Design and development of a European registry for parathyroid carcinoma cases within the scope of the European Registries for Rare Endocrine Conditions (EuRRECa)

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ABSTRACT

Parathyroid carcinoma (PC) is an extremely rare malignant endocrine tumor of the parathyroid glands. Given the extreme rarity of this cancer, many issues regarding its diagnosis, prognosis, clinical management, and tumor-derived complications remain unresolved, and no standardized protocol has yet been defined for its diagnosis. As with all rare clinical conditions, the creation of multicenter national databases and international registries is fundamental in order to collect data on a relatively high number of PC cases and increase knowledge of this rare parathyroid condition, with the ultimate aim of identifying potential factors that influence its diagnostics, natural course, prognosis, skeletal complications, and treatment. In this light, the "parathyroid carcinoma working group" (https://eurreca.net/parathyroid-carcinoma/) designed and developed a specific PC module within the scope of the European Registries for Rare Endocrine Conditions (EuRRECa). The module, finalized and launched at the end of 2022, is now available online to collect data on PC cases. Users must first request access to the e-Reporting of Rare Conditions system (e-REC) and obtain their personal login credentials.

KEYWORDS

Parathyroid carcinoma, rare diseases, European Registries for Rare Endocrine Conditions (EuRRECa), parathyroid carcinoma module

Introduction

Parathyroid carcinoma (PC) is an extremely rare endocrine malignancy involving the parathyroid glands, which is estimated to account for 0.005% of all human cancers. Taken together, all parathyroid tumors are estimated to affect 0.1-0.3% of the general population [1], and less than 1% of them are malignant PC, making PC one of the rarest causes of primary hyperparathyroidism. PC is the least common endocrine cancer worldwide, and since its first clinical description in 1909, the cases reported in the literature number fewer than one thousand [2].

PC is characterized by excessive secretion of parathyroid hormone (PTH), generally manifesting with severe and symptomatic hypercalcemia, and subsequent related renal complications, enhanced bone mass loss, and an increased risk of fragility fracture. Very high levels of PTH (>800 pg/ml or more than 10 times the upper normal value) and calcium (>14 mg/dl), the presence of a single enlarged parathyroid measuring over 3 cm, and signs of invasion of adjacent tissue on ultrasound neck exploration are indicative of a possible malignant carcinoma [2]. However, despite the usually higher levels of calcium and/or PTH, compared with those found in benign parathyroid tumors, it is extremely difficult to distinguish PC from adenoma preoperatively, and the diagnosis of PC is often made only in the post-operative setting, through histological evaluation of the tumor specimen and germinal/somatic genetic screening for the most common PC-associated mutated genes. The presence of four or more features of malignancy are indicative of a diagnosis of carcinoma. These features include capsular invasion with growth into adjacent tissue, vascular or perineural tumor invasion, presence of metastasis, intra-tumoral fibrous bands, tumor necrosis, cellular atypia, high mitotic rate (> 5 mitosis per high power field), presence of macronuclei, and a high nucleus/cytoplasm ratio. The presence of only one to three of these

Article history
Received 11 Aug 2022 – Accepted 15 Oct 2022

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characteristics is diagnostic of a possible atypical parathyroid adenoma [3]. However, despite these indications the differential diagnosis of PC remains a challenge in current clinical practice.

PC most commonly occurs as a sporadic single-gland disease, in the absence of a family history; only a minority of cases manifest as isolated inherited cancer or as part of a complex hereditary syndrome. The most common hereditary form of PC occurs in the context of hyperparathyroidism jaw-tumor syndrome, an extremely rare genetic syndrome caused by germline heterozygote loss-of-function mutations of the *CDC73* tumor suppressor gene, encoding the parafibromin protein. Rarely, other genetic diseases have been associated with the development of PC, such as isolated familial hyperparathyroidism and multiple endocrine neoplasia types 1 and 2.

Because of the extreme rarity of this tumor, both in the sporadic form and, even more so, as a congenital condition, there is as yet no standardized approach to its diagnosis, clinical management and therapy, and no standardized TNM staging algorithm has been universally recognized for PC [4].

In the context of rare diseases, such as PC, the collection of diagnostic, clinical, and genetic characteristics of unselected patients, and of therapeutic outcomes, through the institution of well-designed multicenter national databases and international registries, is an extremely useful approach to increasing knowledge of diagnostic tools, translational aspects, natural course, and prognosis of the disease.

It is with this in mind that the European Registries for Rare Endocrine Conditions (EuRRECa) project was created. Funded by the European Union's Health Program, it is aimed at maximizing the opportunity for patients, health care professionals and researchers to participate in and use high-quality registries on rare endocrine diseases. The EuRRECa project was launched in 2018 and includes the e-Reporting of Rare Conditions (e-REC) electronic reporting system and the Core Registry, which contains condition-specific datasets for a wide range of rare conditions, including those covered by the European Reference Network on Rare Endocrine Conditions (Endo-ERN) and the European Reference Network on rare bone diseases (ERN-BOND).

