Systematic Review

What Lies behind Paraneoplastic Hypercalcemia Secondary to Well-Differentiated Neuroendocrine Neoplasms? A Systematic Review of the Literature

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Abstract: Background: Neuroendocrine neoplasms (NEN) originate from neuroendocrine cells ubiquitously spread throughout the body. Hypercalcemia associated with cancer is the most common life-threatening metabolic disorder in patients with advanced stage cancer. Paraneoplastic hypercalcemia is more commonly associated with hematological malignancies, renal and breast carcinomas, and squamous cell carcinomas, but it has also been described in patients with well-differentiated NEN, where it often remains undiagnosed. Among its causes, systemic secretion of parathyroid hormone-related protein (PTHrP) and ectopic production of 1,25-dihydroxyvitamin D and parathyroid hormone (PTH) may be considered paraneoplastic causes of hypercalcemia. In order to clarify the diagnostic work up of paraneoplastic hypercalcemia in patients with NEN, we perform a systematic review, which is lacking in the literature. Methods: We performed a data search using MEDLINE and SCOPUS including papers from 1961 to 2021. We selected articles on paraneoplastic hypercalcemia associated with well-differentiated NEN. Results: The search led to the selection of 78 publications for a total of 114 patients. Pooled data showed that the most frequent primary tumor site associated with paraneoplastic hypercalcemia was pancreatic NEN, followed by Pheochromocytoma. In most cases, paraneoplastic hypercalcemia was caused by PTHrP production and secretion. In more than two thirds of cases, paraneoplastic hypercalcemia was present at the time of NEN diagnosis and, in metachronous cases, was related to local recurrence, distant metastasis development, or tumor progression. In most patients, a combination of therapeutic approaches was employed, and reduction of the tumor burden was essential to control the paraneoplastic syndrome. Discussion: The onset of hypercalcemia associated with cancer in patients with well-differentiated NEN represents a major clinical challenge. The complex clinical and therapeutical management of paraneoplastic hypercalcemia implies the need for a multidisciplinary approach, aimed at controlling the clinical syndrome and tumor growth.

Keywords: NET; PTHrP; PTH; NEN; 1,25-dihydroxyvitamin D; hyperparathyroidism; hypercalcemia

1. Introduction

 Neuroendocrine neoplasms (NEN) originate from neuroendocrine cells which are distributed throughout the body. These tumors can synthesize and release biologically...
active substances such as hormones, peptides, or cytokines, causing distinct clinical syndromes [1] and differently impacting health-related quality of life [2–4]. Diagnostic and therapeutic management of functioning NEN is complex due to the high heterogeneity of these neoplasms in terms of clinical aggressiveness and the control of secretions. From the perspective of the precision medicine approach to NEN [5], the onset of paraneoplastic syndromes (PNS) should not be overlooked.

PNS are a heterogeneous group of clinical conditions, involving various systems, characterized by signs and symptoms occurring in association with malignancies. PNS are due to tumor-mediated production and release of different bioactive substances, or alternatively, by immune-mediated processes, and are not related to the specific organ or tissue from which they originate. PNS may occur before tumor diagnosis, concomitantly, or late in the course of clinical history and may influence therapeutic management. Consequently, PNS may impact prognosis and patients’ quality of life [6,7].

Hypercalcemia associated with cancer is the most common life-threatening metabolic disorder in patients with advanced-stage cancer. Hypercalcemia is associated with different neoplasms, may occur in up to 20–30% of all cancer patients, and is related to a poor prognosis. Thus, early diagnosis and intervention are of utmost importance in patients’ management. Hypercalcemia is more commonly associated with hematological malignancies, renal and breast carcinomas, and squamous cell carcinomas, but it has been also described in patients with well-differentiated NEN [8].

Hypercalcemia associated with cancer may be caused by: (i) systemic secretion of parathyroid hormone-related protein (PTHrP), a peptide produced by tumors with close homology in the N-terminal sequence to parathyroid hormone (PTH); (ii) osteolytic metastases, or, more rarely, by (iii) ectopic production of 1,25-dihydroxyvitamin D, which leads to intestinal hyperabsorption of calcium and increased osteoclastic bone reabsorption, and (iv) ectopic hyperparathyroidism [9].

Clinical presentation of hypercalcemia is influenced by its rapidity of onset and by its severity. Typical symptoms do not differ from benign hypercalcemia and may be nonspecific and develop gradually, leading to a delayed diagnosis. Signs and symptoms comprise gastrointestinal complaints such as nausea, vomiting, constipation, abdominal pain, and even anorexia, weight loss, bone pain, polyuria, weakness, and fatigue. Cardiovascular complications and arrhythmias may also occur, as well as neurologic symptoms, especially in severe hypercalcemia (>14 mg/dl) [10].

Currently, data about NEN-related hypercalcemia come from case reports or case series. Most NEN-related hypercalcemia is secondary to the ectopic secretion of PTHrP, the so-called humoral hypercalcemia of malignancy, and it is more commonly described in association with pancreatic NEN (p-NEN). Different clinical presentations have been reported in association with different tumor stages, grades, and patient outcomes, as well as various therapeutic management strategies [11].

To provide a core of data about the epidemiology, clinical presentation, treatment, and impact on prognosis in patients with well-differentiated NEN-related hypercalcemia, we performed a systematic review [12].

2. Materials and Methods

We performed a systematic review of the literature according to the Cochrane Collaboration and PRISMA statement [13]. We searched for English-language articles in MEDLINE and SCOPUS, no timeframe restrictions were applied, including papers from 1961 to 2021. We searched for potentially relevant studies through these keywords: PTHrP AND NET/NEN; PTH AND NET/NEN; paraneoplastic hypercalcemia AND NET/NEN; and hypercalcemia AND NET/NEN. Eligibility criteria for study selection included studies on humans with any of the following designs: randomized clinical trials, prospective non-randomized trials, retrospective studies, case series, case reports, brief communications, and letters to the editor. We selected articles on paraneoplastic hypercalcemia associated with well-differentiated NEN, including paragangliomas, pheochromocytomas, medullary
thyroid cancer, thymic and mediastinal, ovarian, uterine, cervical, gastroenteropancreatic, lung, and rectal NEN. For each paper, we analyzed patients’ age, sex, signs, symptoms, time presentation of hypercalcemia and hypercalcemia inducing molecules (PTH, PTHrP, 1,25(OH) vitamin D) or other peptide secretion. We furthermore evaluated the primary NEN’s site, grade, staging (with ENETS classification), type of metastasis at diagnosis of paraneoplastic hypercalcemia, NEN and hypercalcemia therapy, and patients’ survival from the onset of hypercalcemia. Each study was screened by abstract and title, and potentially eligible studies were further assessed in detail by retrieving full-length articles. Each full-length article was independently reviewed by three separate authors (AR, IZ, and FS) following the inclusion criteria. Three authors (AR, IZ, and FS) independently extracted data from the articles that met the inclusion criteria. A standardized form was used to extract relevant data.

Data are expressed as mean and standard deviation (SD) or median and 25–75% interquartile range (IQR), as appropriate. Normally distributed variables were assessed using the Shapiro–Wilk test. Homoscedasticity and homogeneity of variances were assessed by visual inspection and with Levene’s test. Differences between independent groups were evaluated using the t test for normally distributed variables and using the nonparametric Mann–Whitney test for non-normally distributed variables. Differences between the binomial proportions of independent groups of a dichotomous-dependent variable were assessed for homogeneity using the chi-square test or Fisher’s exact test, as appropriate. All statistical analyses were performed with SPSS Statistics version 27.0 (IBM SPSS Statistics Inc., Chicago, IL, USA).

