RESEARCH

Initial clinical and treatment patterns of advanced differentiated thyroid cancer: ERUDIT study

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Abstract

Background: Up to 30% of differentiated thyroid cancer (DTC) will develop advanced-stage disease (aDTC) with reduced overall survival (OS).
Objective: The aim of this study is to characterize initial diagnosis of aDTC, its therapeutic management, and prognosis in Spain and Portugal.
Methods: A multicentre, longitudinal, retrospective study of adult patients diagnosed with aDTC in the Iberian Peninsula was conducted between January 2007 and December 2012. Analyses of baseline characteristics and results of initial treatments, relapse- or progression-free survival ((RP)FS) from first DTC diagnosis, OS, and prognostic factors impacting the evolution of advanced disease were evaluated.
Results: Two hundred and thirteen patients (median age: 63 years; 57% female) were eligible from 23 hospitals. Advanced disease presented at first diagnosis (*de novo* aDTC) included 54% of patients, while 46% had relapsed from early disease (recurrent/progressive eDTC). At initial stage, most patients received surgery (98%) and/or radioiodine (RAI) (89%), with no differences seen between median OS (95% CI) (10.4 (7.3–15.3) years) and median disease-specific-survival (95% CI) (11.1 (8.7–16.2) years; log-rank test $P = 0.4737$). Age at diagnosis being <55 years was associated with a lower risk of death (Wald chi-square (Wc-s) $P < 0.0001$), while a poor response to RAI to a higher risk of death ((Wc-s) $P < 0.05$). In the eDTC cohort, median (RP)FS (95% CI) was of 1.7 (1.0–2.0) years after RAI, with R0/R1 surgeries being the only common significant favourable factor for longer (RP)FS and time to aDTC ((Wc-s) $P < 0.05$).
Conclusion: Identification of early treatment-dependent prognostic factors for an unfavourable course of advanced disease is possible. An intensified therapeutic attitude may reverse this trend and should be considered in poor-performing patients. Prospective studies are required to confirm these findings.

Key Words

- advanced differentiated thyroid cancer
- relapsing differentiated thyroid cancer
- radioiodine-refractory differentiated thyroid cancer
- epidemiological study
- relapsing prognostic factors
- survival prognostic factors

Introduction

Differentiated thyroid carcinoma (DTC) is the most frequent subtype of thyroid cancer (1). In the initial disease scenario, therapeutic approach mainly relies on surgery and treatment with I-131 radioiodine (RAI). Overall survival (OS) rate in this population is high (98.3% and 90% at 5 and 10 years, respectively) after initial diagnosis (2, 3).

However, up to 20% of patients with DTC, excluding those with microcarcinomas, present with metastasis or locally advanced disease at the time of diagnosis (4, 5, 6). Moreover, in up to 30% of patients with initial early-stage diagnosis (eDTC), disease relapses into the advanced stage (aDTC), either as locoregional unresectable or metastatic dissemination (7). Additionally, one-third of the metastatic tumours will show low avidity for iodine at the time of diagnosis and nearly two-thirds will become refractory to RAI (radioiodine-refractory differentiated thyroid cancer; RR-DTC) along treatment (8, 9).

In the aDTC situation, survival rates decrease markedly. The 10-year survival rate for RAI-responder patients is about 56%, whereas in RR-DTC patients, this is only 10% (10). In this scenario, patient's care usually involves a multidisciplinary team whose composition is variable among countries and centres (11, 12).

In this clinical context, available data in Europe are outdated and very limited. In response to this need, the ERUDIT study aimed to characterize the natural evolution of adult aDTC in Spain and Portugal.

Specifically, this communication will describe the demographic and clinical characteristics, usage patterns, and efficacy profile of upfront therapies used to treat aDTC, either presenting at first diagnosis (*de novo* aDTC) or after successive relapses (recurrent/progressive eDTC). We will also explore potential prognostic factors correlating with disease relapse/progression from eDTC into aDTC and death.

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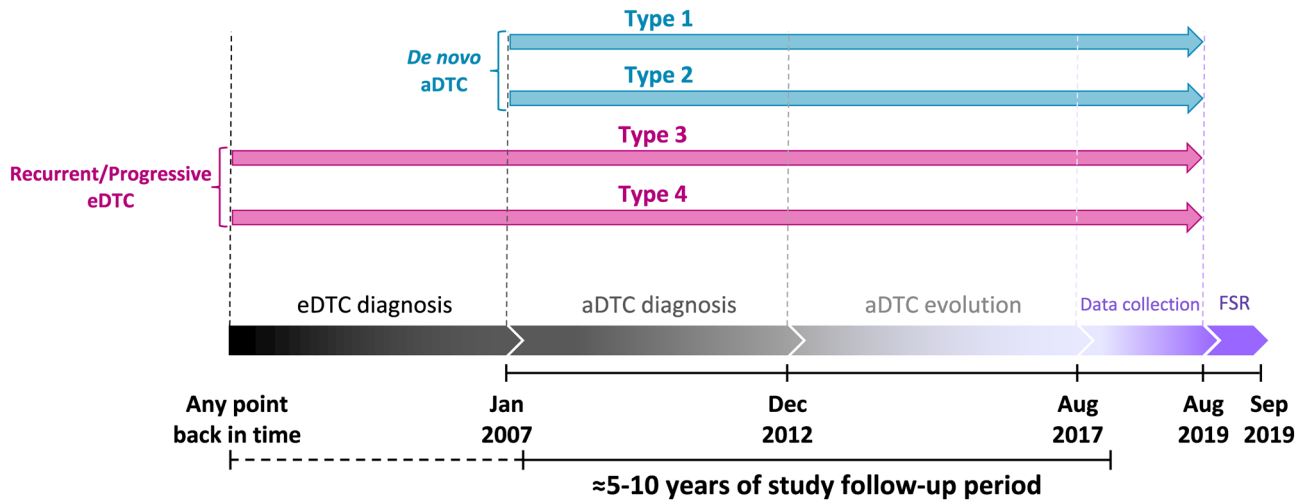

Figure 1
ERUDIT study design and evolution timeline of the aDTC patients included according to the type of their diagnosis. Type 1: *de novo* metastatic with resectable locoregional disease. Type 2: *de novo* locoregional unresectable disease. Type 3: recurrent metastatic without resectable locoregional disease. Type 4: recurrent locoregional unresectable disease, with or without distant metastases. aDTC, advanced differentiated thyroid cancer; eDTC, early stage differentiated thyroid cancer; FSR, final study report.

