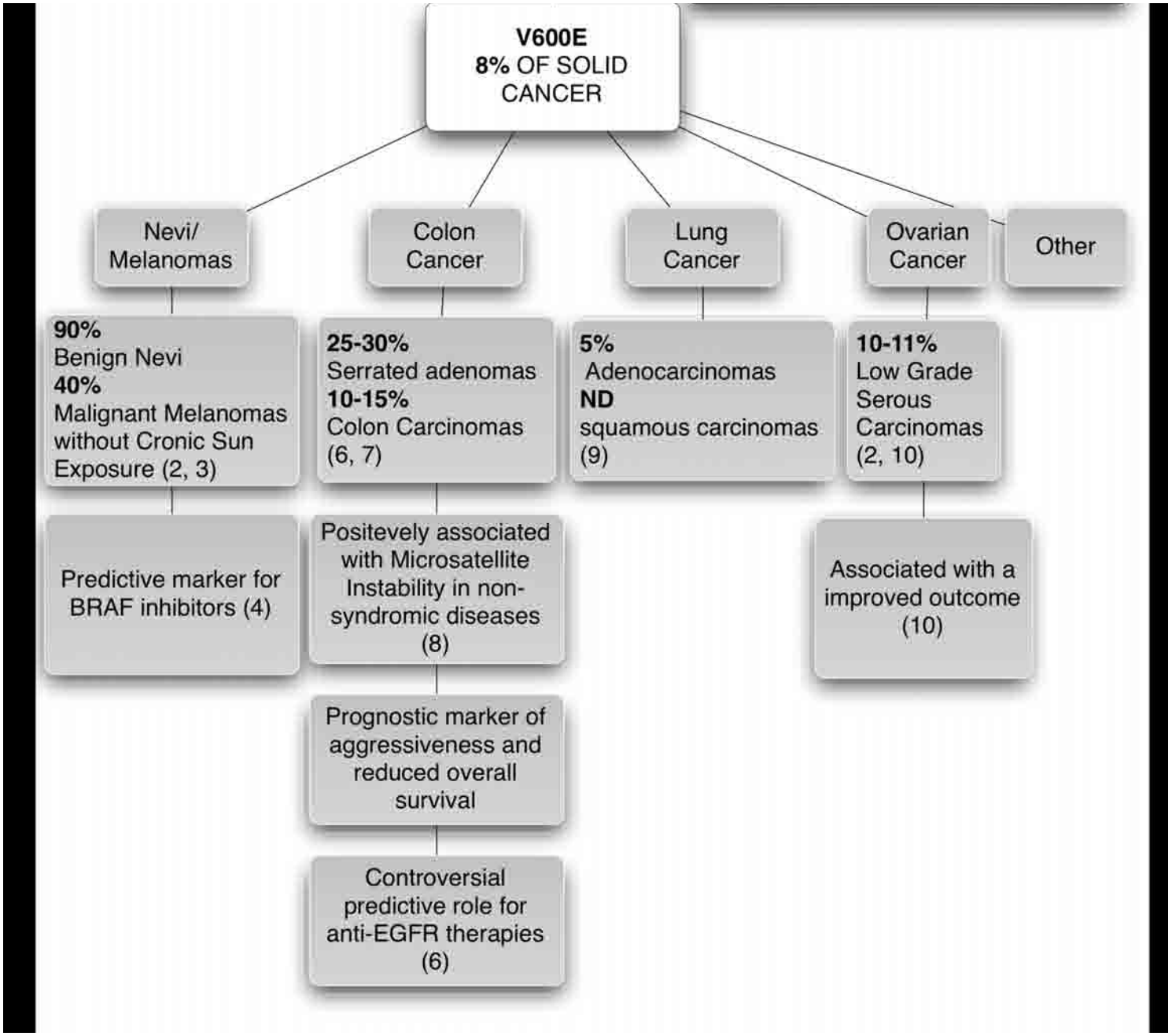
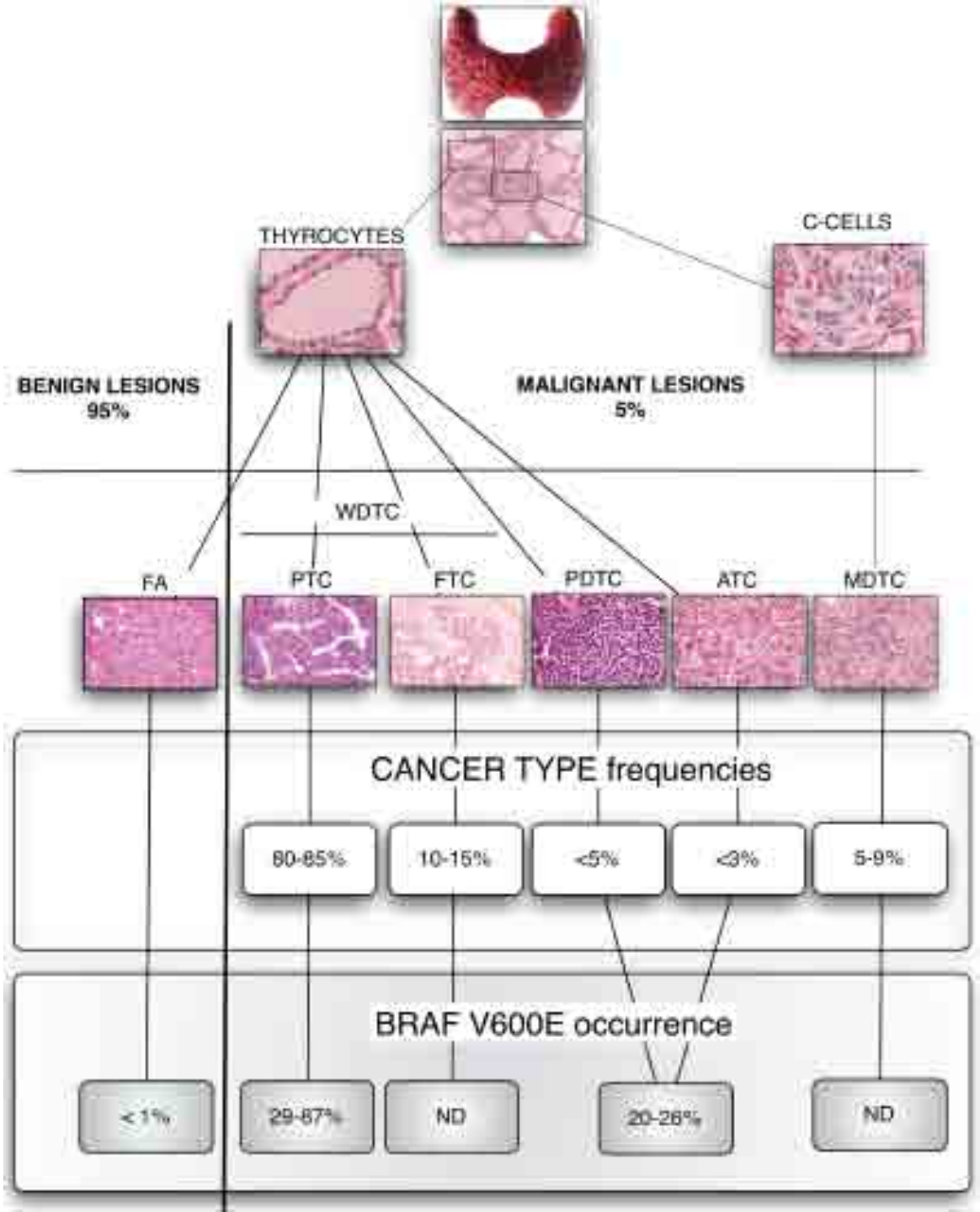