Here, we report the design, setting and creation, by the "parathyroid carcinoma working group" (data available at https://eurreca.net/parathyroid-carcinoma/), of a specific module for the collection of data on PC cases in Europe, within the scope of the EuRRECa.

Methodology

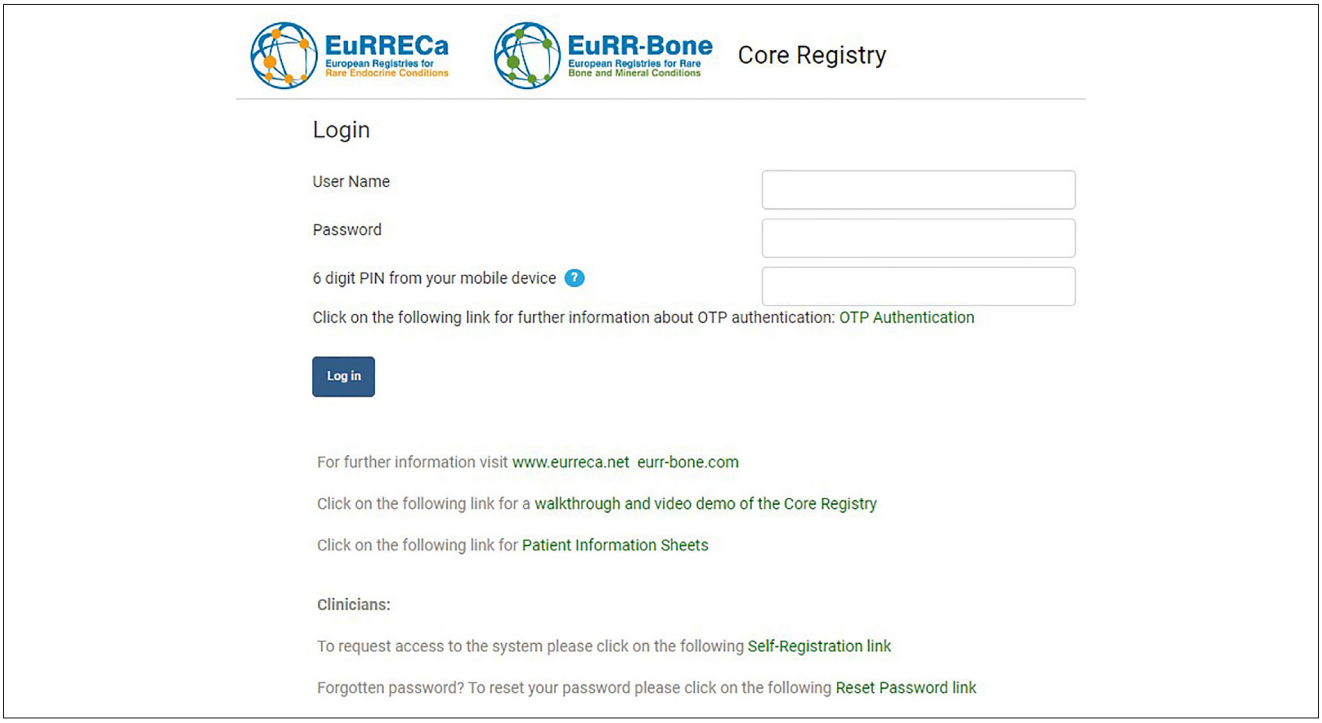
A first draft dataset for the collection of data from patients with PC was initially developed as an Excel file by the research group of the F.I.R.M.O. Italian Foundation for the Research on Bone Disease and the Donatello Bone Clinic, and structured to include clinical history, genetic aspects, histological screenings, and follow-up data of the tumor. It was divided into the following specific data collection sections: 1) clinical history of the patient, pre-diagnosis clinical manifestations, and clinical history of first-degree relatives; 2) genetic diagnosis; 3) clinical, biochemical and instrumental data collected at first evaluation and before parathyroid surgery, with a specific subsection regarding pre-operative evaluation of bone health status; 4) pharmacological therapies administered before parathyroid surgery; 5) data on surgery of affected parathyroid(s), post-surgical histological analyses of the tumor specimen, somatic genetic screening of the tumor sample; 6) post-operative follow-up data (i.e. surgery outcomes such as normalization of calcemia, disease persistence and/or recurrence, occurrence of post-surgical permanent hypoparathyroidism), including biochemical evaluation of parathyroid function and calcium homeostasis and instrumental evaluation of the parathyroid glands and neck area immediately after surgery and during successive follow ups; 7) post-operative evaluation of bone health status 6-12 months after tumor resection.