Methods

Study design and setting

ERUDIT is a multicentre, observational, longitudinal, international, and retrospective study run in 22 representative hospitals from Spain and Portugal (Supplementary Table 1, see section on supplementary materials given at the end of this article). Clinical records from eligible patients diagnosed with aDTC from January 2007 to December 2012, both inclusive, were retrospectively reviewed until August 2017 (expected 5–10 years follow-up) and collected from August 2017 to August 2019 (Fig. 1).

Patients

Patient records were considered if aDTC (papillary, follicular, Hürthle's cell, or mixed or poorly differentiated) diagnosis was confirmed with first evidence of unresectable locally advanced and/or metastatic disease (presenting either *de novo* or relapsed after first treatment) being as such documented during the inclusion period. Accordingly, four patient types were predefined in the study protocol to account for most common situations at diagnosis: Type 1, *de novo* metastatic with resectable locoregional disease; Type 2, *de novo* locoregional unresectable disease; Type 3, recurrent metastatic with resectable locoregional disease; and Type 4, recurrent locoregional unresectable disease, with/without distant metastases. Patients had to be ≥18 years old at initial diagnosis and their medical records be sufficiently complete to allow data analysis until 31 August 2017, death, or lost to follow-up, whichever happened first. Patients with diagnosis of anaplastic or medullary thyroid cancer were excluded.

Patients' informed consent was requested. The study was performed in compliance with all basic principles of the Helsinki Declaration (2013) from World Medical Association (13) and applicable national regulations. Both accredited Research Ethics Committees of Hospital Universitario Gregorio Marañón (Madrid, Spain) and National Ethics Committee for Clinical Research (Portugal) approved it.

Variables at initial diagnosis and clinical endpoints

Demographic and clinical characteristics

Gender, comorbidities, initial diagnosis of DTC (incidental post-surgery, no-incidental), diagnosis type (*de novo* or recurrent), histology result, biochemistry at diagnosis (patients with thyroglobulin (Tg) levels and/or anti-Tg positive in serum), tumour size (mm), lobes involved, tumour focality, tumour invasion (adjacent tissue, vascular, lymphatic nodes, absent, or no invasion), metastases at diagnosis by site, and type of image diagnosis were collected as variables of interest (Table 1 and Supplementary Table 2).

Therapeutic approach and response

(a) Surgery: neck dissection; microscopic complete resection (R0), macroscopic resection with microscopic residual tumour (R1), and gross macroscopic residual tumour (R2) and histological results; (b) ablative

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(adjuvant) I-131 radioiodine (RAI): administered dose, cumulative RAI dose by intervention, RAI refractoriness at initial diagnosis, use of human recombinant thyroid-stimulating hormone (hrTSH) per intervention, RAI response according to American Thyroid Association (ATA) (1) criteria (excellent, structural incomplete, biochemical incomplete, and indeterminate); and (c) radiotherapy: dose and response according to the standard Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 definition (objective response rate as the sum of complete response plus partial response; stable disease and progressive disease as per physician-reported best response to treatment) (Supplementary Table 3) (14).

Medical specialities involved in initial disease management

Department responsible for patient monitoring and the multidisciplinary committee for decision-making were involved.

Potential confounding variables

A total of 33 potential covariates were analysed using the Kaplan–Meier (K–M) method. Later, all covariates were entered into the multivariate Cox model following both forwards addition and backwards removal of non-significant covariates with a type I error ≤ 1. Potential covariates included variables at initial diagnosis described above (baseline characteristics and therapeutic approaches), covariates concerning relapse or progression of eDTC into aDTC (type of relapse, surgery, cumulative RAI dose, therapeutic RAI with stimulating agent (hrTSH), response to therapeutic RAI), and variables related to the advanced disease/RAI-refractory disease (RAI refractoriness (RR) criteria 1, 5, 6; RR criteria 2+3+4, RR criteria 7+8 (15), Eastern Cooperative Oncology Group score (16), watchful waiting (yes/no), watchful waiting duration (months), surgery for advanced/RAI-refractory disease, radiotherapy for advanced/RAI-refractory disease, use of systemic therapy, number of lines, and reason for stopping systemic therapy).

Data were obtained from medical records resulting from standard clinical practice in participating sites and collected in electronic case report forms as mandated in the ERUDIT study protocol (EIS-CDT-2017-01). Investigators received on-site training before data entry to guarantee consistency. The eCRF included a range of filters and logical controls to reduce errors, and an authorized Clinical Research Associate helped data entering at various sites.

Clinical endpoints of interest included OS and disease-specific survival (DSS), which were measured from the initial DTC diagnosis to death in the global study population. Relapse- or progression-free survival ((RP)FS) was defined as a composite time-to-event variable involving only eDTC patients that had relapsed into aDTC or died provided they were free of disease after first treatment or, alternatively, progressed into aDTC or died having residual disease after first treatment. Finally, all potential prognostic factors concerning these survival variables were explored in the global study population and the recurrent/progressive eDTC cohort.

Statistical methods

An estimated sample size of close to 300 patients was originally considered representative of nearly 20% of all aDTC diagnoses made in Spain and Portugal during the inclusion period based on available incidence data at the time of protocol writing.

Description of baseline characteristics and therapeutic approaches received by patients was done for the total study population and for the two mutually exclusive groups *de novo* aDTC (Types 1+2) and recurrent/progressive eDTC (Types 3+4). Additional time-to-event analyses involved other *ad hoc* groups like (a) patients with metastatic disease (Types 1+3) vs those with the locoregional unresectable disease (Types 2+4) or (b) by first RAI ATA response: excellent, structural incomplete, biochemical incomplete, and indeterminate (1). Missing data were not imputed (Fig. 2).

Data were analysed using SAS Institute Inc. Version 8.2 software (Cary, NC, USA). All data were summarised using adequate descriptive statistics (mean, S.D.; median, quartiles, 95% CI; minimum and maximum for continuous variables; and absolute and relative frequencies for categorical variables). Comparisons of continuous variables were done by Wilcoxon rank-sum test, and categorical variables by chi-square test or Fisher's exact test. Parameters based on objective response followed the standard RECIST v1.1 definition (14) as per physician-reported best response to treatment.

