Survey NEN

Inquérito NEN

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ABSTRACT
Introduction: Although new treatments and diagnostic methods for Neuroendocrine Neoplasms (NEN) have been introduced, the level of access to them needs somehow to be further investigated. Objectives: to understand the aspects that influence the access to the diagnosis, follow-up and treatment of patients with NEN in Brazil. Methods: This is a cross-sectional electronic survey conducted by the Brazilian Group of Gastrointestinal Tumors (GTG) and containing sixteen questions sent to Brazilian Oncologists via messaging app, aiming to identify access profiles to diagnostic and follow-up tests among patients with NEN, in addition to proven effective treatments in the Public and Private Brazilian Health Care System. Descriptive analysis was used to report the outcomes.

Results: The survey was carried out with 201 Oncologists. Since (31.8%) of the Oncologists responded that they have been trained for more than 15 years and have been working with clinical practice within the scope of the Brazilian National Health System and/or the Private Health Care. For follow-up, the most requested marker was Chromogranin A (39%). Regarding diagnosis, 35.8% of the 201 participants claim to ask for a slide review in their clinical practice, and their access to tomography and resonance (58%). When contextualizing the performance of PET Scan with Gallium 68, it is available in (15%), but a significant percentage did not have access in the Brazilian National Health System Service, corresponding to (95%). Subgroup analysis revealed statistically significant differences in the availability of Somatostatin Analogue, being offered in 56% in the Brazilian National Health System and 84% in the Private Health Care ($p < 0.05$). Conclusion: This is the first Brazilian research that evaluated access to diagnostic and therapeutic tools in the Brazilian scenario, showing important access limitations, especially in the public sector. In view of the results presented, these restrictions can lead to unfavorable clinical outcomes in patients with NEN in Brazil.

Keywords: Neuroendocrine Carcinoma, antineoplastics, surveys and questionnaires, health system.

RESUMO

Introdução: Embora tenham sido introduzidos novos tratamentos e métodos de diagnóstico para as Neoplasias Neuroendócrinas (NEN), o nível de acesso a elas precisa de alguma forma de ser mais investigado. Objectivos: compreender os aspectos que influenciam o acesso ao diagnóstico, acompanhamento e tratamento dos pacientes com NEN no Brasil.
Métodos: Este é um inquérito electrónico transversal conduzido pelo Grupo Brasileiro de Tumores Gastrointestinais (GTG) e contendo dezasseis perguntas enviadas aos Oncologistas brasileiros através de aplicação de mensagens, com o objectivo de identificar perfis de acesso a testes de diagnóstico e seguimento entre pacientes com NEN, para além de tratamentos comprovadamente eficazes no Sistema de Saúde Público e Privado Brasileiro. A análise descritiva foi utilizada para relatar os resultados. Resultados: O inquérito foi realizado com 201 Oncologistas. Desde então (31,8%) dos Oncologistas responderam que foram formados há mais de 15 anos e têm trabalhado com a prática clínica no âmbito do Sistema Nacional de Saúde brasileiro e/ou do Sistema Privado de Saúde. Para o acompanhamento, o marcador mais solicitado foi a Cromogranina A (39%). Quanto ao diagnóstico, 35,8% dos 201 participantes afirmam solicitar uma revisão de slides na sua prática clínica, e o seu acesso à tomografia e ressonância (58%). Ao contextualizar o desempenho do PET Scan com Gálio 68, este está disponível em (15%), mas uma percentagem significativa não teve acesso no Serviço Nacional de Saúde Brasileiro, correspondendo a (95%). A análise dos subgrupos revelou diferenças estatisticamente significativas na disponibilidade do Somatostatin Analogue, sendo oferecido em 56% no Sistema Nacional de Saúde Brasileiro e 84% no Serviço de Saúde Privado ($p < 0,05$). Conclusão: Esta é a primeira investigação brasileira que avaliou o acesso a ferramentas diagnósticas e terapêuticas no cenário brasileiro, mostrando importantes limitações de acesso, especialmente no sector público. Tendo em conta os resultados apresentados, estas restrições podem levar a resultados clínicos desfavoráveis em pacientes com NEN no Brasil.