3. Results

From the original number of 1281 studies, we excluded 1192 articles after title and abstract screening; reasons for exclusion included duplicates and studies in which hypercalcemia was due to primary hyperparathyroidism associated to genetic syndromes. We furthermore completed our research by analyzing the references of the selected papers (see Figure 1). We finally assessed 78 papers for a total of 114 patients for eligibility (see Table 1) [14–91]. The main clinical features of the gathered cases are summarized in Table 2.

Figure 1. Flowchart of the literature search for the systematic review study. From: Liberati A, Altman DG, Tetzlaff J, Mulrow C, et al. (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med 6(7): e1000100. doi:10.1371/journal.pmed.1000100.
Table 1. Summary of cases of paraneoplastic hypercalcemia in well-differentiated NEN reported in the literature.

| Author, Year | N° of Cases | Sex, Age (y) | Primary Site of NEN | Grade, Ki67 | Initial Staging (ENETS) | Metastasis at Diagnosis of Paraneoplastic Hypercalcemia | Time to Onset of Paraneoplastic Hypercalcemia (Months) | Paraneoplastic Hypercalcemia-Inducing Molecules | Other Peptide Secretion | Paraneoplastic Hypercalcemia Therapy | NEN Therapy | Paraneoplastic Hypercalcemia Responsive to Therapy | Survival from Onset of Paraneoplastic Hypercalcemia (Months) |
|--------------|-------------|--------------|---------------------|-------------|-------------------------|-----------------------------------------------------|---------------------------------------------------|-------------------------------------------|---------------------|--------------------------------|-------------|------------------------------------------------|--------------------------------------------------|
| Giannetta E et al., 2021 [14] | 4 | M, 40 | Pancreatic | G2, Ki67 = 5% | IV | Liver | At diagnosis | PTHrP | Calcitonin | Denosumab | IV hydration Loop diuretics Cinacalcet Biphosphonate Denosumab | SSA PRRT | Denosumab | 36 |
| | | M, 45 | Pancreatic | G2, Ki67 = 5% | II | - | 96 | NA | - | surgery | SSA Everolimus PRRT | Corticosteroids | 60 |
| | | F, 49 | Pancreatic | G1, Ki67 < 1% | III | - | At diagnosis | 1,25(OH) vitamin D | - | Hemodialysis Biphosphonate Calcitonin | TAE Surgery | Surgery | 156 |
| | | M, 69 | Pulmonary | Atypical carcinoid, Ki67 = 9% | IV | Liver | At diagnosis | PTHrP | Calcitonin | Biphosphonate | Surgery | Surgery | NA |
| Copur MS et al., 2020 [15] | 1 | F, 62 | Pancreatic | G3, Ki67 = 30% | IV | Liver | At diagnosis | PTHrP | - | Biphosphonate IV hydration | SSA 5-FU Oxaliplatin Surgery Pembrolizumab | Biphosphonate IV hydration | 6 |
| Ataallah B et al., 2020 [16] | 1 | F, 22 | Pancreatic | NA | IV | Liver | At diagnosis | NA | VIP | Biphosphonate IV hydration | Surgery CapTem Nivolumab | - | Biphosphonate | NA |
| Van Lierop AH et al., 2019 [17] | 1 | M, 50 | Pancreatic | G2, Ki67 = 10% | IV | Spleen Liver | 94 | 1,25(OH) vitamin D | - | Biphosphonate IV hydration | Surgery CapTem Nivolumab | Surgery | 24 |
| Gild ML et al., 2018 [18] | 1 | M, 47 | Pancreatic | G1, Ki67 < 1% | NA | Lymphonodes | At diagnosis | NA | Glucagon | Biphosphonate Denosumab | SSA Surgery | Surgery | 27 |
| Daskalakis K et al., 2018 [19] | 1 | NA | Pancreatic | NA | IV | Liver | NA | PTHrP | - | Biphosphonate IV hydration Cinacalcet | Surgery SSA Streptozotocine 5-FU IFNα PRRT Bevacizumab CapTem TAE Everolimus Sunitinib | TAE CapTem | NA |
| Author, Year | N° of Cases | Sex, Age (y) | Primary Site of NEN | Grade, Ki67 | Initial Staging (ENETS) | Metastasis at Diagnosis of Paraneoplastic Hypercalcemia | Time to Onset of Paraneoplastic Hypercalcemia (Months) | Paraneoplastic Hypercalcemia-Inducing Molecules | Other Peptide Secretion | Paraneoplastic Hypercalcemia Therapy | NEN Therapy | Paraneoplastic Hypercalcemia Responsive to | Survival from Onset of Paraneoplastic Hypercalcemia (Months) |
|-------------|-------------|-------------|---------------------|-------------|------------------------|------------------------------------------------------|-------------------------------------------------|---------------------------------|---------------------|-------------------------------|-------------|--------------------------------------|--------------------------------------------------|
| Symington et al., 2017 [20] | 1 | F, 54 | Pancreatic | G1, Ki67 < 1% | IV | Liver | At diagnosis | PTHrP | Gastrin | Bisphosphonate IV hydration | SSA | SSA | 3 |
| Lu C et al., 2017 [21] | 1 | M, 65 | Mediastinal | Typical carcinoid | NA | - | At diagnosis | PTH | - | - | Surgery | Surgery | NA |
| Ranade R et al., 2017 [22] | 1 | M, 49 | Pancreatic | G2, Ki67 = 12% | IV | Liver | Bone | At diagnosis | PTHrP | - | NA | SSA | PRRT CapTem | PRRT CapTem | 21 |
| Valdes-Socin H et al., 2016 [23] | 1 | M, 52 | Pancreatic | G1, Ki67 = 2% | IV | Liver | Spleen | At diagnosis | - | Calcitonin | Bisphosphonate Calcitonin IV hydration Cincalcet | Streptozotocin Adriamycin FOLFOX SSA Sunitinib | Cinacalcet | 48 |
| Iluta IA et al., 2015 [24] | 1 | M, 48 | Pancreatic | NA | IV | Liver | At diagnosis | PTHrP | - | Bisphosphonate Calcitonin IV hydration Cincalcet Corticosteroids | SSA Everolimus PRRT | PRRT | NA |
| Teng J et al., 2014 [25] | 1 | M, 38 | Pancreatic | G1, Ki67 < 2% | IV | Liver | At diagnosis | PTHrP | - | Hemo dialysis Bisphosphonate Calcitonin IV hydration Denosumab Corticosteroids | Carboplatin Etoposide PRRT | Bisphosphonate Denosumab PRRT | 22 |
| Zhu V et al., 2014 [26] | 1 | F, 43 | Pancreatic | G1-2, Ki67 = 2–5% | IV | Liver | 96 | 1.25(OH) vitamin D | - | Bisphosphonate IV hydration Denosumab Calcitonin | SSA HACE Sunitinib CapTem | CapTem | 24 |
| Kamp K et al., 2014 [27] | 9 | M, 41 | Pancreatic | NA | IV | Liver | At diagnosis | PTHrP | - | NA | NA | NA | NA |
| | | M, 58 | Pancreatic | G1 | IV | Liver Lymphnodes | NA | PTHrP | - | NA | NA | NA | NA |
| | | F, 40 | Pancreatic | NA | IV | Liver Lymphnodes | NA | PTHrP | VIP | NA | NA | NA | NA |
| | | M, 61 | Pancreatic | G1 | IV | Liver | At diagnosis | PTHrP | - | Bisphosphonates IV hydration Denosumab | SSA PRRT Sunitinib | SSA PRRT | NA |
| | | M, 60 | Unknown | G2 | IV | Liver | At diagnosis | PTHrP | - | NA | NA | NA | NA |
| | | M, 38 | Pancreatic | G1 | IV | Liver | At diagnosis | PTHrP | - | NA | NA | NA | NA |
| | | F, 42 | Pancreatic | NA | IV | Liver Lymphnodes | At diagnosis | PTHrP | - | NA | NA | NA | NA |
Table 1. Cont.