OS and (RP)FS survival functions were analysed and compared using K–M and Mantel–Haenszel (log-rank) methods. Prognostic risk factors for OS, (RP)FS, and time to develop aDTC/RR-DTC were analysed by univariate and multivariate Cox proportional risk-based regression model. Non-evaluable medians in K–M curves were identified

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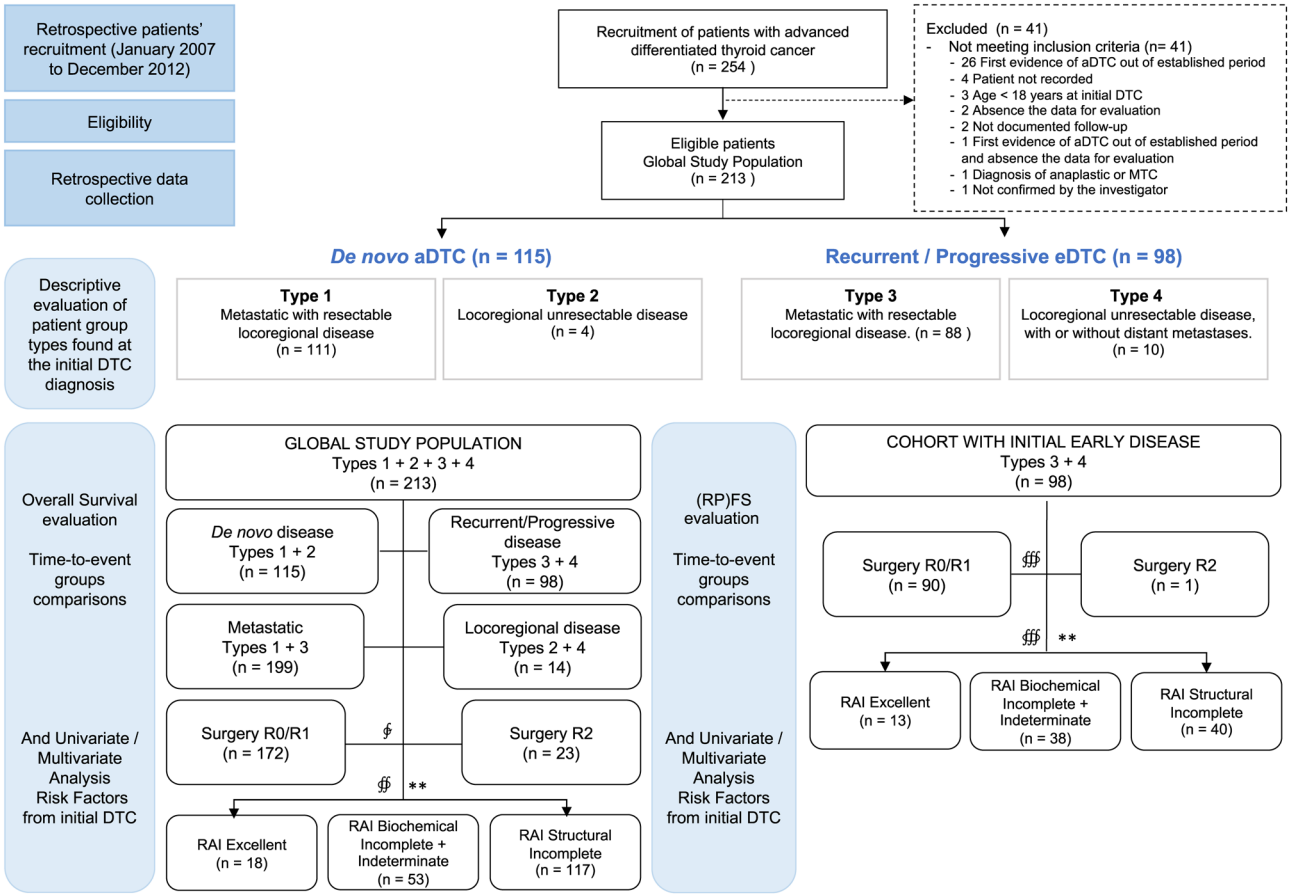

Figure 2
Flow diagram of eligible patients and analysed groups with evaluable data from the initial diagnosis of differentiated thyroid cancer (DTC). The (relapse/progression) free survival ((RP)FS) evaluation describes the time elapsed from an upfront treatment until death, relapse into advanced DTC (aDTC) in patients who were initially free of disease, or structural progression into aDTC in patients who had initial residual disease, respectively. n, number of patients with available data evaluable. ∮, from 208 total patients with evaluable outcome from first surgery to death, of which, 13 patients were excluded because of 'metastases resection' (n = 8) and 'other results' (n = 5). ∯, only 188 patients had evaluable response from the first RAI therapy to death. ∯∮, from 98 total patients in the cohort with initial early disease with evaluable outcome from first surgery to death or from the first RAI therapy to death, of which, 7 patients were excluded because of 'metastases resection' (n = 3) and 'other results' (n = 4). **, ATA RAI response.

as NE. All *P*-values were nominal and when <0.05 were considered statistically significant.

Results

A total of 213 eligible patients were identified from the initial 254 patients diagnosed with aDTC from January 2007 to December 2012 in 23 participant hospitals (22 Spanish and 1 Portuguese). Patients were grouped according to the time and disease extension at aDTC diagnosis for the descriptive and comparative analysis (Fig. 2). Fifty-four per cent (115/213) were diagnosed with *de novo* aDTC and 46% (98/213) with eDTC that, eventually after one or more relapses to previous interventions, became aDTC.

Demographic, clinical, and treatment characteristics of patients at initial DTC diagnosis

Study population had a median (Q1–Q3) age of 63.0 (51.0–71.0) years, and 59% (126/213) were female. Forty-three per cent (91/213) of patients had comorbidities at the time of DTC diagnosis, being cardiovascular disease in 28.6% (61/213) of them. Concerning primary tumour characteristics, median (Q1–Q3) size was 40 (25.0–57.0) mm. Almost 60% (125/209) of patients presented with papillary thyroid carcinoma, 18.7% (39/209) with follicular thyroid carcinoma, 10.0% (21/209) with Hürthle cell carcinoma, and 3.8% (8/209) with poorly differentiated carcinoma. Initial imaging techniques showed unilateral primary involvement in 66.1% (119/180), extrathyroidal invasion in 26.7% (48/180),

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Table 1 Demographic and clinical characteristics of the study population at initial disease presentation (*N* = 213).