Palavras-chave: Carcinoma Neuroendócrino, antineoplásticos, inquéritos e questionários, sistema de saúde.

1 INTRODUCTION

Neuroendocrine Neoplasms (NEN) are heterogeneous malignancies that arise in secretory cells of the diffuse Neuroendocrine System, and which have distinct clinical and biological characteristics compared to other neoplasms. It can be originated in almost all organs, being more prevalent in the gastroenteropancreatic tract and in the bronchopulmonary tree. NEN have epidemiological characteristics, diagnostic particularities, prognostic factors and varied therapeutic approaches.[1]

The incidence of NENs has steadily increased over the last three decades, with gastroenteropancreatic neuroendocrine tumors (GEP-NENs) currently representing the second most common digestive cancer in terms of prevalence.[2] Therefore, the multidisciplinary discussion in the management of cases is an important process, based on an integration of knowledge on the part of Clinical Oncologists, Oncology Surgeons with experience in NENs, as well as Pathologists, Radiologists, Interventionists, Endocrinologists, Gastroenterologists, Endoscopists, Colonoscopists, Nuclear Doctors and Radiotherapists.[3]

It is worth mentioning that for the diagnosis of NENs, there is not only one protocol to be followed until diagnosis, due to the wide variety of tests that can be asked by the Oncologist. The standard treatment is surgery, as the need for adjuvant therapies is questionable. However, surgery may not be possible due to the extension and spread of the disease, making necessary the treatment to relieve symptoms and suppress tumor growth.[4] According to O'Dorisio et al.[5], on April 2nd 1986, a Symposium was promoted with the participation of scientists, preclinical and multidisciplinary physicians, and among its purposes, neuroendocrine disorders of the gastroenteropancreatic systems were considered (GEP) and preclinical and clinical applications of the somatostatin analogue peptide SMS 201 -995 were introduced (octreotide [Sandostatin]).

Three years later, in 1989, Octreotide was the first drug approved by the US Food and Drug Administration (FDA) for the symptomatic control of Carcinoid Syndrome and Verner-Morrison Syndrome, characterized by Watery Diarrhea. Currently, both Octreotide and Lanreotide present themselves as first-line therapies for all symptomatic neuroendocrine tumors.[5]

It is acknowledged that originally the dosage to control and/or prevent the symptoms of hormonal excess of the Carcinoid Syndrome, as well as to achieve an improvement in progression-free survival, allowed these drugs to become first-line agents for the treatment of low-grade Neuroendocrine Tumors4 , which was evidenced by international PROMID and CLARINET studies that focused on the use of Octreotide and Lanreotide respectively, in patients with small intestine without Metastatic Degeneration.

As for Interferon Alpha (IFN-α), Oronsky et al.[4] stated, based on initial tests, that a reduction in hormone production could be observed, as well as a significant improvement in tumor markers in more than 50% of patients. Objective rates of tumor response were in the range of 4% to 10%, with high rates of disease stabilization.

A suggestion of synergy between Somatostatin Analogues (SSAs) and IFN-α in small phase 1 studies resulted in three randomized controlled trials investigating SSAs alone versus its combination with IFN-α. It was found, in two of these studies, that compared Octreotide alone and its combination with IFN-α, that the 5-year survival rate was improved in the combination group; however, the differences were not statistically significant.[4]

Targeted liver procedures, Metastectomy, Ablative Therapy, Embolization, Transarterial Chemoembolisation, and Selective Internal Radiation Therapy with yttrium-90 microspheres may also be used, as well as targeted Systemic Therapies involving Somatostatin Analogues, Radionuclide Receptor Peptide Therapy (PRRT), Inteferon , Everolimus and Sunitinib.

In terms of the Brazilian scenario, Brazilian statistics do not separate tumors based on histological type, choosing the anatomical parameter of the organ of origin instead.[6] Takano[7] complements by stating that as this is a heterogeneous group of neoplasms, the study of its incidence in the general population, is fragmented according to topography, so it is natural to observe that more comprehensive epidemiological studies are rare.

There is a clinical perception of important barriers to this access; however, this has not been quantified, so its magnitude is unknown. It is understood that this study can contribute to filling this gap regarding the lack of data on the treatment of Neuroendocrine Tumors in Brazil, having as a parameter the Brazilian National Health and the Private Health Care Systems.