| Author, Year | N° of Cases | Sex, Age (y) | Primary Site of NEN | Grade, Ki67 | Initial Staging (ENETS) | Primary Site | Metastasis at Diagnosis of Paraneoplastic Hypercalcemia (Months) | Time to Onset of Paraneoplastic Hypercalcemia (Months) | Paraneoplastic Hypercalcemia-Inducing Molecules | Other Peptide Secretion | Paraneoplastic Hypercalcemia Therapy | NEN Therapy | Paraneoplastic Hypercalcemia Responsive to Therapy | Survival from Onset of Paraneoplastic Hypercalcemia (Months) |
|--------------|-------------|-------------|---------------------|-------------|-------------------------|--------------|---------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|--------------|-------------------------------------------------|-------------------------------------------------------------|
| Kamp K et al., 2014 [27] | 9 | F, 51 | Pancreatic | NA | IV | Liver | At diagnosis | PTHrP | - | Biphosphonates | Corticosteroids | Cisplatin | Surgery | SSA PRRT | - | 18 |
| | | | | | | | | | | | | | | | | |
| Rossi RE et al., 2014 [28] | 1 | F, 25 | Pancreatic | G2, Ki67 = 5% | IIA | - | At diagnosis | PTHrP | - | Biphosphonates | IV hydration | Streptozotocin 5-FU | Surgery | TAE OLT | Surgery | 192 |
| | | | | | | | | | | | | | | | | |
| Milanesi A et al., 2013 [29] | 5 | F, 49 | Pancreatic | G1, Ki67 < 2% | IV | Liver | 18 | PTHrP | Somatostatin PP | Biphosphonates | SSA PRRT | Surgery | SSA HACE | HACE | Biphosphonates | 36 |
| | | | G2, Ki67 = 5-10% | IV | Liver | 108 | PTHrP | - | Biphosphonates | IV hydration | Surgery | SSA HACE | CapTem | Biphosphonates | 96 |
| | | | | | | | | | | | | | | | | |
| Shah RH et al., 2013 [30] | 1 | M, 54 | Pancreatic | G1, Ki67 = 2% | IV | Liver | At diagnosis | PTHrP | - | Biphosphonates | Calcitonin | SSA | CapTem | CapTem | - | 17, DOD |
| | | | | | | | | | | | | | | | | |
| Kanakis G et al., [31] | 1 | M, 58 | Pancreatic | G2, Ki67 = 4% | IV | Liver | 48 | PTHrP | PP | Biphosphonates | SSA | Streptozotocine 5-FU IFNα SSA PRRT CapTem HACE Bevacizumab Everolimus | HACE Combined chemotherapy | - | 72 |
| | | | | | | | | | | | | | | | | |
| Kandil E et al., 2011 [32] | 1 | F, 73 | Neck | NA | NA | - | At diagnosis | PTH | - | - | Surgery | Surgery | - | - | - | 6 |
| Author, Year | N° of Cases | Sex, Age (y) | Primary Site of NEN | Grade, Ki67 | Initial Staging (ENETS) | Metastasis at Diagnosis of Paraneoplastic Hypercalcemia | Time to Onset of Paraneoplastic Hypercalcemia (Months) | Paraneoplastic Hypercalcemia-Inducing Molecules | Other Peptide Secretion | Paraneoplastic Hypercalcemia Therapy | NEN Therapy | Paraneoplastic Hypercalcemia Responsive to Surgery | Survival from Onset of Paraneoplastic Hypercalcemia (Months) |
|--------------|-------------|-------------|---------------------|-------------|-------------------------|------------------------------------------------------|-------------------------------------------------|-----------------------------------------|------------------------------------------|-----------------------------------------------|-------------|------------------------------------------------|-----------------------------------------------------------|
| Ghazi AA et al., 2011 [33] | 1 | F, 35 | Pancreatic | G1-2, Ki67 = 1–3% | IIIA | - | At diagnosis | PTHrP | - | IV hydration Biphosphonates Calcitonin | Surgery Etoposide Platinum | Biphosphonates Surgery | 6 |
| Shirai K et al., 2011 [34] | 1 | F, 53 | Pancreatic | NA | IIIA | - | At diagnosis | PTHrP | Glucagon | IV hydration | Surgery HACE RFA | Surgery | 84 |
| Takeda K et al., 2010 [35] | 1 | M, 12 | Pheochromocytoma | NA | NA | - | At diagnosis | PTHrP | - | Biphosphonates Loop diuretics | Surgery | Surgery | 12 |
| Morita Y et al., 2010 [36] | 1 | F, 58 | Pancreatic | NA | IV | Liver | At diagnosis | PTHrP | Gastrin | - | Surgery | Surgery | 19 |
| Demura M et al., 2010 [37] | 1 | F, 20 | MTC | NA | NA | Lymphnodes | At diagnosis | PTH | Calcitonin | - | Surgery | Surgery | NA |
| Srirajaskanthan R et al., 2009 [38] | 5 | | | | | | | | | SSA TAE Surgery OLT | Surgery | NA |
| | | | | | | | | | SSA Streptozotocine 5-FU | SSA | NA |
| | | | | | | | | | SSA Streptozotocine 5-FU Cisplatin Etoposide | SSA Streptozotocine 5-FU Cisplatin Etoposide | NA |
| | | | | | | | | | SSA Streptozotocine 5-FU Cisplatin Etoposide | SSA Streptozotocine 5-FU Cisplatin Etoposide | NA |
| | | | | | | | | | SSA Streptozotocine 5-FU Cisplatin Etoposide | Surgery TAE | SSA Streptozotocine 5-FU Cisplatin Etoposide | NA |
| Author, Year | N° of Cases | Sex, Age (y) | Primary Site of NEN | Grade, Ki67 | Initial Staging (ENETS) | Metastasis at Diagnosis of Paraneoplastic Hypercalcemia | Time to Onset of Paraneoplastic Hypercalcemia (Months) | Paraneoplastic Hypercalcemia-Inducing Molecules | Other Peptide Secretion | Paraneoplastic Hypercalcemia Therapy | NEN Therapy | Paraneoplastic Hypercalcemia Responsive to Therapy | Survival from Onset of Paraneoplastic Hypercalcemia (Months) |
|-------------|-------------|--------------|---------------------|-------------|-------------------------|-----------------------------------------------|-------------------------------------------------|---------------------------------|-------------------------------|---------------------------|---------------------------------|-----------------------------|----------------------------------------------------------------|
| Brzozowska MM et al., 2009 [39] | 1 F, 77 | Unknown | NA | IV | Liver Spleen | At diagnosis | PTHrP | - | Biphosphonates Corticosteroids | Etoposide Carboplatin SSA | - | 14 |
| Van den Eynden GG et al., 2007 [40] | 1 M, 59 | Pancreatic | GI | IIIA | - | At diagnosis | PTHrP | Calcitonin | Biphosphonates IV hydration | Surgery SSA IFNα | IFNα | 57 |
| Barakat MT et al., 2004 [41] | 1 F, 47 | Pancreatic | NA | IV | Liver | 24 | PTHrP | - | Biphosphonates IV hydration | SSA | TAE SSA | 40 |
| Mullerpatan PM et al., 2004 [42] | 1 F, 56 | Pancreatic | NA | IIB | - | At diagnosis | NA | Calcitonin VIP | IV hydration | Surgery | IV hydration | 18 |
| Abraham P et al., 2002 [43] | 1 F, 25 | Pancreatic | NA | NA | - | At diagnosis | PTHrP | - | Biphosphonates | Surgery | Biphosphonates Surgery | 24 |
| Clemens P et al., 2003 [44] | 1 M, 34 | Pancreatic | NA | IIIA | - | At diagnosis | PTHrP | - | IV hydration Biphosphonates Calcitonin Corticosteroids | Streptozotocin 5-FU Doxorubicin SSA Carboplatin Etoposide | Chemotherapy | 32, DOD |
| Papazachariou JM et al., 2003 [45] | 2 F, 33 | Pancreatic | NA | IV | Liver | At diagnosis | PTHrP | Somatostatin | Biphosphonates IV hydration | Surgery SSA | Surgery TAE | 60 |
| Loh K et al., 1998 [46] | 1 M, 15 | Retroperitoneal paraganglioma | - | IV | Liver Bone Mediastinum | At diagnosis | PTHrP | - | Biphosphonates Calcitonin IV hydration | Surgery | Biphosphonates Surgery | 4 |
| van de Loosdrecht AA et al., 1998 [47] | 1 F, 45 | Pancreatic | NA | IV | Liver | 128 | PTHrP | - | IV hydration Corticosteroids | SSA | - | 16, DOD |
| Mantzoros CS et al., 1997 [48] | 1 F, 59 | Unknown | NA | IV | Liver | At diagnosis | PTHrP | - | IV hydration Biphosphonates Calcitonin Plicamycin Gallium nitrate | 5-FU Carboplatin | - | 3, DOD |
Table 1. Cont.