Parameter	Global study population	*De novo* aDTC	Recurrent/progressive eDTC	*P*-value
Patient, no. (%)	213 (100)	115 (54.0)	98 (46.0)	NA
Age at initial diagnosis, median (Q1–Q3), years	63.0 (51.0–71.0)	67.0 (57.0–73.0)	56.5 (45.0–67.0)	0.0002[c]
Gender, patient no. (%)				
Female	126 (59.2)	65 (56.5)	61 (62.2)	0.3970
Male	87 (40.8)	50 (43.5)	37 (37.8)	
Comorbidities, patient no. (%)				
≥1 comorbidity	91 (42.7)	50 (43.5)	41 (41.8)	0.7667
Cardiovascular	61 (28.6)	33 (28.7)	28 (28.6)	0.9841
Metabolic	40 (18.8)	26 (22.6)	14 (14.3)	0.1211
Other clinically relevant	23 (10.8)	13 (11.3)	10 (10.2)	0.7965
Initial diagnosis of DTC and method, patient no. (%)				
Incidental post-surgery	45 (21.1)	15 (13.0)	30 (30.6)	0.0017[c]
No incidental	168 (78.9)	100 (87.0)	68 (69.4)	
Echography	101 (60.1)	54 (54.0)	47 (69.1)	0.0671
Others	65 (38.7)	45 (45.0)	20 (29.4)	
Not available	2 (1.2)	1 (1.0)	1 (1.5)	
Fine needle aspiration result, patient no. (%)	129 (60.6)	71 (61.7)	58 (59.2)	0.7037
Malignant	100 (77.5)	60 (84.5)	40 (69.0)	0.0085[c]
Indeterminate	17 (13.2)	4 (5.6)	13 (22.4)	
Benign	6 (4.7)	5 (7.0)	1 (1.7)	
Nondiagnostic	6 (4.7)	2 (2.8)	4 (6.9)	
Histological result, patient no. (%)				0.0497[c]
Papillary thyroid carcinoma	125 (59.8)	67 (60.4)	58 (59.2)	
Follicular thyroid carcinoma	39 (18.7)	26 (23.4)	13 (13.3)	
Hürthle cell carcinoma	21 (10.0)	5 (4.5)	16 (16.3)	
Poorly differentiated	8 (3.8)	5 (4.5)	3 (3.1)	
Mixed carcinoma (papillary and follicular)	7 (3.3)	4 (3.6)	3 (3.1)	
Others	9 (4.3)	4 (3.6)	5 (5.1)	
Biochemistry at diagnosis,[a] patient no. (%)	74 (34.7)	42 (36.5)	32 (32.7)	0.5545
Diagnosis images, patient no. (%)	180 (100)	93 (51.7)	87 (48.3)	0.1120
Measurable disease, no. (%)	106 (58.9)	58 (62.4)	48 (55.2)	0.3270
Tumour size, median (mm) (Q1–Q3)	40.0 (25.0–57.0)	40.0 (26.0–60.0)	38.5 (25.0–50.5)	0.3478
Lobes involved, no. (%)				0.8248
Left or right	119 (66.1)	60 (64.5)	59 (67.8)	
Both	51 (28.3)	27 (29.0)	24 (27.6)	
Not available	10 (5.6)	6 (6.5)	4 (4.6)	
Tumour invasion,[b] no. (%)				
Present	48 (26.7)	34 (36.6)	14 (16.1)	[d]
Absent	34 (18.9)	12 (12.9)	22 (25.3)	[d]
Unknown	78 (43.3)	39 (41.9)	39 (44.8)	[d]
Pathological lymph nodes	37 (20.6)	24 (25.8)	13 (14.9)	[d]
Metastases by site, no. (%)				
Lung	66 (71.0)	66 (71.0)	[d]	
Liver	5 (5.4)	5 (5.4)	[d]	
Bone	33 (35.5)	33 (35.5)	[d]	
Others	3 (3.2)	3 (3.2)	[d]	

[a]Refers patients with thyroglobulin (Tg): Tg levels and/or anti-Tg positive in serum; [b]tumour invasion refers to disease invading either adjacent tissues and structures and/or vascular spaces. Patients could be part of more than one tumour invasion category making statistical testing not feasible; [c]statistically significant ($P < 0.05$); [d]recurrent/progressive eDTC patients, by definition, had no metastases at diagnosis.
aDTC, advanced differentiated thyroid cancer; eDTC, early differentiated thyroid cancer.

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and/or pathological lymph nodes in 20.6% (37/180). Distant metastases were evidenced in 51.7% (93/180) of patients, mostly in lung (71.0%) and bone (35.5%) (Table 1). Baseline characteristics showed that *de novo* aDTC patients were significantly older, the results of tumour FNA were more likely to be malignant, and with preferential follicular histology, compared to recurrent/progressive eDTC patients at initial diagnosis (Wilcoxon rank-sum test $P=0.0002$, Fisher's exact test $P=0.0085$, and Fisher's exact test $P= 0.0497$; respectively) (Table 1).

Standard upfront treatments were used to manage DTC after initial diagnosis (Supplementary Table 3). Concisely, at least one surgery was given to 98.1% (209/213) of patients and 75.1% (157/209) of them were subjected to any sort of neck dissection. Microscopic local complete resection R0 was achieved in 68.4% (143/209) of cases. Eighty-nine per cent (190/213) of patients received at least one RAI treatment, and 30% (57/190) had a median (Q1–Q3) cumulative dose of 450.0 (400.0–500.0) mCi after three doses. Most frequent ATA response to treatment was 'structural incomplete,' being 61.6% (117/190) after the first RAI dose. Ten per cent (21/213) of patients received at least one course of locoregional external beam radiotherapy, and 52% (11/21) showed subsequent 'stable disease' according to RECIST v1.1 (14). Significant differences were observed between results attained by *de novo* aDTC and recurrent/progressive eDTC, potentially favouring a better course of disease in eDTC patients (surgical results, post-RAI response, etc) (Supplementary Table 3).