2 METHODS

2.1 STUDY DESIGN

In order to achieve the proposed objectives of this study, it was proposed to carry out a “Survey” research among Medical Oncologists who are members of the Brazilian Group of Gastrointestinal Tumors (CTG) and those who work in recognized institutions in Brazil offering leading cancer treatments in the Private and Public Health Care Systems. Allowing to identifying the view of doctors, their perceptions and difficulties, related to the assessment of oncology performance in the public and private scope in 2021.

This survey consists of sixteen multiple-choice closed-ended questions, sent via messaging app. The target population of the research was composed of Oncologists who are

members of the Brazilian Group of Gastrointestinal Tumors (GTG) and professionals who are specialists in the referred field who have been working in recognized institutions in Brazil that offer leading cancer treatments for the Private and/or Public Health Care System (Sistema Único de Saúde-SUS). We chose to select as participants Medical Oncologists linked to the group or at least related closely to the Board of Directors because we inferred that they could contribute to qualitatively better reports in NENs due to the greater knowledge and time dedicated to the performance of this particular tumor.

The initial contact with the target audience was conducted by the directors of the Brazilian Group of Gastrointestinal Tumors (GTG). The electronic survey was sent to all potential candidates within 30 days, and consent to participate in this study was obtained by acceptance to complete the questionnaire; all participant data were treated anonymously, without the electronic research tool capturing any participant identifying data. Due to its characteristic of investigation on the practices of diagnosis, follow-up and treatment, the present study was not submitted to a Research Ethics Committee-CEP.

For the purposes of this study, it was decided to use the SurveyMonkey tool for the composition of the questionnaire to be later sent to the target population via messaging app, thus allowing the survey not to be carried out in person, respecting the necessary social distance, and in such a way that the questionnaires could be answered by several people simultaneously. The questionnaire is an instrument that allows reaching a higher number of participants, quickly and simultaneously, and besides, since the questions are standardized, it also contributes to the stage of compilation and comparison of responses that will later be reworked in the form of graphs and analyses.[8]

The survey instrument assessed current practices in terms of treatment options for patients with NENs, diagnostic and follow-up tests recommended by national and international guidelines, and their respective availability in the Private and Public Health Care Systems [9,10] The instrument allowed to obtain data on years of practice in clinical oncology and how much of each oncology practice was dedicated to NEN. Table 1- We describe the questions that made up our research. The time to complete the survey was estimated as an average of three to four minutes.

Table 1. Questions that made up our research:

How long have you been working in the field of Oncology?
In relation to your workplaces, identify your field of activity, defining between Public, Private or both of them.
Please inform the number of patients undergoing treatment or follow-up with ENT in the last year.
What serum markers do you usually request for diagnosis and follow-up?
On average, what percentage of ENT patients do you request tumor tissue slide review?
What imaging tests do you have access for the diagnosis and staging of NET?
Check, in the alternatives below, if you have access to any form of Pet-Scan Gallium 68.
Check the option of access to NET treatment, with the use of Somatostatin Analogues.
Check the option of access to NET treatment, with the use of Lutetium-177.
Check the option of access to NET treatment, with the use of Everolimus.
Check the option of access to NET treatment, with the use of Sunitinib.
Check the option to access TNE treatment, using CapTem.
Check the option of access to the treatment of NET, with the use of Intravenous Chemotherapy.
Check the option of access to NET treatment, with the use of Hepatic Embolization.
Check the option of access to NET treatment, with the use of Alpha Interferon.
Check the option of access to NET treatment, with the use of Metastectomy Statistical Analysis.

