TITRE DE L'ETUDE : Prognostic factors of survival in RAI-refractory differentiated thyroid cancer

ACRONYME : PRONOSTHYC

RESPONSABLE SCIENTIFIQUE : Lamartina/Hadoux

BIOSTATISTICIEN : Borget

HISTO DE REFRACTAIRE CONCERNE : RAI-refractory differentiated thyroid cancer

RATIONNEL DE L'ETUDE :

Differentiated thyroid cancer (DTC) with distant metastases is rare (less than 10% of all cases). The overall survival (OS) of the patients with radioiodine responsive diseases is excellent (>90% at 10 years) while those patients that disclose RAI-refractory disease have a significantly reduced OS (30-10% at 10 years) (Durante 2006). Still, the disease behavior appears heterogeneous with a spectrum spanning form microscopic disease not disclosing significative disease progression within decades to rapidly evolving disease. Some prognostic factors of worse survival in metastatic patients are known, such as older age, presence of 18 FDG PET uptake, larger disease burden (Durante 2006, Deandreis 2011, Nunes 2021). Some molecular alterations are also associated to a worse outcome (namely TERT promoter) (Xing 2014, Liu 2017). This information derives from retrospective and relatively small cohorts of metastatic patients.

The aim of this study is to analyze the overall survival and the prognostic factors of survival in a large cohort of RAI-refractory DTC patients from the TUTHYREF database.

OBJECTIF PRINCIPAL :

To study the overall survival of the patients with RAI-refractory DTC

CRITERE DE JUGEMENT PRINCIPAL :

Overall survival time of the patients with RAI-refractory DTC

OBJECTIFS SECONDAIRES :

Analyze the following prognostic factors of OS and disease specific survival (DSS) in RAI-refractory DTC: age, gender, timing of metastases diagnosis (synchronous or metachronous metastases), symptomatic metastases at diagnosis, presence of 18 FDG uptake, disease burden (micro vs macro-metastases, site and number of metastatic organs involved), progression free survival, molecular profile, primary surgery (performed or not; R0/R1 vs R2/not possible), definition of RAI-refractory disease, lymphocyte/neutrophile ratio, Tg doubling time, time period (before TKI/after TKI), time to 1st line systemic treatment.

Sous études

Explore the impact of the TUTHYREF national multidisciplinary tumor board (MTB) in the outcome of RAI-refractory DTCs (Grenoble)

Characterization of the patients with central nervous system (CNS) metastases (Grenoble)

Characterization of the geriatric patients with RAI-refractory DTC

Estimation du cout en vie réelle du traitement par Lenvatinib dans la période 2015- 2018 COTHYREF (Isabelle Borget)

Characterization of the patients receiving 2 lines or more of TKI

Characterization of the patients according to the molecular profile

Role of TSH suppression in OS of RAI-refractory DTC

CRITERE DE JUGEMENT SECONDAIRES :

Time to OS and DSS according to age, gender, timing of metastases diagnosis (synchronous or metachronous metastases), symptomatic metastases at diagnosis, presence of 18 FDG uptake, disease burden (micro vs macrometastases, site and number of metastatic organs involved), progression free survival, molecular profile, primary surgery (performed or not; R0/R1 vs R2/not possible), definition of RAI-refractory disease, lymphocyte/neutrophile ratio, Tg doubling time, time period (before TKI/after TKI), time to 1st line systemic treatment.

Rate of patients discussed in the national MTB, rate of adherence to the national MTB advice, reason for non-adherence, OS of the patients according to the adherence to national MTB advice.

Rate and OS of patients CNS metastases and prognostic factors of OS and DSS in this cohort

Rate and OS of patients with ≥75 at the time of diagnosis of the RAI-refractory DTC and prognostic factors of OS and DSS in this cohort

Appariement avec les donnes du Système national des données de Santé (SNDS) pour estimation du cout et de l'impact en termes de polimedication, arrêt de travail, hospitalisation, soins externes (HAD…) des patients sous Lenvatinib

Rate and OS of patients receiving 2 lines or more of TKI and prognostic factors of OS and DSS in this cohort

Rate, time to 1st line systemic treatment and PFS under antiagiogenicTKI vs selective TKI if used

OS according to median TSH values (TSH <0.1, 0.1-0.5, 0.5-2, 2-4, >4) (in patients with more than 50% of TSH values available)

NOMBRES DE CENTRE TUTHYREF : tous

NOMBRES DE PATIENTS INCLUS : DTC métastatiques de la base Tuthyref (estimé environ 2000 sujets)

DUREE DU RECUEIL : Nov 2022 – Nov 2023

CRITERE D'INCLUSION :