| Author, Year | N° of Cases | Sex, Age (y) | Primary Site of NEN | Grade, Ki67 | Initial Staging (ENETS) | Metastasis at Diagnosis of Paraneoplastic Hypercalcemia | Time to Onset of Paraneoplastic Hypercalcemia (Months) | Paraneoplastic Hypercalcemia-Inducing Molecules | Other Peptide Secretion | Paraneoplastic Hypercalcemia Therapy | NEN Therapy | Paraneoplastic Hypercalcemia Responsive to | Survival from Onset of Paraneoplastic Hypercalcemia (Months) |
|--------------|-------------|-------------|---------------------|-------------|-------------------------|--------------------------------------------------------|--------------------------------------------------|---------------------------------|------------------------|-----------------------------|-------------|------------------------------------------|---------------------------------------------------------------|
| Wu TJ et al., 1997 [49] | 9           | M, 66       | Pancreatic           | NA          | IV                      | Liver, Spleen                                         | NA                                               | NA                              | NA                     | NA                         | NA          | NA                                      | NA                                                            |
|               |             | F, 42       | Pancreatic           | NA          | IV                      | Liver, Spleen                                         | NA                                               | PTHrP                          | NA                     | NA                         | NA          | NA                                      | NA                                                            |
|               |             | F, 45       | Pancreatic           | NA          | IV                      | Liver, NA                                             | NA                                               | PTHrP                          | NA                     | NA                         | NA          | NA                                      | NA                                                            |
|               |             | M, 64       | Pancreatic           | NA          | IV                      | Liver, NA                                             | NA                                               | PTHrP, Glucagon                | NA                     | NA                         | NA          | NA                                      | NA                                                            |
|               |             | M, 61       | Pancreatic           | NA          | IV                      | Liver, NA                                             | NA                                               | PTHrP                          | NA                     | NA                         | NA          | NA                                      | NA                                                            |
|               |             | F, 38       | Pancreatic           | NA          | IV                      | Liver, NA                                             | NA                                               | PTHrP                          | NA                     | NA                         | NA          | NA                                      | NA                                                            |
|               |             | M, 20       | Pancreatic           | NA          | IV                      | Liver, NA                                             | NA                                               | PTHrP                          | NA                     | NA                         | NA          | NA                                      | NA                                                            |
|               |             | F, 47       | Pancreatic           | NA          | IV                      | Liver, NA                                             | NA                                               | PTHrP                          | NA                     | NA                         | NA          | NA                                      | NA                                                            |
|               |             | F, 51       | Pancreatic           | NA          | IV                      | Liver, NA                                             | NA                                               | PTHrP, Somatostatin            | NA                     | NA                         | NA          | NA                                      | NA                                                            |
| Mao C et al., 1995 [50] | 3       | M, 41       | Pancreatic           | NA          | IV                      | Liver, Lymphnodes                                     | 0.5                                              | NA                              | IV hydration, Calcitonin, Plicamycin | Surgery       | -                                         | 32, DOD |
|               |             | M, 43       | Pancreatic           | NA          | IV                      | Liver, 120                                           | PTHrP                                          | -                               | Surgery, Chemotherapy        | -                                         | 6, DOD |
|               |             | M, 64       | Pancreatic           | NA          | IV                      | Liver, Lymphnodes, Kidney, Pleurae                    | At diagnosis PTHrP                              | -                               | Corticosteroids              | -                                         | 1.5, DOD |
| Anthony LB et al., 1995 [51] | 1       | F, 75       | Pancreatic           | NA          | NA                      | -                                                     | 60                                              | PTHrP                          | PP                      | IV hydration, Plicamycin, Streptozotocin 5-FU, SSA | SSA       | 3                                         |
| Ratcliffe WA et al. [52] | 1       | F, 39       | Pancreatic           | NA          | NA                      | -                                                     | At diagnosis PTHrP                              | -                               | IV hydration, Calcitonin, Biphosphonates | Surgery       | Surgery                                  | 9                                                 |
| Yoshikawa T et al., 1994 [53] | 1       | M, 43       | Thymic               | NA          | NA                      | -                                                     | At diagnosis PTH (serum), PTHrP (immunohistochemistry) | -                               | -                      | RT                             | -                                         | 15                                                 |
| Mune T et al., 1993 [54] | 1       | M, 58       | Pheochromocytoma     | NA          | NA                      | -                                                     | At diagnosis PTHrP                              | -                               | Alpha-blockers              | Surgery       | Alpha-blockers                           | NA                                                 |
| Williams EJ et al., 1992 [55] | 1       | M, 30       | Pancreatic           | NA          | IIIA                     | -                                                     | At diagnosis PTHrP, Somatostatin PP              | Biphosphonates, IV hydration, Calcitonin, Plicamycin | Streptozotocin, Plicamycin, Streptozotocin | 23, DOD |

ENETS: European Neuroendocrine Tumor Society; NA: Not available; IV: Intravenous; SSA: Somatostatin analogs; PP: Preoperative; RT: Radiation therapy; DOD: Died of disease.
Table 1. Cont.

| Author, Year | N° of Cases | Sex, Age (y) | Primary Site of NEN | Grade, Ki67 | Initial Staging (ENETS) | Metastasis at Diagnosis of Paraneoplastic Hypercalcemia | Time to Onset of Paraneoplastic Hypercalcemia (Months) | Paraneoplastic Hypercalcemia-Inducing Molecules | Other Peptide Secretion | Paraneoplastic Hypercalcemia Therapy | NEN Therapy | Paraneoplastic Hypercalcemia Responsive to | Survival from Onset of Paraneoplastic Hypercalcemia (Months) |
|--------------|-------------|-------------|---------------------|-------------|-------------------------|-------------------------------------------------------|-----------------------------------------------|---------------------------------------------|-------------------------------|---------------------------------|-------------|---------------------------------|-------------------------------------------------|
| Bridgewater JA et al., 1993 [56] | 1 | M, 68 | Pheochromocytoma | NA | III | Lymphonodes | 94 | PTHrP | - | Biphosphonates | Surgery | Biphosphonates | 1, DOD |
| Miraliakbari BA et al., 1992 [57] | 1 | F, 47 | Pancreatic | NA | IIIA | - | At diagnosis | PTHrP | - | IV hydration | Calcitonin | Corticosteroids | Surgery | Surgery | 36 |
| Tarver DS et al., 1992 [58] | 1 | M, 36 | Pancreatic | NA | IV | Liver | 48 | PTHrP | - | IV hydration | Calcitonin | Biphosphonates | TAE | TAE | 18 |
| Mitlak BH et al., 1991 [59] | 1 | F, 77 | Pancreatic | NA | NA | - | At diagnosis | PTHrP | - | Biphosphonates | Surgery | Streptozotocin | 5-FU | Surgery | Biphosphonates | Streptozotocin | 5-FU | 58 |
| Bresler L et al., 1991 [60] | 1 | M, 45 | Pancreatic | NA | NA | - | At diagnosis | NA a | - | NA | Surgery | Streptozotocin | 5-FU | Surgery | 60 |
| Harrison M et al., 1990 [61] | 1 | M, 51 | Pheochromocytoma | NA | NA | - | At diagnosis | PTHrP | - | Biphosphonates | IV hydration | Surgery | Cisplatin | Doxorubicin | Metotrexate | 5-FU | Lomustine | SSA | Surgery | SSA | 49 |
| Kimura S et al., 1990 [62] | 1 | M, 54 | Pheochromocytoma | NA | NA | - | At diagnosis | PTHrP | - | - | Surgery | Surgery | Surgery | NA |
| Rizzoli R et al., 1990 [63] | 2 | M, 30 | Pancreatic | NA | IV | Liver | At diagnosis | PTHrP | - | Biphosphonates | Surgery | Surgery | NA |
| Dodwell D et al., 1990 [64] | 1 | F, 42 | Pancreatic | NA | IV | Liver | At diagnosis | PTHrP | - | Corticosteroids | Biphosphonates | IFN x | Biphosphonates | 12, DOD |
| Wynick D et al., 1990 [65] | 1 | F, 37 | Pancreatic | NA | IV | Liver | At diagnosis | PTHrP | - | Corticosteroids | SSA | SSA | 48 |
| Heitz PU et al., 1989 [66] | 1 | F, 52 | Pancreatic | NA | NA | NA | NA | NA | NA | NA | SSA | SSA | SSA |