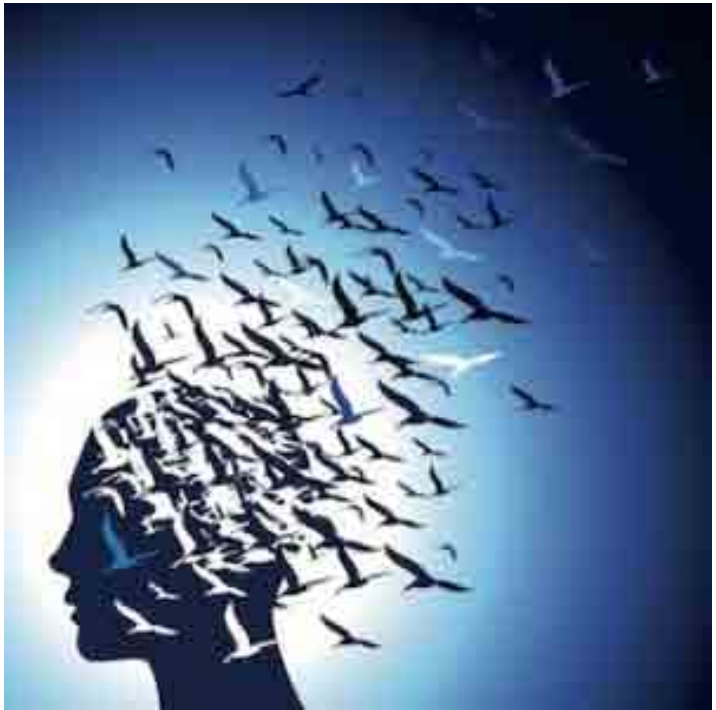