Multidisciplinary committees monitored initial management in 73.2% (152/231) of the cases, the Endocrinology department being the most frequently involved followed by Nuclear Medicine and Oncology (Table 2).

Time-to-event endpoints in the global study population

Median (Q1–Q3) study follow-up was 6.2 (4.5–9.0) years from initial DTC diagnosis and, specifically, 5.2 (3.3–7.0) years from aDTC diagnosis to end of the study. No statistical differences were observed between median OS (mOS) and median DSS (mDSS) from initial DTC diagnosis to death (mOS (95% CI): 10.4 (7.3–15.3) years and mDSS (95% CI): 11.1 (8.7–16.2) years; log-rank test $P=0.4737$) (Fig. 3A).

mOS (95% CI) of *de novo* aDTC was significantly shorter compared to that in recurrent/progressive eDTC patients (6.4 (5.1–NE) vs 15.3 (10.4–17.8) years, respectively; log-rank test $P<0.0001$) (Fig. 3B). However, the extension of advance disease (metastatic vs locoregional) did not have statistical impact on mOS (10.4 (7.3–16.0) vs 8.6 (0.7–12.5) years, respectively; log-rank test $P=0.1869$). Additionally, mOS (95% CI) after first surgery was 10.4 (8.1–16.0) years, being 7.8 years longer in patients with complete macroscopic resection (R0/R1) compared to those with incomplete (R2) resections (12.5 (8.8–16.8) vs 4.7 (2.3–5.2) years, respectively; log-rank test $P<0.0001$) (Fig. 3C). Finally, mOS (95% CI) after first RAI treatment was 10.1 (7.6–17.5) years, being significantly higher in patients achieving ATA 'excellent response' compared to those with 'incomplete biochemical' or 'incomplete structural' response (NE (8.2–NE) vs 10.1 (6.8–NE) vs 8.3 (5.7 - 17.5) years; log-rank test $P=0.0212$) (Fig. 3D).

Time-to-event endpoints in the recurrent/progressive eDTC population

Median (RP)FS (95% CI) after initial radical surgery was 2.3 (1.7–2.9) years ($n=90$), and 1.7 (1.0 - 2.0) years ($n=91$) after initial RAI, being significantly higher for patients

Table 2 Medical specialities involved in disease management after initial diagnosis (N = 213).

Parameter	***De novo* aDTC** (N = 115)	**Recurrent/progressive eDTC** (N = 98)	**Global study population** (N = 213)
Service responsible for patient monitoring, patient no. (%)			
Endocrinology	75 (65.2)	67 (68.4)	142 (66.7)
Nuclear medicine	19 (16.5)	15 (15.3)	34 (16.0)
Oncology	15 (13.0)	12 (12.2)	27 (12.7)
Surgery	1 (0.9)	1 (1.0)	2 (0.9)
Others		1 (1.1)	1 (0.5)
Not available[a]	5 (4.3)	2 (2.0)	7 (3.3)
Presence of multidisciplinary committee, patient no. (%)			
No	28 (24.3)	22 (22.4)	50 (23.5)
Yes	82 (71.3)	74 (75.5)	156 (73.2)
Not available	5 (4.3)	2 (2.0)	7 (3.3)

[a]Records could not be retrieved from the electronic case report form.

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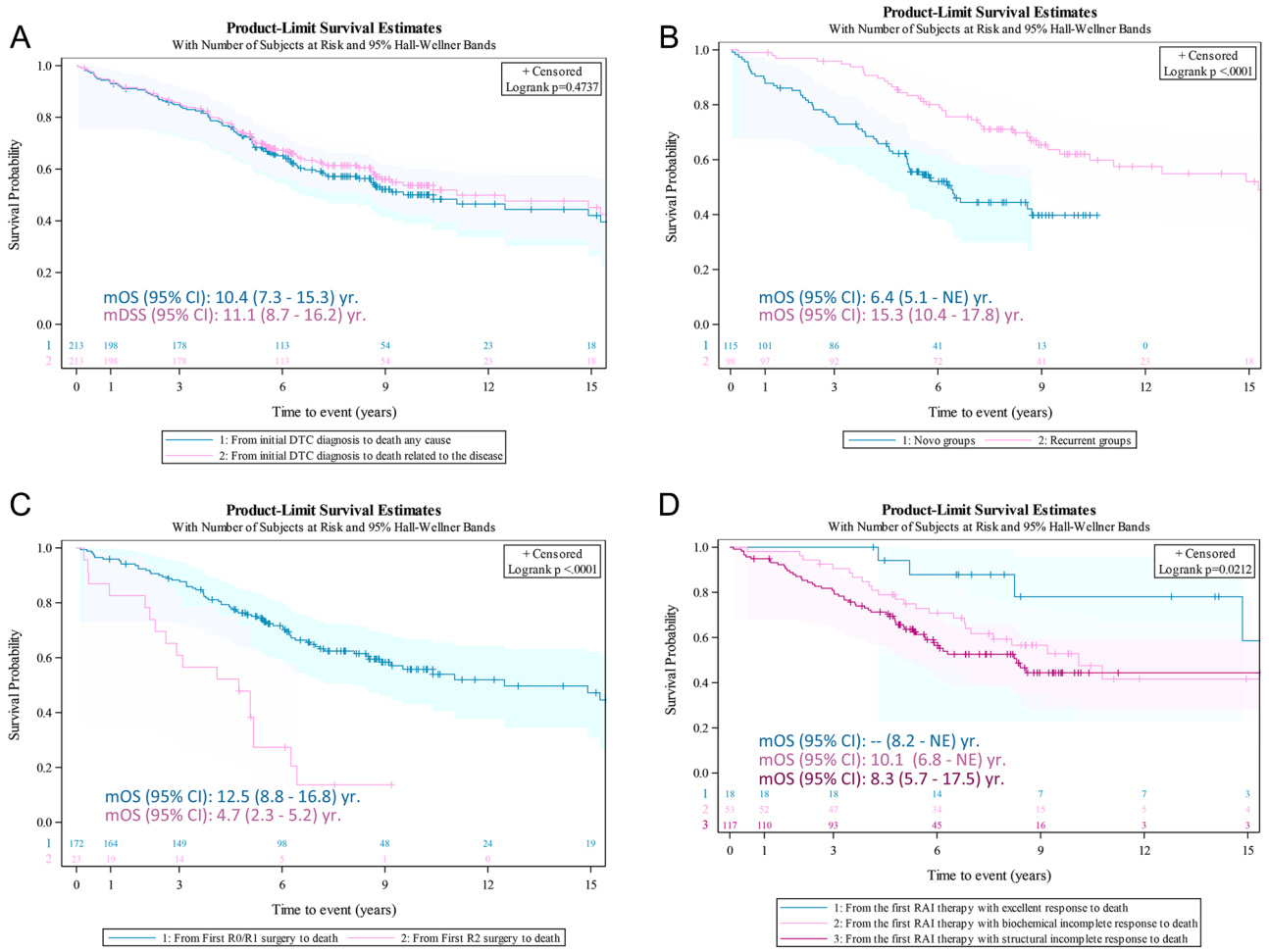

