Contribution of *TERT* promoter mutation status to preoperative diagnosis of thyroid carcinoma.

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CONFLICT OF INTEREST DECLARATION

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INTRODUCTION

- Thyroid nodules are common among population, but barely 4% corresponds to malignant neoplasms.

- Ultrasound-guided fine needle aspiration biopsy (FNAB) is a worldwide used tool to guide the patients' management.

- In some entities the main diagnostic criteria of malignancy must be evaluated in the surgical specimen.

IMPLIED RISK OF MALIGNANCY IN A LARGE SERIES OF THYROID FINE NEEDLE ASPIRATION CYTOLOGY SPECIMENS BASED ON THE BETHESDA SYSTEM

1989-2013

Bethesda IV

HISTOLOGICAL DIAGNOSIS	CYTOLOGICAL DIAGNOSIS II Benign	III AUS	III FLUS	III FOLUS	IV FN	IV FON	V Suspicious M.	VI Malignant	
Nodular hyperplasia	444	9	94	35	10	6	1		599
Follicular adenoma	25	1	24	15	11	10	1		87
Hyal. Trab. Adenoma					2				2
Follicular carcinoma	5		20	7	12	3			47
Papillary carcinoma	1	10	4	4	9	4	8	100	140
Poorly diff. Carcinoma					8			1	9
Anaplastic carcinoma								3	3
Medullary carcinoma							1	7	8
Metastasis								1	1
	475	20	142	61	52	23	11	112	896
Cancer risk	1,26%	50,00%	16,90%	18,03%	55,76%	30,43%	81,81%	100%	
			216		75				
Cancer risk			20,17%		48,00%				

Diagnostic lobectomy or total thyroidectomy???

Lisboa, 2013

INTRODUCTION

- C228T mutation of telomerase reverse transcriptase promoter (*TERTp*) has been identified as specific of malignancy in thyroid neoplasms, being the most frequent mutation.

- Its detection by pyrosequencing has been slightly reported.
- Pyrosequencing is used in our laboratory.

AIM OF THE STUDY

- To determine the incidence of C228T *TERTp* mutation
  - by pyrosequencing
  - in thyroid nodules classified by FNAB as Bethesda IV (consistent with/suggestive of follicular neoplasm or Hürthle cell neoplasm)

- To establish the profitability of its detection in the corresponding FNAB material.

