European Journal of Cancer 92 (2018) 40–47

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Predictive factors of outcome in poorly differentiated thyroid carcinomas

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Received 11 June 2017; received in revised form 10 December 2017; accepted 26 December 2017

KEYWORDS
Poorly differentiated thyroid carcinoma;
RAI-resistant;
Recurrence risk;
TERT promoter mutations;
RAS mutations

Abstract ***Background:*** The prognosis of poorly differentiated thyroid carcinomas (PDTC) is heterogeneous though generally poor. The objectives of this study were to identify clinical and molecular factors of poor prognosis.

Methods: One hundred four consecutive patients treated for a PDTC between 01/01/2000 and 31/12/2010 were included in this study. A pathological review was done for all cases (blinded to clinical data and outcome).

Results: All patients underwent thyroidectomy. Adjuvant radioactive-iodine was administered in 95.2% of them. Tumours were pT3 or pT4 in 68.3% of cases and metastatic in 38.5% of patients. Extrathyroidal extension (ETE) was observed in 40% of patients. At the end of the initial treatment, only 37% of patients were considered in remission. Fifty-two patients (50%) became refractory to radioiodine during follow-up. The 5-year overall survival was 72.8% and the 5-year recurrence-free survival (RFS) was 45.3%. Remission after initial treatment was an independent factor of RFS (HR = 0.22; [0.10–0.49]). ETE was the only significant parameter influencing the overall survival in multivariate analysis. TERT promoter

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https://doi.org/10.1016/j.ejca.2017.12.027

mutations at positions −124 (C228T) and −146 (C250T) were present in 38.1% of analysed patients and significantly associated with radioiodine resistance but not with overall survival. Half of TERT promoter mutant tumours harboured also RAS or BRAF mutations.
Conclusion: PDTC form a heterogeneous group of patients with usual late-stage diagnosis, low radioactive iodine avidity and frequent metastatic spread. TERT promoter mutations could help to identify patients with high risk of radio-iodine refractoriness.

1. Introduction

Poorly differentiated thyroid carcinomas (PDTCs) are defined as follicular cell-derived carcinomas producing thyroglobulin but showing limited evidence of structural follicular cell differentiation with high-grade features. It accounts for a small proportion of thyroid carcinomas (TCs; between 3 and 5%) [1,2]. They have been individualised as a distinct entity in 2004 and are nowadays diagnosed using the Turin consensus criteria algorithmic approach, recently adopted in the new WHO classification [3]. This algorithm includes cytoarchitectural criteria (follicular cell's origin and presence of a solid, trabecular and/or insular architecture without nuclear features of papillary carcinoma criteria) and at least one of the following features: convoluted nuclei (irregular, small, round, hyperchromatic), mitotic activity $>$ 3 mitoses $\times$ 10 HPF ($\times$400) and/or tumour necrosis (absent or present) [4]. We previously reported the negative impact of a poorly differentiated component on overall survival for metastatic WDTC patients [5]. Based on our prior knowledge of PDTC, we decided to analyse this special population to identify those at risk for recurrence and metastatic evolution. Furthermore, we evaluated in our PDTC's patients, as it was done for differentiated thyroid cancer, the prognostic value of the response to initial therapy and analysed in a subgroup of patients, molecular biomarkers as TERT (telomerase reverse transcriptase), BRAF and RAS mutations.

2. Material and methods

One hundred four consecutive patients from 2 centres (Hospital Louis Pradel and Center Leon Berard) were included in our study between 01/01/2000 and 31/12/2010. The study was approved by an Institutional Review Board. The patients' management was conducted according to the current guidelines for thyroid cancer. The initial treatment consisted in a total or near-total thyroidectomy, with a compartment-oriented lymph nodes dissection in cases of preoperatively suspected and/or intraoperative proven lymph node metastases. Adjuvant radioactive iodine (RAI) therapy was administered according to the recurrence risk status. Radioiodine refractory (RAIR) patients were defined by the presence of at least one metastatic site without any uptake of radioiodine, the progression of the disease during the year after a radioiodine treatment course or the persistence of disease after the administration of a cumulative activity of 22 GBq (600 mCi) 131I. Archived histopathology slides of patients were all reviewed by one referent pathologist (M.D-P), blinded to clinical data and outcome. PDTC were defined using the TURIN criteria. Molecular analyses were performed on tumour samples to identify somatic mutations in TERT promoter and BRAF and RAS genes. DNA was isolated from formalin-fixed paraffin-embedded tissue blocks of tumour thyroid tissue, using the QIAamp DNA FFPE tissue kit on a QIAcube instrument (Qiagen) according to the manufacturer's instructions. Mutations of BRAF exon 15, NRAS exon 3 and HRAS exon 3, were screened using real-time PCR and fluorescence high-resolution melting curve analysis on a LightCycler 480 instrument (RocheDiagnostics, Vienna, Austria). Positive samples were confirmed by Sanger sequencing. We used the following set of PCR primers: BRAF_F 5′ AAAAATAGGTGATTTTGGTCTAGC 3′ and BRAF_R 5′ AATAGCCTCAATTCTTACCATCC 3'; NRAS_F 5′ CCCCTTACCCTCCACACC 3′ and NRAS_R 5′ GCTTCCTCTGTGTATTTGCCA 3'; HRAS_F 5′ ATTCCTACCGGAAGCAGGTGG 3′ and HRAS_R 5′ CGCATGTACTGGTCCCGCAT 3'. The two somatic TERT promoter mutations located at −124 (C228T) and −146 (C250T) pb upstream from the ATG start site were analysed with nested PCR protocol and sequenced as previously described [6]. Thyroid cancer was categorised according to the 7th TNM (tumour node metastasis) classification system [7].

3. Statistical analysis

Categorical variables were presented as number and percentage for each variable. Continuous variables were described as mean, standard deviation, median and first and third quartile. To select a relevant ablation Tg cut-off score to describe overall survival and relapse, receiver-operating characteristic (ROC) curve analysis was carried out. For each ablation Tg level score, the