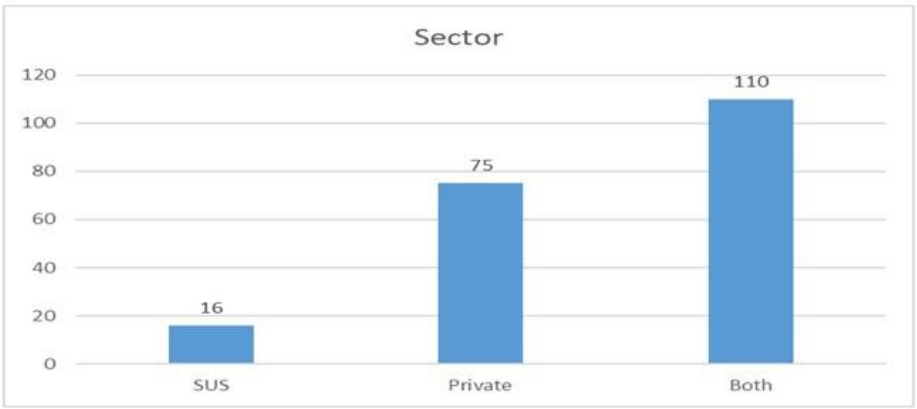
2.2 STATISTICAL ANALYSIS

Only fully completed questionnaires were included in the analyses. It was set that descriptive statistics would be reported for all responses. Subgroup comparisons were analyzed with $\chi 2$ tests for binary variables. A two-tailed p-value <0.05 was considered statistically significant. The sample size was not formally calculated in the study, and due to the dynamics of the questionnaire distribution, we sought to enroll the largest possible sample size to better estimate the diagnostic, follow-up and treatment practices for NEN.

3 RESULTS

The survey was completed within a 30-day period (March 24, 2021 to April 22, 2021) and consisted of 201 Medical Oncologists who agreed to participate throughout the country.

Graph 1. Sample

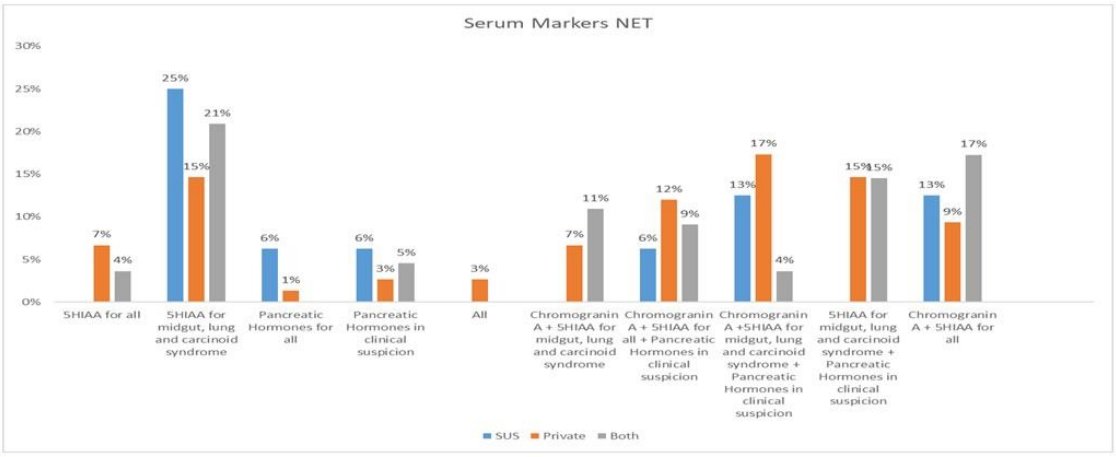


Source: Own Authorship (2021)

Respondent Medical Oncologists have been under Oncology Practice for more than 15 years (31.8%). Among those, (54.7%) work in both Public and Private Health System practices. The Private Health System corresponds to more than 50%, among those with more than 15 years of practice, and only 32.3% of the participants had more than 10 patients in follow-up and related treatment only in Neuroendocrine Tumor.