Figure 3

Survival Kaplan–Meier curves from the initial differentiated thyroid cancer (DTC) diagnosis to death in the global study population. (A) Comparison of overall survival (OS) from initial DTC diagnosis to death by any cause (blue) vs disease-specific survival (DSS) from initial DTC diagnosis to death related to the disease (pink). No differences were found (log-rank $P = 0.474$). (B) Comparison of OS from initial DTC diagnosis to death by any cause according to the time of advanced DTC (aDTC) diagnosis: *de novo* (blue) vs recurrent/progressive (pink). The OS from the initial DTC diagnosis was a median 8.9 years shorter in patients with *de novo* aDTC (log-rank test $P < 0.0001$). (C) Comparison of OS from first surgery: complete macroscopic resection, R0/R1 (blue) vs incomplete resection, R2 (pink). The OS from initial surgery was a median 7.8 years longer in patients with R0/R1 outcome (log-rank test $P < 0.0001$). (D) Comparison of OS from first RAI (±surgery) according to ATA response criteria: excellent (blue) vs biochemical incomplete (pink) vs structural incomplete response (magenta) (log-rank $P = 0.0212$). mOS (95% CI): median OS (95% CI) years.

achieving ATA 'excellent response' compared to those with 'incomplete biochemical' or 'incomplete structural' response after this initial treatment (4.3 (0.9–9.0) vs 2.0 (1.1–2.8) vs 0.6 (0.4 - 1.8) years, respectively; log-rank test $P=0.0034$) (Fig. 4).

Analysis of prognostic factors

OS

In the global study population, initial DTC diagnosis under 55 years was confirmed as a favourable prognostic factor associated with lower risk of death (adjusted hazard ratio (aHR): 0.39, 95% CI: 0.2–0.7; Wald chi-square $P=0.0018$). In contrast, cumulative RAI dose <600 mCi, no RAI treatment, and RAI-scan positivity after the initial RAI treatment were all significantly associated with a higher risk of death (aHR (95% CI): 5.3 (2.3–12.0), Wald chi-square $P=0.0001$; aHR (95% CI): 6.75 (2.4–18.9), Wald chi-square $P=0.0003$; and aHR (95% CI): 2.4 (1.1–5.3), Wald chi-square $P=0.0307$; respectively) (Table 3 and Supplementary Table 4).

(RP)FS

In the recurrent/progressive eDTC cohort, attaining R0/R1 surgical result and being eligible for rescue surgeries was associated to a longer time to disease relapse or progression

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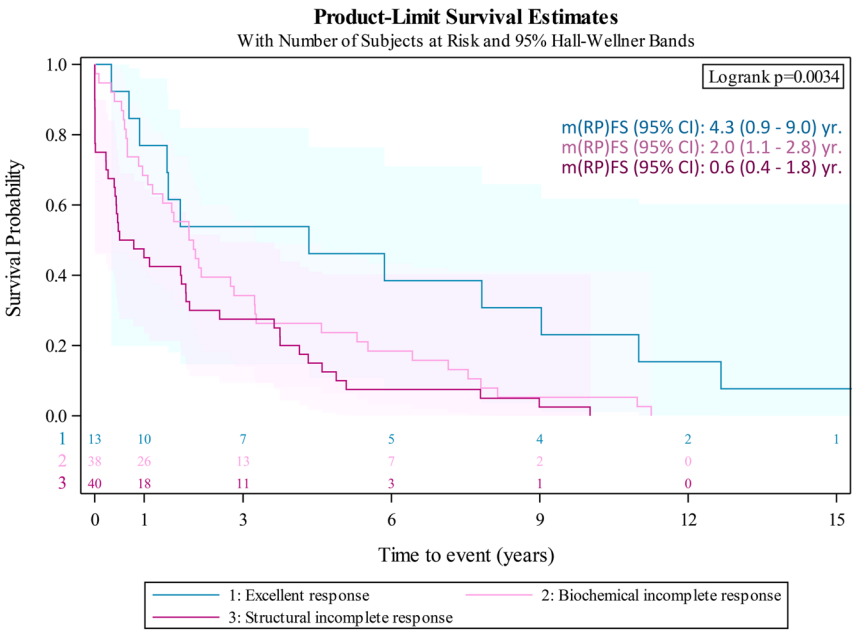

Figure 4
(Relapse/progression)-free survival ((RP)FS) after the first RAI treatment in patients with early disease condition stratified by ATA response (log-rank $P = 0.0034$). 1: excellent (blue); 2: incomplete biochemical (pink). 3: incomplete structural response (magenta). m(RP)FS (95% CI): median (95% CI) years.

into aDTC/RR-DTC compared to having an R2 outcome (aHR (95% CI): 0.003 (0.00–0.05), Wald chi-square $P=0.0001$ and aHR (95% CI): 0.003 (0.00–0.05), Wald Chi-square $P=0.0001$; respectively). Regarding RAI therapy, both cumulative RAI doses <600 mCi and use of a pre-RAI hrTSH were positively associated to shorter time to relapse, progression, or death aDTC (aHR (95% CI): 2.45 (1.4–4.4), Wald chi-square $P=0.0025$ and aHR (95% CI): 3.78 (1.1–12.6), Wald chi-square $P=0.0304$; respectively). Resulting in ATA incomplete response (biochemical, structural, or both) after the first RAI treatment was also associated with an increased risk of earlier relapse, progression, or death (aHR (95% CI): 4.3 (2.0–9.2), Wald chi-square $P=0.0002$ and aHR (95% CI): 2.47 (1.2–5.3), Wald chi-square $P=0.0188$; respectively) (Table 4 and Supplementary Table 5).