a: Not available
Table 1. Cont.

| Author, Year               | N° of Cases | Sex, Age (y) | Primary Site of NEN | Grade, Ki67 | Initial Staging (ENETS) | Metastasis at Diagnosis of Paraneoplastic Hypercalcemia | Time to Onset of Paraneoplastic Hypercalcemia (Months) | Paraneoplastic Hypercalcemia-Inducing Molecules | Other Peptide Secretion | Paraneoplastic Hypercalcemia Therapy | NEN Therapy | Paraneoplastic Hypercalcemia Responsive to Survival from Onset of Paraneoplastic Hypercalcemia (Months) |
|----------------------------|-------------|--------------|---------------------|-------------|--------------------------|---------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------|---------------------------------|-----------------------------------|-------------|-----------------------------------------------------------------------------------|
| Venkatesh S et al., 1989 [67] | 1           | M, 54        | Pancreatic          | NA          | IV                       | Liver                                                   | 72                                                    | NA                              | VIP                             | IV hydration | TAE, Surgery, SSA                                                            | IV hydration | 48                                                                                |
| Friesen SR, 1987 [68]       | 1           | M, 8         | Pancreatic          | NA          | IV                       | Liver                                                   | At diagnosis                                          | NA                              | -                               | Phosphate enemas | Surgery, Phosphate enemas                                                    | Surgery      | 2, DOD                                                                             |
| Sarfati E et al., 1987 [69] | 1           | M, 64        | Pulmonary           | NA          | NA                       | -                                                      | At diagnosis                                          | NA                              | -                               | Surgery            | Surgery, Surgery                                                              | Surgery      | 18                                                                                |
| Shetty MR, 1987 [70]        | 1           | M, 44        | Pancreatic          | NA          | IV                       | Liver                                                   | NA                                                    | NA                              | NA                             | Surgery            | Surgery, Surgery                                                              | NA          |                                                                                  |
| Vair DB et al., 1987 [71]   | 1           | F, 47        | Pancreatic          | NA          | NA                       | -                                                      | At diagnosis                                          | NA                              | -                               | Surgery            | Surgery, Surgery                                                              | NA          |                                                                                  |
| Arps H et al., 1986 [72]    | 1           | M, 48        | Pancreatic          | NA          | IV                       | Liver                                                   | 76                                                    | PTH                             | -                               | Surgery            | TAE, Surgery, IV hydration                                                       | -            | 7                                                                                 |
| Grossman E et al., 1985 [73]| 4           | M, 16        | Pheochromocytoma    | NA          | NA                       | NA                                                     | At diagnosis                                          | NA                              | -                               | Surgery            | Surgery                                                                 | NA          |                                                                                  |
|                            |             | M, 75        | Pheochromocytoma    | NA          | NA                       | NA                                                     | At diagnosis                                          | NA                              | -                               | Surgery            | Surgery                                                                 | NA          |                                                                                  |
|                            |             | M, 26        | Pheochromocytoma    | NA          | NA                       | NA                                                     | At diagnosis                                          | NA                              | -                               | Surgery            | Surgery                                                                 | NA          |                                                                                  |
|                            |             | M, 58        | Pheochromocytoma    | NA          | NA                       | At diagnosis                                            | NA                                                    | -                               | -                               | Surgery            | Surgery                                                                 | NA          |                                                                                  |
| Baba T et al., 1985 [74]    | 1           | M, 15        | Pheochromocytoma    | NA          | IV                       | Bone                                                   | 204                                                   | NA                              | -                               | IV hydration, Calcitonin, Plicamycin | Surgery      | Plicamycin, 3, DOD                                                                |
| Loveridge N et al., 1985 [75]| 1           | F, 68        | Pulmonary           | NA          | IV                       | Liver                                                   | At diagnosis                                          | NA                              | -                               | Biophosphonates, IV hydration, Corticosteroids | -            | IV hydration, 12, DOD                                                            |
| Shunberg AM et al., 1985 [76]| 1           | M, 53        | Pheochromocytoma    | NA          | NA                       | -                                                      | At diagnosis                                          | NA                              | -                               | IV hydration, Corticosteroids | Surgery      | IV hydration, Surgery                                                               |
| Stewart AF et al., 1985 [77] | 1           | F, 11        | Pheochromocytoma    | NA          | NA                       | -                                                      | At diagnosis                                          | NA                              | -                               | Surgery            | Surgery                                                                 | NA          |                                                                                  |
| Rashbash DA et al., 1985 [78]| 1           | F, 68        | Pancreatic          | NA          | IV                       | Liver                                                   | At diagnosis                                          | NA                              | -                               | IV hydration, Prednisone | Streptozotocine 5-FU, Streptozotocine 5-FU | 3           |                                                                                      |
## Table 1. Cont.