MATERIAL / METHODS

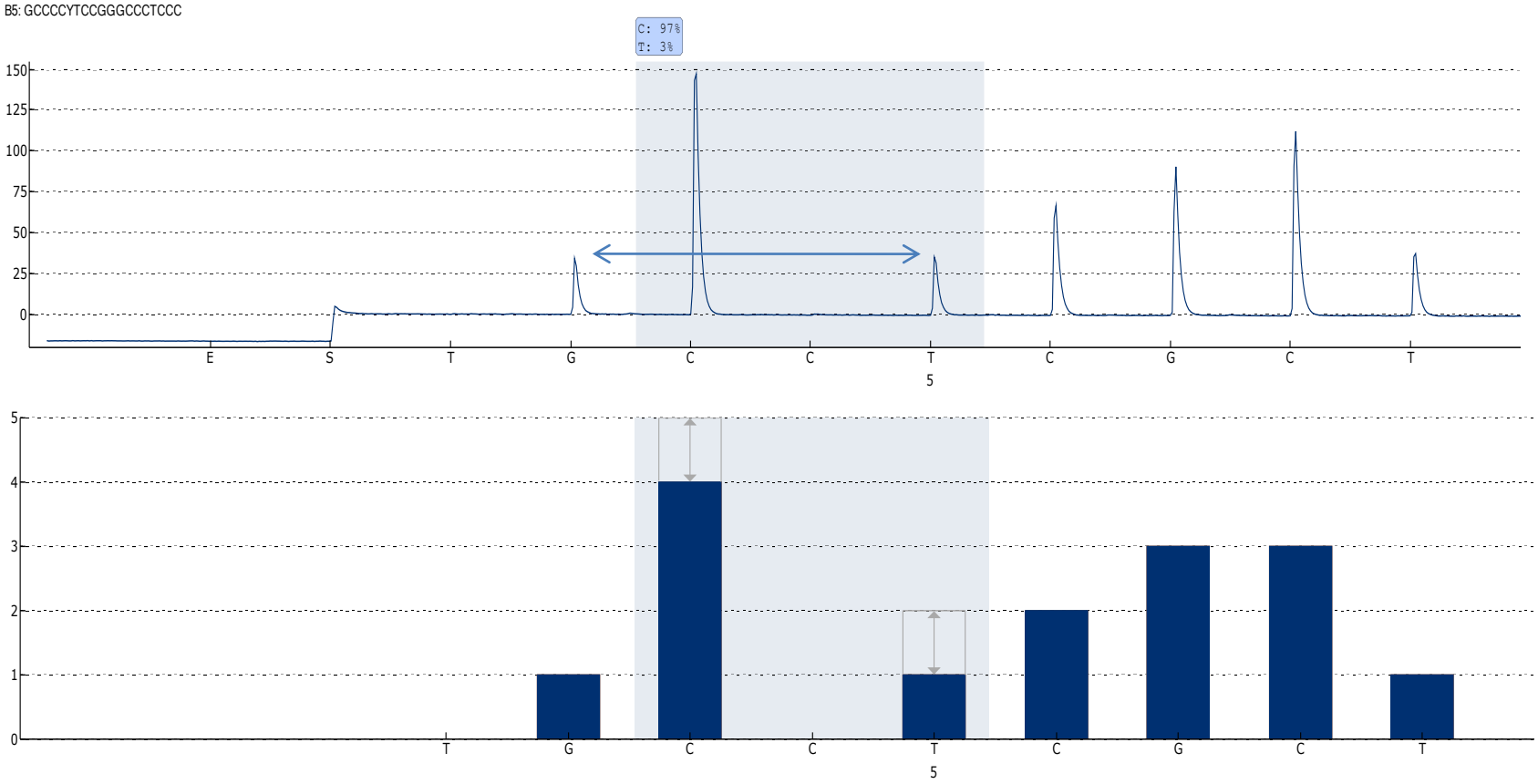
- Retrospective observational study
- Inclusion criteria: Patients with thyroid nodules classified by FNAB as consistent with follicular or Hürthle cell neoplasm and followed by thyroidectomy between 1993 and 2015.
- RCIC approval. Reasonable effort to obtain informed consent.

- Cases were retrieved from the Pathology Department archives. Demographics, clinical data, and cytological and histological diagnoses were recorded.
- Primers (forward, reverse and sequencing) were designed from public data bases with Pyromark assay design 2.0.
- Selected material from paraffin blocks of the neoplasms was processed by pyrosequencing to detect C228T *TERTp* mutation. In mutated cases, material from the FNAB material was also studied (from cell blocks or smears).
- LOD established in 14%