Time to aDTC/RR-DTC

Additionally, we analysed prognostic factors associated with the time of eDTC relapse or progression into aDTC or RR-DTC. Same as with (RP)FS, attaining R0/R1 surgical result and being eligible for rescue surgeries was associated with a longer time to relapse or progression into aDTC/RR-DTC compared to the R2 result (aHR (95% CI): 0.002 (0.00–0.03), Wald chi-square $P=0.0002$ and aHR (95%

Table 3 Multivariate analyses for overall survival in the global study population.

Covariates[a]	*N*	**Overall survival** (Cox proportional hazard model)	
		Adjusted hazard ratio (95% CI)	Wald chi-square *P*-value
General variables			
Age at diagnosis in years			
≥55 (ref.)	149		
<55	64	0.39 (0.214–0.703)	0.0018[d]
Variables of initial diagnosis and first treatment			
RAI cumulative dose			
≥600 mCi (ref.)	29		
<600 mCi	160	5.32 (2.352–12.037)	<0.0001[d]
No RAI treatment[b]	23	6.75 (2.406–18.946)	0.0003[d]
RAI-scan positivity after initial RAI treatment[c]			
No (ref.)	26		
Yes	133	2.41 (1.085–5.345)	0.0307[d]

[a]All covariates were entered into a Cox regression model, [b]patients not receiving RAI because of it not being clinically indicated or having tumours with negative RAI scans; [c]refers to 6–12 months follow-up post-treatment scans in patients that could have received surgery ± RAI as first therapeutic approach; [d]Statistically significant ($P < 0.05$).
(ref.), reference category; OS, overall survival; RAI, radioactive iodine (I-131).

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Table 4 Multivariate analyses for (relapse/progression) free survival and time to develop aDTC/RR-DTC in the eDTC cohort (*N* = 98).

Covariates[a]	*N*	**(RP)FS** (Cox proportional hazard model)		**Time to develop aDTC/RR-DTC** (Cox proportional hazard model)	
		Adjusted hazard ratio (95% CI)	Wald chi-square *P*-value	Adjusted hazard ratio (95% CI)	Wald chi-square *P*-value
Variables of initial diagnosis and first treatment					
Surgical outcome					
R2 (ref.)	1				
R0/R1	90	0.003 (0.000–0.048)	<0.0001[f]	0.002 (0.000–0.034)	<0.0001[f]
Others[b]	7	0.003 (0.000–0.048)	<0.0001[f]	0.004 (0.000–0.064)	0.0001[f]
RAI cumulative dose					
≥600 mCi (ref.)	5				
<600 mCi	87	3.78 (1.13–12.60)	0.0304[f]		
No RAI treatment[c]	5	2.8 (0.53–14.76)	0.2237		
RAI with stimulating agent at first instance[d]					
No (ref.)	71				
Yes	18	2.45 (1.37–4.38)	0.0025[f]	1.82 (1.02–3.26)	0.0438[f]
RAI Response at first instance ATA criteria[e]					
Excellent (ref.)	13				
Biochemistry incomplete + indeterminate	38	2.47 (1.16–5.26)	0.0188[f]	2.34 (1.08–5.07)	0.0315[f]
Structural incomplete	40	4.32 (2.03–9.21)	0.0002[f]	3.35 (1.55–7.23)	0.0021[f]

[a]All covariates were entered into a Cox regression model; [b]pathological lymph node dissections or metastasectomies; [c]patients not receiving RAI because of it not being clinically indicated or having tumours with negative RAI scans; [d]following standard practice in Spain and Portugal, patients not receiving hrTSH prior to RAI, were deprived of LT4; [e]Haugen *et al*., 2016;[(1)] [f]statistically significant ($P < 0.05$).
(ref.), reference category; (RP)FS, relapse/progression-free survival; aDTC, advanced differentiated thyroid cancer; R0, microscopic complete resection; R1, macroscopic resection with microscopic residual tumour; R2, gross macroscopic residual tumour; RAI, radioactive Iodine (I-131); RR-DTC, radioiodine-refractory differentiated thyroid cancer.

CI): 0.004 (0.00–0.06), Wald chi-square $P=0.0001$; respectively). Finally, both use of pre-RAI hrTSH (aHR (95% CI: 1.8 (1.0–3.2); Wald chi-square $P=0.0438$) and incomplete response to first RAI were positively associated with earlier relapse or progression into aDTC/RR-DTC ('incomplete biochemical' aHR (95% CI): 2.3 (1.1–5.1), Wald chi-square $P=0.0315$ and 'incomplete structural' aHR (95% CI): 3.35 (1.5 - 7.2); Wald chi-square $P=0.0021$) (Table 4).

Discussion

ERUDIT is a retrospective and longitudinal study of Spanish and Portuguese aDTC patients that reviewed, among others, their relevant demographic and clinical data at the time of their initial diagnosis and the therapeutic management that ensued. Prognostic factors impacting their survival as well as their relapse/progression from early into advanced stages have been also examined.

In total, 213 advanced DTC patients were retrospectively followed for a median of 6.2 years from their initial DTC diagnosis. The median age at diagnosis was 63 years, being more frequent in females than males, and with half of patients presenting at least one comorbidity, in most cases, a cardiovascular disorder. Papillary thyroid carcinoma was the most common histological type. Despite our study expressly selecting aDTC patients, these characteristics at initial diagnosis did not differ much from those previously reported in European or North American series covering a wider range of population (2, 17, 18, 19, 20).

Half (54%) of our patients were diagnosed with *de novo* aDTC and, of them, 98% presented with distant metastases affecting mainly lungs and bones. These findings are consistent with other studies also describing half of the advanced patients present with distant metastases at first diagnosis (4, 21, 22). In addition, more recent studies reported a higher prevalence of lung metastasis (49–75%) compared to bone metastasis (17–39%) in patients with aDTC at presentation regardless of the histological type (23, 24, 25). The remaining 46% in our series were eDTC patients who progressed into aDTC stages after receiving standard therapy (surgery ± RAI).