| Author, Year | N° of Cases | Sex, Age (y) | Primary Site of NEN | Grade, Ki67 | Initial Staging (ENETS) | Metastasis at Diagnosis of Paraneoplastic Hypercalcemia | Time to Onset of Paraneoplastic Hypercalcemia (Months) | Paraneoplastic Hypercalcemia-Inducing Molecules | Other Peptide Secretion | Paraneoplastic Hypercalcemia Therapy | NEN Therapy | Paraneoplastic Hypercalcemia Responsive to Therapy | Survival from Onset of Paraneoplastic Hypercalcemia (Months) |
|--------------|-------------|-------------|---------------------|-------------|-------------------------|------------------------------------------------------|------------------------------------------|-----------------------------------------------|----------------------------------|--------------------------|----------------|---------------------------------|-------------------------------------------------|
| Fairhurst JB et al., 1981 [79] | 1 | M, 47 | Pheochromocytoma | NA | NA | - | At diagnosis | NA | - | Surgery | Surgery | 9 |
| Öberg K et al., 1981 [80] | 3 | M, 52 | Pancreatic | NA | NA | - | At diagnosis | NA | Calcitonin VIP, Gastrin PP | IV hydration | Surgery/Streptozotocin | Surgery | 20 |
| | | M, 38 | Pancreatic | NA | IV | Liver | Omentum | 94 | NA | Calcitonin VIP | IV hydration | Surgery/Streptozotocin | Surgery | 7 |
| | | F, 54 | Pancreatic | NA | IV | Omentum | At diagnosis | NA | Calcitonin PP | IV hydration | Surgery/Streptozotocin | Streptozotocin | 6 |
| De Plaen JF et al., 1976 [81] | 1 | M, 45 | Pheochromocytoma | NA | NA | - | At diagnosis | NA | - | Surgery | Surgery | 1, DOD |
| Ghose RR et al., 1976 [82] | 1 | M, 14 | Pheochromocytoma | NA | NA | - | At diagnosis | PTH | - | Surgery | Surgery | NA |
| Gray RS et al., 1976 [83] | 1 | M, 66 | Pheochromocytoma | NA | NA | - | At diagnosis | NA | - | Surgery | Surgery | 18 |
| Cryer PE et al., 1976 [84] | 1 | F, 61 | Pancreatic | NA | IV | Liver | 189 | NA | Gastrin | Calcitonin Plicamycin | Streptozotocin | Streptozotocin | 13 |
| Deftos LJ et al., 1976 [85] | 1 | F, 27 | Gastric | NA | IV | Liver | At diagnosis | PTH | Calcitonin | - | Melphalan | - | 38, DOD |
| Hirose S et al., 1975 [86] | 1 | M, 62 | Pancreatic | NA | IV | Liver | At diagnosis | PTH | - | IV hydration | - | - | 4, DOD |
| Kukreja SC et al., 1973 [87] | 1 | M, 16 | Pheochromocytoma | NA | NA | - | At diagnosis | PTH | - | Diuretics | Surgery | Surgery | 36 |
| DeWys WD et al., 1973 [88] | 1 | M, 57 | Pancreatic | NA | IV | Liver | At diagnosis | NA | ACTH | IV hydration | Calcitonin | Streptozotocin | Streptozotocin | 14 |
| Swinton NW et al., 1972 [89] | 1 | M, 12 | Pheochromocytoma | NA | NA | - | At diagnosis | NA | - | Surgery | Surgery | 25 |
Table 1. Cont.

| Author, Year | N° of Cases | Sex, Age (y) | Primary Site of NEN | Grade, Ki67 | Initial Staging (ENETS) | Metastasis at Diagnosis of Paraneoplastic Hypercalcemia | Time to Onset of Paraneoplastic Hypercalcemia (Months) | Other Peptide Secretion | Paraneoplastic Hypercalcemia-Inducing Molecules | Other Peptide Secretion | Paraneoplastic Hypercalcemia Therapy | NEN Therapy | Paraneoplastic Hypercalcemia Responsive to Therapy | Survival from Onset of Paraneoplastic Hypercalcemia (Months) |
|--------------|-------------|--------------|---------------------|-------------|-------------------------|----------------------------------------------------------|-----------------------------------------------------|---------------------------|------------------------------------------|---------------------------|------------------------------------------|-------------|-----------------------------------------------|--------------------------------------------------|
| Lopes VM et al., 1970 [90] | 1 | F, 42 | Pancreatic | NA | NA | - | At diagnosis | NA | -<sup>b</sup> | IV hydration | Surgery | Surgery | 24 |
| Murray JS et al., 1961 [91] | 1 | M, 49 | Pancreatic | NA | NA | - | At diagnosis | NA | -<sup>b</sup> | IV hydration | Surgery | - | 14 |

<sup>a</sup> Evidence for secretion of PTH-like substance (probably PTHrP);<sup>b</sup> Probably VIP. Abbreviations: 5-FU, 5-fluorouracil; CapTem, Capecitabine + Temozolomide; DOD, died of disease; ENETS, European Neuroendocrine Tumor Society; F, female; HACE, hepatic artery chemoembolization; IFNα, Interferon-alpha; IV, intravenous; M, male; MTC, medullary thyroid cancer; NA, not available; NEN, neuroendocrine neoplasia; OLT, orthotopic liver transplantation; PP, pancreatic polypeptide; PRRT, peptide receptor radionuclide therapy; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; RT, radiotherapy; SSA, somatostatin analogue; TAE, transarterial embolization; VIP, vasoactive intestinal peptide.
Table 2. Demographic, pathological, and clinical characteristics of well-differentiated NEN patients with paraneoplastic hypercalcemia reported in the literature.

| Total Number of Cases | 114 (100%) |
|-----------------------|------------|
| **Sex**               | n = 113    |
| Male                  | 62 (54.9%) |
| Female                | 51 (45.1%) |
| **Mean age ± standard deviation** | 46.3 ± 15.8 |
| **Primary NEN histology** | n = 114 |
| Pancreatic NEN        | 83 (72.8%) |
| Pheochromocytoma      | 18 (15.8%) |
| Unknown NEN           | 4 (3.5%)   |
| Lung NEN              | 3 (2.6%)   |
| Gastric NEN           | 1 (0.9%)   |
| Neck NEN              | 1 (0.9%)   |
| Mediastinal NEN       | 1 (0.9%)   |
| Medullary thyroid cancer | 1 (0.9%) |
| Paraganglioma         | 1 (0.9%)   |
| Thymic NEN            | 1 (0.9%)   |
| **Tumor grade**       | n = 23     |
| G1                    | 10 (43.5%) |
| G2                    | 12 (52.2%) |
| G3                    | 1 (4.3%)   |
| **Metastatic disease at paraneoplastic hypercalcemia onset** | 66 (57.9%) |
| **Metastatic sites**  | n = 110    |
| Liver                 | 65 (59.1%) |
| Lymphnode             | 9 (8.2%)   |
| Bone                  | 6 (5.5%)   |
| Lung                  | 1 (0.9%)   |
| Other sites           | 12 (10.1%) |
| **Presence of paraneoplastic hypercalcemia at NEN diagnosis** | 79 (69.3%) |
| **Mean time to onset of paraneoplastic hypercalcemia, months ± standard deviation** | 83.4 ± 56.3 |
| **Causes of metachronous paraneoplastic hypercalcemia** | n = 16 |
| Local recurrence/development of distant metastases | 7 (43.8%) |
| Tumor progression     | 8 (50%)    |
| No disease progression | 1 (6.3%)  |
| **Calcemic levels at onset of paraneoplastic hypercalcemia, mean ± SD (mg/dl)** | 14 ± 2.7 |
| Calcemic levels at onset of paraneoplastic hypercalcemia in pancreatic NEN patients | 14.3 ± 2.9 |
| Calcemic levels at onset of paraneoplastic hypercalcemia in Pheochromocytoma patients | 12.4 ± 1.4 |
| **Paraneoplastic hypercalcemia-producing molecules** | n = 80 |
| PTHrP                 | 68 (85%)   |
| PTH                   | 9 (11.3%)  |
| 1,25(OH) vitamin D    | 3 (3.8%)   |
| **Cosecretion of other peptides** | 32 (28.1%) |
| Calcitonin            | 10 (31.3%) |
| VIP                   | 8 (25%)    |
| Pancreatic polypeptide | 6 (18.8%) |
| Gastrin               | 5 (15.6%)  |
| Somatostatin          | 5 (15.6%)  |
| Glucagon              | 4 (12.5%)  |
| ACTH                  | 1 (3.1%)   |
| **Cosecretion of more than one peptide** | 7 (21.9%) |

**Abbreviations:** ACTH, adrenocorticotropic hormone; IQR, interquartile range; NEN, neuroendocrine neoplasms; PTH, parathyroid hormone; PTHrP, PTH-related peptide; VIP, vasoactive intestinal peptide.
The mean age of the patients was 46.3 ± 15.8 years and a slight majority of them was male (54.9%). The most frequent histological origin, with more than two thirds of the reported cases (72.8%), was p-NEN, followed by Pheochromocytoma (15.8%). All other NEN types were present only in a few patients. At the time of paraneoplastic hypercalcemia onset, most patients had a metastatic NEN disease (57.9%); in particular, the most common metastatic site by far was the liver, followed by the lymph nodes, bone, and lungs. Only 13.3% of patients with p-NEN (11/83) had a localized disease at paraneoplastic hypercalcemia onset, while the great majority of Pheochromocytoma cases (94.4%; 17/18) showed no sign of metastatic involvement at paraneoplastic hypercalcemia onset, although the adrenal tumors were, in the reports with available data, on average, quite large (mean size 5.5 × 6.6 cm).