V600E
8% OF SOLID CANCER
Nevi/ Melanomas
Colon Cancer
Lung Cancer
Ovarian Cancer
Other
90% Benign Nevi
40% Malignant Melanomas without Cronic Sun Exposure (2, 3)
25-30% Serrated adenomas
10-15% Colon Carcinomas (6, 7)
5% Adenocarcinomas
ND squamous carcinomas (9)
10-11% Low Grade Serous Carcinomas (2, 10)
Predictive marker for BRAF inhibitors (4)
Positevely associated with Microsatellite Instability in non-syndromic diseases (8)
Associated with a improved outcome (10)
Prognostic marker of aggressiveness and reduced overall survival
Controversial predictive role for anti-EGFR therapies (6)


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

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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, 1.35-9.98). 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, 16.14-64.55) in *BRAF* V600E–positive vs mutation-negative patients (unadjusted HR, 2.83 [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 treatments 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.[3,4] Several clinicopathological risk factors have been

See also pp 1529 and 1533.

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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.

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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]).

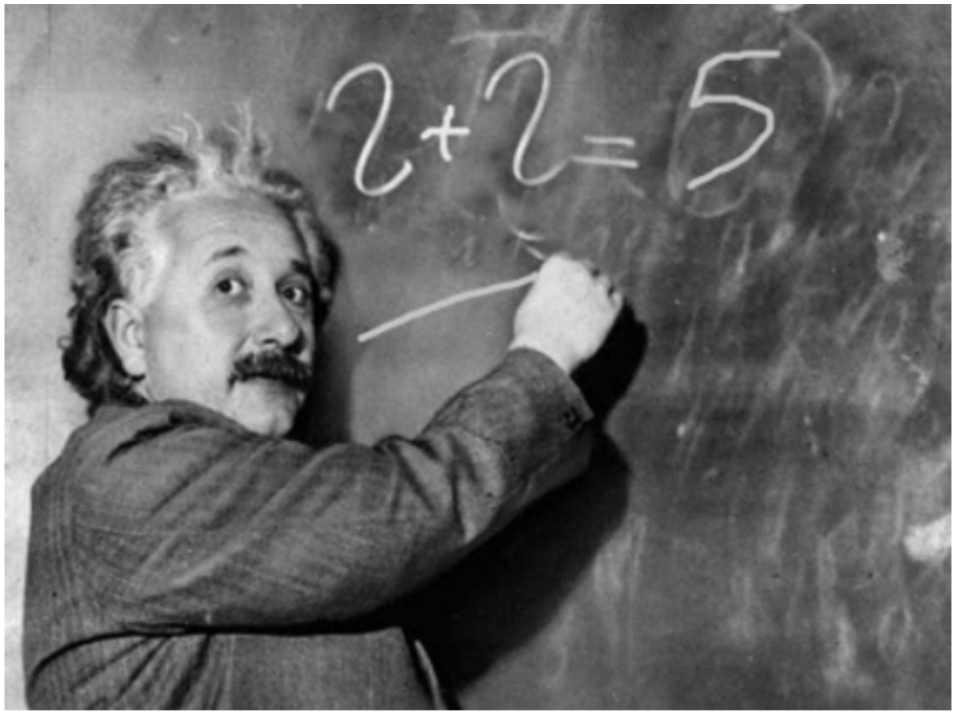
Virchows Arch (2014) 464:333–346
DOI 10.1007/s00428-013-1521-2

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.