Initial DTC treatment followed standard recommendations, thus relying on surgery and RAI treatment (1). Consequently, different medical specialities were involved in disease management under a multidisciplinary team in over 73% of the cases after initial diagnosis. It is known that the implementation of multidisciplinary teams can help to optimise therapeutic results both for patients and for the healthcare system itself

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(11, 12) and, according to our observations, this aspiration was already becoming the standard in the Iberian Peninsula even before this was established as usual clinical practice (11, 26). ERUDIT data show that Endocrinology was the main responsible department followed by Nuclear Medicine and Oncology departments.

In this study, both mOS and mDSS measured since the initial DTC diagnosis were around 10 years in the global study population with no statistical differences observed between them. This observation implies that aDTC is the leading cause of death in these patients.

OS analyses by groups showed that recurrent/progressive eDTC patients had longer survival expectancy than those with advanced *de novo* aDTC diagnosis, independently of their disease extension. As previously reported, multivariate Cox model revealed that initial DTC diagnosis <55 years, RAI responsiveness (no evidence of post-RAI uptake and initial cumulative RAI (≥600 mCi)) were positive independent prognostic risk factors of longer OS in the global study population. Unlike other studies, gender, histological type, and metastatic localizations had no statistically significant impact on OS (21, 22, 25, 27). These discrepancies might be explained by the heterogeneity of the global population analysed, our limited sample size, and the many differences found in the published literature (21, 22, 25, 27). For example, Schlumberger *et al*. (22) in a similar study with 394 metastatic patients showed that age at the discovery of metastases and radioiodine avidity were favourable predictors of survival. Other studies found that older age at diagnosis, male sex, metastatic site (lung), and histology (follicular type) were significant factors for poor prognosis in patients with metastases at presentation (23, 24, 25, 27).

Regarding the recurrent/progressive eDTC cohort, we found an m(RP)FS of 2.3 years and an mOS of 15 years. Most relevant risk factors found in univariate and multivariate analysis showed that R0/R1 initial surgery and being eligible for rescue surgeries (local or metastatic) were protective factors for death, early relapse, or progression into aDTC/RR-DTC. However, this observation must be taken cautiously due to the small sample classified in the R2 group. Additionally, poor RAI responsiveness (low cumulative RAI doses, need for use of pre-RAI hrTSH, and ATA biochemical and structural incomplete RAI responses) after initial treatment was positively associated with a higher likelihood of death, premature relapse, or progression into advanced stages. Interestingly, not only patients achieving structural incomplete (0.6 years) but even biochemical incomplete responders (2.0 years) had a shorter m(RP)FS compared to those attaining excellent response (4.3 years), somewhat speaking of the precocious biological aggressiveness of the persistent tumours identified within our series. These observations not just confirm the prognostic relevance of the dynamic ATA risk stratification system (28) but also provide real estimates of the expected evolution that high-risk patients may have. This, in addition, to contradict the widely accepted evidence on the similar prognosis of these two populations (biochemical incomplete and excellent ATA response), should encourage second thoughts when first dealing with high-risk tumours in daily practice. In line with this, Sciuto *et al.* (19) retrospectively analysed 1553 subjects diagnosed with DTC and highlighted the relevance of RAI responsiveness as the strongest predictor of a good outcome in terms of survival. Several studies have described other independent predictors of disease persistence/recurrence which include male gender, diagnosis age >45, histology, high serum Tg levels, and the presence of distant metastases (19, 27, 29, 30). In our study, age at diagnosis, gender, and disease extension were statistically significant only in univariate analysis but not in the adjusted multivariate Cox model, probably due to sample size limitations and the aggressive behaviour that characterize our sample selection. However, common sense dictates early identification of these poor prognostic indicators since the initial DTC diagnosis and rapid implementation of commensurate therapeutic measures could greatly change the time to relapse, progression, or eventually death of these patients with aggressive tumour profile.

ERUDIT study presents several limitations and strengths. The main limitations involve its retrospective nature and limited sample size that very likely have underrepresented the actual aDTC incidence in the Iberian Peninsula despite this being outside the scope of the study. The reduced sample size, however, could have affected groups' distribution, statistical power of uni- and multivariate analyses, and potentially introduced a selection bias mainly in the recurrent/progressive eDTC cohort. On the other hand, this study longitudinally follows for the first time relevant clinical data of European aDTC patients first diagnosed *de novo* or as recurrent/progressive from initial eDTC that have resulted in descriptive and prognostic information useful in everyday practice decision-making.

Conclusion

ERUDIT is the first epidemiological study that reviews the natural history of aDTC in Spain and Portugal. It has

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revealed interesting findings such that most aDTC tumours (93%) present with metastases at diagnosis of advanced disease (*de novo* or recurrent/progressive), patients die from their disease and not from other causes, and early disease diagnosis (eDTC) can utterly extend survival compared to advanced ones (*de novo* aDTC). Additionally, the study identified early poor treatment-dependent prognostic factors impacting both the pace at which early disease progresses into advanced stages and the overall survival expectancy of aDTC patients once they are as such diagnosed. These observations should be promptly considered and translated into a proactive follow-up and an intensified therapeutic attitude in this subpopulation. This could, at least potentially, reverse its doomed prognosis and positively impact disease evolution in many cases.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-21-0111.

Declaration of interest

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Author contribution statement

J A V C, C L L and M S contributed equally to methodology design, critical review of the study proposal, results and interpretation, data collection and writing of the original draft. M D P contributed to the critical review of results and interpretation. L O R and J R V G the conceived the idea, methodology design, coordination, execution of the research, and provided the financial support leading to this publication. J A V C and L O R contributed as corresponding authors on behave of the ERUDIT Study Group of Co-authors. R J S, M L, E N G, J A, V P, S G, G C, C G, C Z, M N, J S S, A S, P G, M G B, J V, M P D, J C G, B C, M J V and I A contributed to data collection and final draft review. All the above authors confirm that the study was performed in compliance with all basic principles of the Helsinki Declaration (2013) and applicable national regulations. Both accredited Research Ethics Committees of Hospital Universitario Gregorio Marañón (Madrid, Spain) and National Ethics Committee for Clinical Research (Portugal) approved it.

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