3.1. Clinical Presentation

In 69.3% of cases, paraneoplastic hypercalcemia was present at the time of NEN diagnosis; this finding was especially true for those patients with Pheochromocytoma, among which 88.9% presented with paraneoplastic hypercalcemia at the time of tumor diagnosis. In the remaining cases, paraneoplastic hypercalcemia arose later in the course of the neoplastic disease, with a mean time from NEN diagnosis of 83.4 ± 56.3 months. The metachronous onset of paraneoplastic hypercalcemia was associated with the development of local recurrence or distant metastases and tumor progression in 43.8% and 50% of cases, respectively.

Among all cases, mean calcemic levels at paraneoplastic hypercalcemia onset were 14 ± 2.7 mg/dl. Calcemic levels in patients with p-NEN were higher than those in patients with a Pheochromocytoma, and this difference was found to be statistically significant (p < 0.001). No significant difference in the degree of hypercalcemia was found when comparing patients based on paraneoplastic hypercalcemia-producing molecules or paraneoplastic hypercalcemia onset (at NEN diagnosis vs. metachronous onset).

Data regarding the humoral factors responsible for paraneoplastic hypercalcemia were available only for 80 patients. In most cases (85%), PTHrP was considered the peptide implicated in paraneoplastic hypercalcemia onset and progression; PTH was elevated in 11.3% of patients with paraneoplastic hypercalcemia, while paraneoplastic hypercalcemia was driven by 1,25(OH) vitamin D in only three patients [14,17,26].

Besides hypercalcemia-producing molecules, 28.1% of the patients (mostly p-NEN) showed cosecretion of other peptides: the most frequent was calcitonin, followed by vasoactive intestinal peptide (VIP), pancreatic polypeptide, gastrin, somatostatin, and glucagon; there was a cosecretion of adrenocorticotrophic hormone (ACTH) in only one case [88]. Interestingly, in seven cases, cosecretion of multiple peptides was reported [18,29,42,45,80].

3.2. Symptomatology

In 25.4% of cases, the clinical presentation of paraneoplastic hypercalcemia was not described; in the other 85 patients (74.6%), multiple signs and symptoms associated with paraneoplastic hypercalcemia were reported. Symptoms can develop gradually and become clinically evident only when blood calcium levels are very high. The severity of the onset depends not only on the age and the comorbidities of the patients, but also on the site of onset of the malignancy and on the grading of the primary NEN. It is very interesting to underline that the symptomatology of hypercalcemia could be synchronous with the diagnosis of the tumor or metachronous, and often correlated, with the progression of disease, even after many years.

The most recurring symptoms are anorexia and fatigue, which are described, respectively, in 37.6% and 31.8% of patients. For both symptoms, a progressive onset, often associated with other gastrointestinal symptoms, was reported. Anorexia is characterized by a typical gradual and involuntary weight loss, suggestive of neoplastic pathology. Among the typical symptoms of hypercalcemia, vomiting and nausea are described, respectively, in 24.7% and 21.2% of patients. Abdominal pain is another common clinical
manifestation (21.2%) of paraneoplastic hypercalcemia, and it is depicted as an “indigestion pain” [20], an “abdominal discomfort” [34,55], and is associated with abdominal cramps without a well-defined localization. Constipation is the least frequent gastrointestinal symptom, complained about by only 9.4% of patients. This clinical picture is often evident at the diagnosis of NEN; however, it is difficult to discern with certainty whether it is caused by the neoplasm itself or by hypercalcemia. Regarding genitourinary manifestations of paraneoplastic hypercalcemia, synchronous polyuria and polydipsia are described, respectively, in 14.1% and 11.8% of patients and were linked to the onset of nephrogenic diabetes insipidus disease in one patient [74]. Paraneoplastic hypercalcemia, moreover, rarely causes dehydration up to the development of acute renal failure (2.4%); dehydration is often caused by diarrhea triggered by vasoactive hormones such as VIP [80,90].

The synchronous diagnosis of nephrolithiasis associated with NEN is mentioned in only four patients [32,45,63,81]. Neuropsychiatric symptoms are outlined in 7.1% of patients by the progressive development of cognitive dysfunction. Mental confusion at the diagnosis of NEN with an inability to maintain concentration and, in some cases, with an impaired short-term memory are described in 8.2% of patients. Hypercalcemia could, moreover, cause unexpected changes in patients’ behavior, anxiety, and depression up to the development of drowsiness, lethargy, and coma. Musculoskeletal symptoms are poorly described in the literature; however, muscle weakness is the most prevalent one (10.6%), followed by cramps, myopathy, and osteopenia and/or osteoporosis. With regard to bone pain (3.5%), Ataallah et al. and Rasbach er al. described two cases of arthralgia associated with hypercalcemia [16,78]. Cardiovascular manifestations are typically synchronous with the NEN diagnosis and include arrhythmias and hypertension, which are complained about by 14.1% of patients; however, in 10 of these patients, paraneoplastic hypercalcemia was caused by a Pheochromocytoma [35,61,73,76,77,81,89], thus is difficult to define if hypertension was caused by the effect of catecholamines or by paraneoplastic hypercalcemia. Lastly, Abraham et al. described a case report of paraneoplastic hypercalcemia correlated with diagnosis of p-NEN in a pregnant woman at 29 weeks’ gestation, which caused a symptomatology comparable with pre-eclampsia characterized by consciousness, headache, hypertension, and proteinuria [43].

3.3. Treatment Approach for Paraneoplastic Hypercalcemia

Only 85 cases had available data about the treatment used for the management of paraneoplastic hypercalcemia.

In most patients, a combination of therapeutic approaches was employed, mostly intravenous hydration, loop diuretics, and bisphosphonates (mainly pamidronate and zoledronate). In fewer cases, calcitonin and glucocorticoid were also employed, while the use of denosumab and cinacalcet was reported in only six and four cases, respectively. See Table 1.

Regarding antineoplastic therapy, data were available for 95 patients. In most cases, a combination of antineoplastic approaches was used. A total of 60 (63.2%) patients underwent surgery, both at the primary site and for metastatic or recurrent disease. Local techniques (embolization or radiofrequency ablation) were used in 17.9% patients for treating their liver metastases. Regarding medical therapy, somatostatin analogues (SSAs) were used in 37.9% of patients, chemotherapy was employed in 32.6% of patients, peptide receptor radionuclide therapy (PRRT) was administered in 10.5% patients, and target therapy with sunitinib and everolimus were both employed in five cases. See Table 1.

Data regarding paraneoplastic hypercalcemia response to therapy (both medical and antineoplastic) were available for 84 cases. Disease burden-reducing techniques (surgery, embolization) were able to control paraneoplastic hypercalcemia in 39.3% of cases, mainly in patients with localized, operable disease. Medical therapy alone could control paraneoplastic hypercalcemia in only 13.1% of patients, primarily through the utilization of bisphosphonates; in particular, intravenous hydration alone determined normalization of calcemic levels in only two patients and, when associated with other treatments, in three more cases.
Medical antineoplastic treatments alone controlled paraneoplastic hypercalcemia in 20.2% of patients. In the remaining cases (27.4%), different combinations of therapies, including medical therapy for paraneoplastic hypercalcemia and antineoplastic (both surgical and medical), were used together to achieve paraneoplastic hypercalcemia control. Survival data were available for 74 patients; median overall survival was 18 months (IQR range, 7–37). Among patients with p-NEN, median survival was 23.5 months (IQR range, 9.8–48).