This initial draft dataset was reviewed by the "parathyroid carcinoma working group", which included experts in the fields of endocrinology, radiology, parathyroid surgery, anatomopathology, and genetics, and representatives of two important associations of patients with hereditary endocrine tumor syndromes that can, rarely, develop parathyroid carcinoma (the European MEN Alliance, EMENA, and the *Associazione Italiana Neoplasie Endocrine Multiple*, AIMEN 1&2). Following comments and suggestions from the working group, the dataset was optimized and implemented.

From the revised Excel file, the Leiden University research group developed a first version of the "parathyroid carcinoma module" within the Core Registry containing the following five sections, and respective subsections: 1) anamnestic data (anamnestic data, history of elective neck irradiation prior to diagnosis of parathyroid carcinoma, clinical history and therapy of hyperparathyroidism prior to diagnosis of parathyroid carcinoma, family history); 2) diagnosis of parathyroid cancer (genetic testing, clinical symptoms, biochemical tests at baseline evaluation); 3) instrumental investigations (neck ultrasound, parathyroid scintigraphy with 99mTc-Sestamibi, neck CT scan, PET/CT scan with choline, PET/CT scan with 11C-methionin, PET/CT scan with 18F-FDG, DXA analysis); 4) surgical and post-operative data (surgical intervention, post-operative histological findings, somatic genetic testing on the removed parathyroid tumor, post-operative clinical follow up, post-operative evaluation of parathyroid function, post-operative biochemical tests, post-operative neck ultrasound, parathyroid scintigraphy with 99mTc-Sestamibi, neck CT scan, PET/CT scan with choline, PET/CT scan with 11C-methionin, PET/CT scan with 18F-FDG, DXA analysis); 5) medical treatment(s).

After revision by all the members of the "parathyroid carcinoma working group", the module was modified and restructured into its final version, containing the following seven sections, and respective subsections: 1) general (anamnestic data, clinical history prior to diagnosis of parathyroid carcinoma, family history, history of neck irradiation prior to diagnosis); 2) diagnosis (clinical symptoms, biochemical tests at baseline evaluation, genetic testing); 3) imaging at time of diagnosis (parathyroid scintigraphy, PET/CT scan with choline, neck ultrasound, neck CT scan, PET/CT scan with 18F-FDG, PET/CT scan with 11C-methionin, DXA analysis); 4) medical treatment (medical treatment, adverse event 1 related to the current therapy, adverse event 2 related to the current therapy); 5) surgery

Figure 1 Login page to access the EuRRECa Core Registry system.



and histology (surgical intervention, post-operative histological findings, somatic genetic testing on the removed parathyroid tumor, post-operative evaluation of parathyroid function, post-operative biochemical tests, post-operative clinical follow up); 6) recurrence 1 (recurrence 1, parathyroid scintigraphy at time of recurrence, PET/CT scan at time of recurrence, MRI at time of recurrence, CT scan at time of recurrence, neck ultrasound at time of recurrence, complications screening; 7) recurrence 2 (assessment date, localization of tumor, region of interest).

The EuRRECa parathyroid carcinoma module

The parathyroid carcinoma module, released and launched within the EuRRECa Core Registry by the end of 2022, is now available online to collect data on this rare parathyroid condition.

To register their cases, clinicians need to request access to the EuRRECa Core Registry (https://eurreca.net/core-registry/) and create a personal account. Once they have obtained their personal login credentials, they can access the system through the EuRRECa Core Registry login page (https://eurreca.lumc.nl/CoreRegistry/Account/Login). Accessing is a two-step process: a first step requiring personal login credentials, and a second one (OTP authentication) requiring a temporary 6-digit PIN sent to the mobile device registered in the user's personal account (Figure 1).

Having logged in, the clinician can access the general page of the EuRRECa Core Registry, which is common to all the rare conditions currently included in the system. At this point they can register PC cases by selecting the condition group "calcium and phosphate". Each clinical case has to be inserted separately, and it will be registered in a completely anonymous way, exclusively associated with a unique numerical ID, which is automatically assigned by the system.

After selection of the "calcium and phosphate" disease group, the clinician accesses a second page in which, from a drop-down menu, "hyperparathyroidism including parathyroid cancer" must be selected as the primary condition, and "parathyroid carcinoma" as the specific diagnosis.

The clinician then enters the PC module, in which they can insert the available data on their PC case. Each case can be edited and/or updated with new follow-up data and/or additional available data, at any time.

The EuRRECa parathyroid carcinoma module includes questions aimed at identifying factors influencing PC diagnostics, natural course, prognosis, skeletal complications, and treatment.

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Conflict of Interest: *The authors declare that there is no conflict of interest.*