Age <45 years

Stage I

Any T, any N, M0

Stage II

Any T, any N, M1

Age ≥45 years

Stage I

T1, N0, M0

Stage II

T2, N0, M0

Stage III

T3, N0, Mo

T1, N1a, M0

T2, N1a, M0

T3, N1a, M0

Stage IVA

T4a, N0, M0

T4a, N1a, M0

T1, N1b, M0

T2, N1b, M0

T3, N1b, M0

T4a, N1b, M0

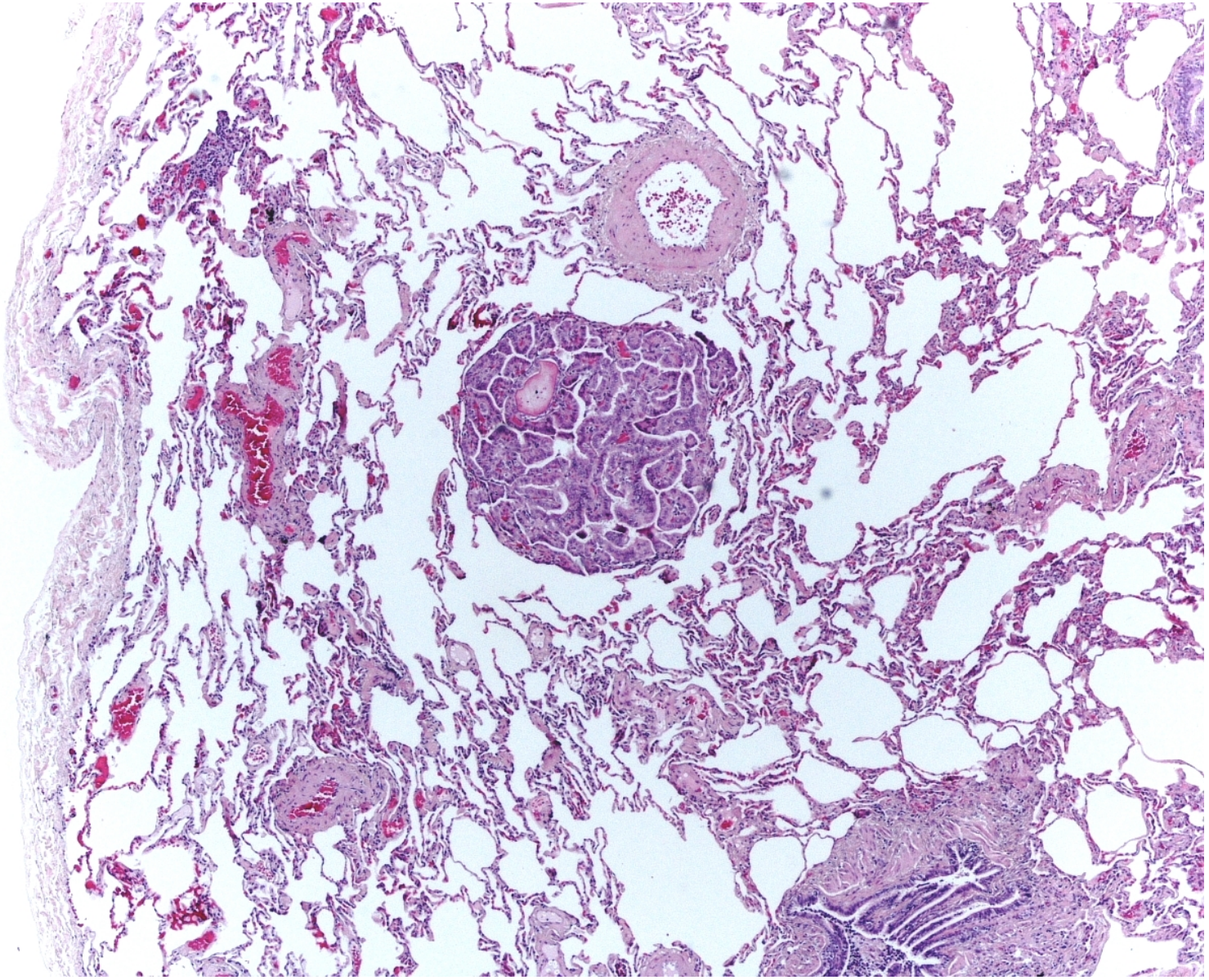
Stage IVB

T4b, Any N, M0

Stage IVC

Any T, any N, M1

AGGRESSIVITA' (VERA) = METASTASI



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

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47 PTC CON METASTASI A DISTANZA

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

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132 PTC CON O SENZA METASTASI LINFONODALI E CORRISPONDENTI LINFONODI

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)

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.

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.

Forse i fondi destinati all' implementazione di diversi test molecolari potrebbero essere investiti nella formazione delle risorse umane.

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

Tale risultato è reso possibile dalla competenza dei professionisti e dal controllo attento dei processi, ma anche dalla comunicazione quotidiana e dalla condivisione delle scelte.

GRAZIE
ALLA THYROID
CANCER UNIT
DELL'IRCCS-ASMN