RAI-refractory DTC according to TUTHYREF definition

Presence of distant metastases from DTC

Follow up of 12 months or until death

CRITERE DE NON INCLUSION :

Any anaplastic component or anaplastic transformation

Data on death non available (date of death missing + update of clinical information older than 12 months)

PERIODE D'OBSERVATION : 2000-2021

DEROULEMENT DE L'ETUDE :

1- Set-up of the database + quality controls
2- Data input

3- Data cutoff and analysis for primary and secondary endpoints
4- Manuscripts redaction

ANALYSE STATISTIQUE : statistiques descriptives, courbe de Kaplan Meier, analyse univariée et multivariée avec modèle de Cox

DONNEES DEJA PRESENTES DANS TUTHYREF 3 : age, sexe, mutation somatique, traitements antérieurs

DONNEES SUPPLEMENTAIRES : cf CRF annexe 1

CALENDRIER ENVISAGE :

1- Set-up of the database + quality controls (1 months)
2- Data input (6 months)
3- Data cutoff and analysis for primary and secondary endpoints (3 months)
4- Manuscripts redaction and data presentation at the TUTHYREF annual meeting

Table 1. Summary of available evidence on prognostic factors of survival in metastatic DTCs

Paper	N	Relevant prognostic factors	Comments
Qiu, Front Endocrinol (Lausanne) (IF: 5.55) . 2021	57 age ≥65 yo	gross extrathyroidal extension and RR-DTC were independent prognostic factors for poor OS (P=0.04 and P=0.03, respectively), while gross extrathyroidal extension, extrapulmonary distant metastases, and RR-WDTC were independent prognostic factors for poor DSS at the end of follow-up (P=0.02, P=0.03, and P=0.02, respectively).	
Albano, Endocrine (IF: 3.63) 2019	174	Loss of RAI avidity independent predictor of disease specific survival	Metachoronous metastases shorter DSS on univariate analysis
Manohar Clin Nucl Med (IF: 7.79) 2018	62	Tg/LT4 and Tg doubling time <6 moths, higher metabolic tumor volume and total lesion glycolsis worse OS	
Sohn, Clin Endocrinol (Oxf) (IF: 3.48) . 2018	89 (lung M only)	RAI avidity was an independent predictor of cancer-specific death	Older age at diagnosis (≥55 years), radioactive iodine (RAI) nonavidity, preoperative or late diagnosis of metastasis and macro-nodular metastasis (≥1 cm) were predictive of decreased PFS and CSS.

Sabet, Eur J Nucl Med Mol Imaging (IF: 9.24) 2017	89	Metachronous M1 (>12 months form DTC diagnosis) were associated to worse 5 and 10 yr DSS after adjusting for age	
Kim, Thyroid (IF: 6.57) 2017	112 (lung M only)	After adjusting for age, sex, primary tumor size, extrathyroidal invasion, cervical lymph node metastasis, time of lung metastasis, and RAI avidity, the macronodular group also had shorter PFS and CSS (p = 0.009 and p = 0.03, respectively) than the micronodular group.	RAI avidity was a significant prognostic factor associated with better PFS and CSS (p = 0.013 and p = 0.021, respectively) in the micronodular group only.
Hirsch Endocr Pract (IF: 3.44) 2017	138	Improved OS (and disease progression) were associated with younger age, lung-only DM, and metastatic RAI avidity	
Choi, Eur J Endocrinol (IF: 6.66) 2016	93 (bone M only)	pre-RAIT group demonstrated significantly poorer overall survival (OS) (HR=1.86, P=0.04) than those in the post-RAIT group	In the post-RAIT group, older age (>45years), elevated serum thyroglobulin level (>250ng/mL), and the presence of skeletal-related events were significantly associated with poor OS.
Song, Eur J Endocrinol (IF: 6.66) 2015	372	Independent OS predictors: RAI uptake, age, combination with other distant metastases and pulmonary node size	
Lang, Ann Surg Oncol (IF: 5.34) 2013	52	osseous metastasis (RR 6.849, 95 % CI 1.495-31.250, P = 0.013) and non-RAI avidity (RR 7.752, 95 % CI 2.198-27.027, P = 0.001) were the two independent poor prognostic factors for CSS	Older age almost reached statistically significance (RR 1.055, 95 % CI 0.996-1.117, P = 0.068).
Mihailovic, Thyroid (IF: 6.57) 2009	77	multivariate analysis age had significantly greater influence on survival compared with iodine avidity (p < 0.001, p = 0.078, respectively)	
Lin, Thyroid (IF: 6.57) . 1999	68 PTC 69 FTC	Stage at diagnosis, follicular histotype, Tg>25 ng/mL	