4. Discussion

Nowadays, paraneoplastic hypercalcemia is a well-established paraneoplastic syndrome that is associated with many malignancies, even if the relationship between NEN and hypercalcemia is still little considered. Systematically reviewing the literature, we extracted that this rare condition was described in a total of 114 cases of patients with well-differentiated NEN. The pancreas represents the most frequent localization of NEN associated with paraneoplastic hypercalcemia (72.8%), followed by Pheochromocytoma (15.8%). This observation is particularly interesting if we consider that, in an animal study, it has been demonstrated that PTHrP acts as a growth factor for pancreatic beta-cells [92] and that, in chronic pancreatitis, PTHrP functions as a mediator of proinflammatory and profibrotic cytokines, which in turn regulate PTHrP expression [93]. As in other malignancies, paraneoplastic hypercalcemia may also occur in NEN through several different mechanisms, including PTHrP secretion, PTH secretion, and calcitriol overproduction. In NEN, as in all other types of solid cancers, the most common cause of paraneoplastic hypercalcemia is the tumor production and release of PTHrP (85% of cases). PTHrP carries out a physiologic role in embryologic development and in mammary gland function, but it has no other known functional role in the adult metabolism [94]. PTHrP shares its amino acid sequence homology with PTH at its N-terminus and activates the type 1 PTH receptor, but it is encoded by a different gene [95]. Like PTH, PTHrP also increases calcium reabsorption in the kidney and stimulates osteoblasts to secrete receptor activators of nuclear factor-B ligands (RANKL), which bind to the RANK receptor on osteoclasts [96,97]. This interaction mediates the differentiation of osteoclast precursors into mature osteoclasts and increases bone resorption by osteoclasts. Since the most frequent cause of paraneoplastic hypercalcemia in NEN is PTHrP secretion, PTHrP levels should be checked in all patients with this clinical and biochemical suspect. The accuracy and reliability of laboratory assays for PTHrP have improved because of newer double-antibody techniques. Furthermore, when elevated at tumor diagnosis, PTHrP can be used as a biomarker to assess treatment response to therapy.

A less common cause of paraneoplastic hypercalcemia is the paraneoplastic ectopic secretion of PTH by tumors, which has been described in association with several malignancies, most of which are of the lung [98–100]. Only three cases of well-differentiated NEN associated with paraneoplastic hypercalcemia secondary to tumor-mediated overproduction of calcitriol are described in the literature [14,17,26]. Over production of calcitriol is a typical cause of paraneoplastic hypercalcemia in lymphomas [101,102], in which tumor cells or surrounding lymphocytes overexpress 1α-hydroxylase, which causes ectopic conversion of 25 hydroxyvitamin D to 1,25-dihydroxyvitamin D [103,104]. Calcitriol-related hypercalcemia derives from both increased intestinal and bone reabsorption of calcium.

This review showed the timing of paraneoplastic hypercalcemia occurrence during the “natural history” of well-differentiated NEN disease. In most cases, hypercalcemia is already present at diagnosis (69.3% of cases); in others, it develops during the disease (mean time from NEN diagnosis of 83.4 ± 56.3 months). In most cases, the metachronous occurrence of hypercalcemia is associated with disease progression/relapse. In the case of Pheochromocytoma, hypercalcemia was already present at diagnosis in 88.9% of cases, while in two cases, hypercalcemia was observed at the recurrence of the disease 94 and 204 months after the first surgical treatment, respectively. Hypercalcemia is almost always
associated with the presence of distant metastases, except in 10.5% of cases, in which there were no metastases or there were only metastases to the local regional lymph nodes. Therefore, it seems that the tumor burden at diagnosis or during disease progression determines the capacity of hormone secretion by the neoplasm, which is different to what is described in the literature for Pheochromocytoma.

Paraneoplastic hypercalcemia is typically associated with severe clinical signs and symptoms and is often an oncologic emergency [9], while the paraneoplastic hypercalcemia of the NEN as a whole seems to give more moderate symptoms, similar to those of primary hyperparathyroidism. The most frequent symptoms are asthenia, gastrointestinal, and genitourinary disturbances. Severe symptoms such as pre-eclampsia, coma, lethargy, and arrhythmia have been described in extremely rare cases.

The management of paraneoplastic hypercalcemia in well-differentiated NEN is challenging. In fact, in our review, we observed that, in 27.4% of cases, the combination of multiple treatments (medical therapy for paraneoplastic hypercalcemia and different antineoplastic (both surgical and medical) treatments, variously combined) was required to obtain control of hypercalcemia. Disease burden-reducing techniques (surgery, embolization) were able to control paraneoplastic hypercalcemia, mainly in patients with localized, operable disease. Medical therapy alone could control paraneoplastic hypercalcemia in selected patients, primarily through the employment of bisphosphonates; in particular, intravenous hydration alone determined calcemic normalization in only two patients and, when associated with other treatments, the improvement is measured in very few cases. Medical antineoplastic treatments alone controlled paraneoplastic hypercalcemia in less than a quarter of reported patients. Therefore, the pooled data from our systematic review show that tumor debulking plays a key role in controlling paraneoplastic hypercalcemia in patients with well-differentiated NEN, so surgical treatment should be indicated whenever feasible. PRRT was administered in a limited number of cases; however, given its capability to control functioning tumors [105] and its potential role as a neoadjuvant therapy [106–108], PRRT could be prescribed either before surgery or in patients with progressive metastatic inoperable disease to reduce tumor secretion and tumor burden.

The onset of hypercalcemia associated with cancer in patients with well-differentiated NEN represents a major clinical challenge. Prior to the diagnosis of paraneoplastic hypercalcemia, physicians should rule out multiple endocrine neoplasia (MEN) 1 and 2 [109,110], in which the hypercalcemia could be due to primary hyperparathyroidism. Paraneoplastic hypercalcemia caused by ectopic production of PTH, although uncommon, should be considered in patients with p-NET when PTH levels are significantly elevated and there is no evidence of a parathyroid-related cause. Recognizing the association between elevated PTH levels and paraneoplastic hypercalcemia can prevent unnecessary parathyroid or exploratory neck surgery. Since paraneoplastic hypercalcemia must be recognized and framed promptly, and as it often remains undiagnosed, the complex clinical and therapeutic management of paraneoplastic hypercalcemia implies the need for a multidisciplinary approach, aimed at controlling the clinical syndrome and tumor growth. With the present review we have shown how paraneoplastic hypercalcemia in well-differentiated NEN was diagnosed and managed over the years and how important it is to conduct a personalized diagnostic and therapeutic process that provides an overview of the patient and his status.

In summary, compared with paraneoplastic hypercalcemia of solid and hematological tumors, paraneoplastic hypercalcemia in NEN shares PTHrP as the most common causal agent with solid tumors, while paraneoplastic hypercalcemia in lymphomas is more frequently caused by 1,25(OH) vitamin D. Furthermore, paraneoplastic hypercalcemia in NEN seems to be less severe than in solid and hematological tumors. Finally, the prognosis of paraneoplastic hypercalcemia of solid and hematological tumors seems to be worse than in NEN; this could be related to the milder symptomatology of NEN patients and to their better oncological prognosis.

A limitation of this review is represented by the difficulty of bibliographic research and data extraction. Since paraneoplastic hypercalcemia in NEN is a rare condition, we decided
not to place timeframe restrictions in the selection of the articles; this allowed us to include a considerable number of cases in the review. However, it led to a lot of missing data, especially from the oldest articles. Indeed, relevant information such as grading, staging, and the paraneoplastic hypercalcemia-inducing molecule were not reported in some older case reports; interestingly, in cases from 1961 to 1991, an unspecified PTH-like substance was considered responsible for paraneoplastic hypercalcemia. Given that PTHrP was first isolated in 1987, we could speculate that, in those patients, PTHrP was the paraneoplastic hypercalcemia-driving molecule. See Table 1.

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