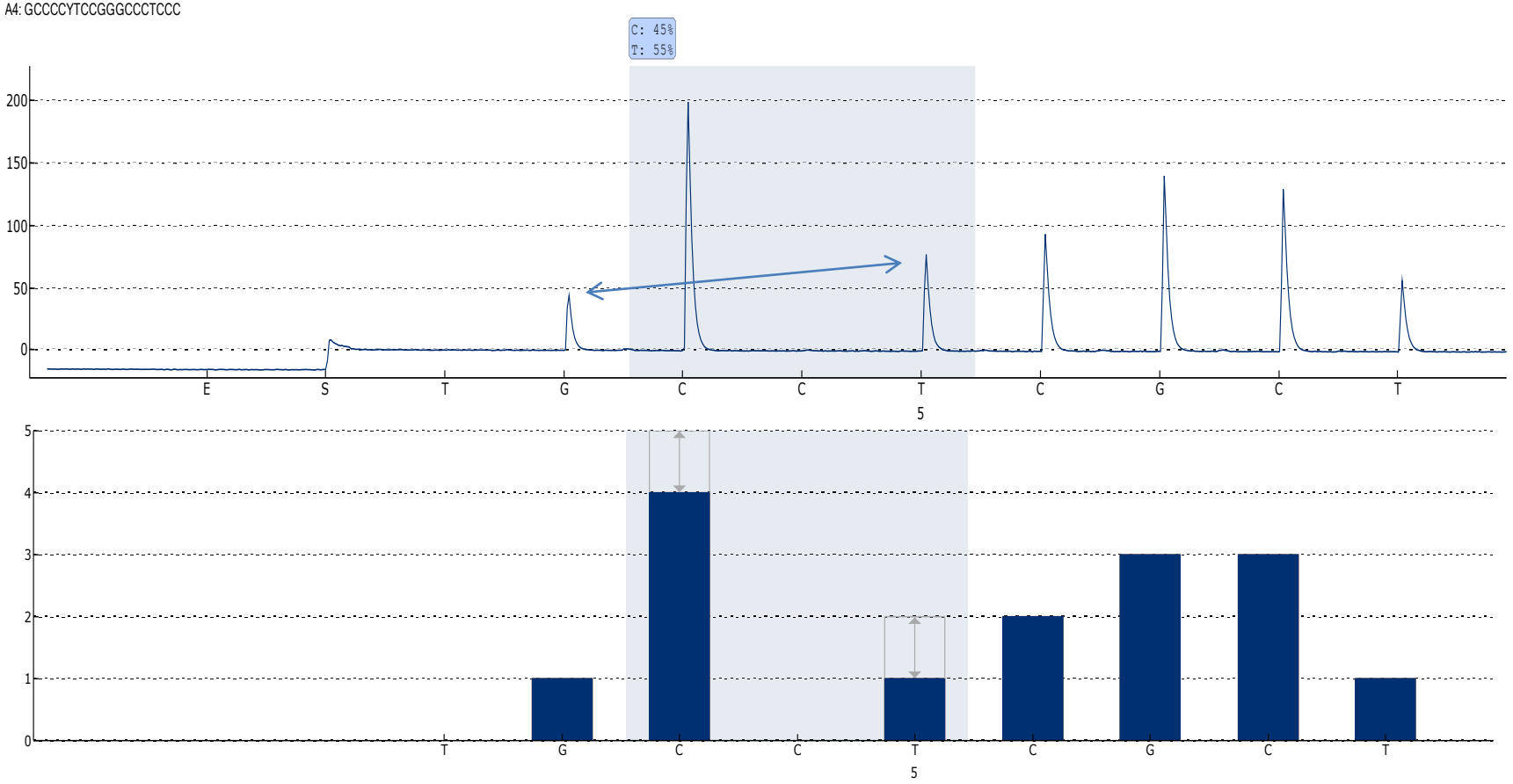
RESULTS

- 62 cases fulfilled the inclusion criteria.
  - 26 benign (25 neoplasms)
  - 36 malignancies (58%)
  - 18 males, 44 females, mean 48 years (7-83)

- C228T *TERTp* mutation was detected in 9 cases (14,5%):
  - all them malignant tumours
  - in the corresponding FNAB material of 7 of them
    - the ones with enough material to perform the study



Wild type (5 cytosine, 1 thymine)



Mutated case (4 cytosine, 2 thymine)

HISTOLOGY	CASES	MUTATED	FOLLOW-UP	
Nodular hyperplasia	1	0		
Follicular adenoma	15	0		0/26
Hürthle cell adenoma	8	0		
Hyalining trabecular adenoma	2	0		
Well differentiated carcinoma NOS	1	1	AFD	
Follicular carcinoma	9	0		
Hürthle cell carcinoma	6	1	DOD	4/25 (16%)
Follicular variant of PTC	7	1	AFD	
Oncocytic PTC	2	1	AFD	
Well diff. ca.NOS + **Poorly** DC.	1	0		
Follicular carcinoma + **Poorly** DC.	2	1	AFD	5/11 (45,5%)
FVPTC + **Poorly** DC. + Anaplastic ca.	2	1	DOD	
Poorly DC + Follicular carcinoma	2	2	DOD,DOD	
Poorly differentiated carcinoma	4	1	AWD	

TOTAL:	**62**	**9**	**(14,5%)**

AFD: alive free of disease; AWD: alive with disease; DOD: died of disease.

RESULTS

- In 4/9 cases a delayed completion thyroidectomy was needed.

- Lost follow-up: 3 (2 carcinomas)
- Follow-up: 4-26 years
  - Benign cases (25): all alive without disease
  - Malignant cases (34):
    - 4 died of disease (4 mutated)
    - 2 alive with disease (1 mutated)
    - 2 died other causes (0 mutated)
    - 26 alive without disease (4 mutated)

CONCLUSION

- Study of C228T *TERTp* mutation by pyrosequencing could be of help to detect malignant thyroid nodules, eventually indicating total thyroidectomy as the first and definitive surgery, avoiding a second intervention.

- C228T *TERTp* mutation is more frequent in cases with poorly differentiated component and in cases with bad evolution (4/4 died of disease, 1/2 alive with disease).

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