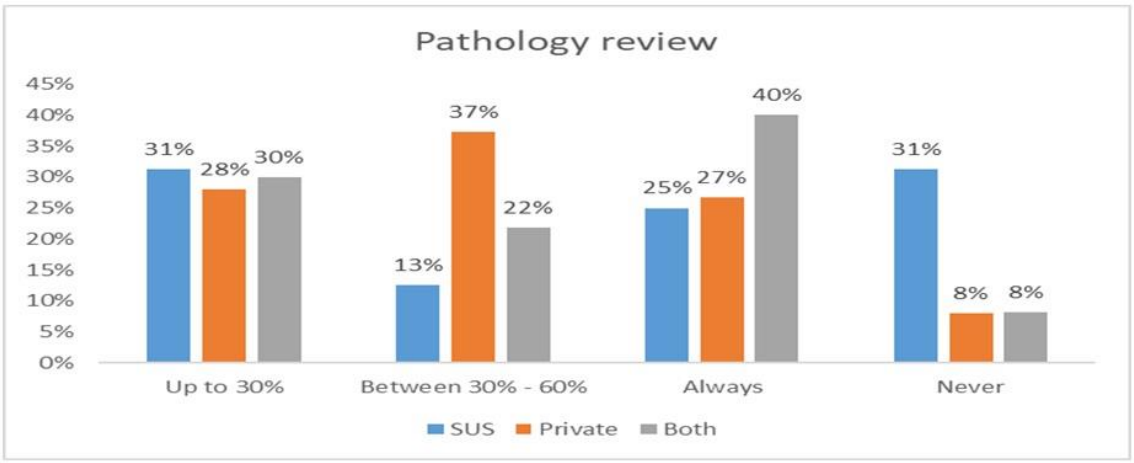
Graph 2 shows the percentage that Tumor markers are requested, in relation to the Public and Private Health Care System, highlighting the clinical indications that have been performed. While Graph 3 presents a periodicity in clinical practice of slide review to the diagnosis of Rare Tumor.

Chart 2. Serum Markers NET



Source: Own Authorship (2021)

Graph 3. Blade review



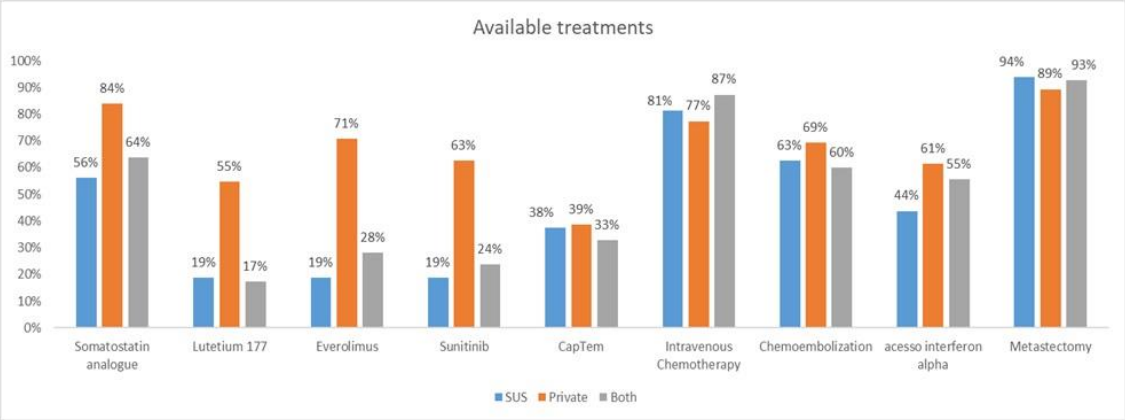
Source: Own Authorship (2021)

Among the options regarding diagnosis and follow-up in Neuroendocrine Tumors, most Medical Oncologists (54.7%) chose for Chromogranin A diagnosis and follow-up, and urinary measurement of 5-hydroxyindoleacetic acid (5-HIAA) for patients with Down Syndrome.

Carcinoid; being represented by Midgut and Lung with (61%) and (5-HIAA) for all, only (11%). Regarding Pancreatic Hormones (14%) they are requested in clinical suspicion in (39%) for all. When it comes to diagnosis, in clinical practice, Tissue Revision is always performed in (27%), and represented by only (8%) in those who never request Tissue Revision, to indicate treatment. It can be seen that 30-60% were represented by (37%) requesting a review, and up to 30% carry the review out (28%).

Treatment options according to Public and Private Health Care System availability

Graph 4: Available treatments



Source: Own Authorship (2021)

After analyzing the graphs, we can see that the research participants reported that Somatostatin Analogues were available in the Public Health Care for 56%, and for 84% in the Private Health Care. Regarding Lutétium-177, it was available in the Public Health Care for 19% and for 55% of Medical Oncologists in the Private Health Care, which represents 68 of the 201 participating professionals.

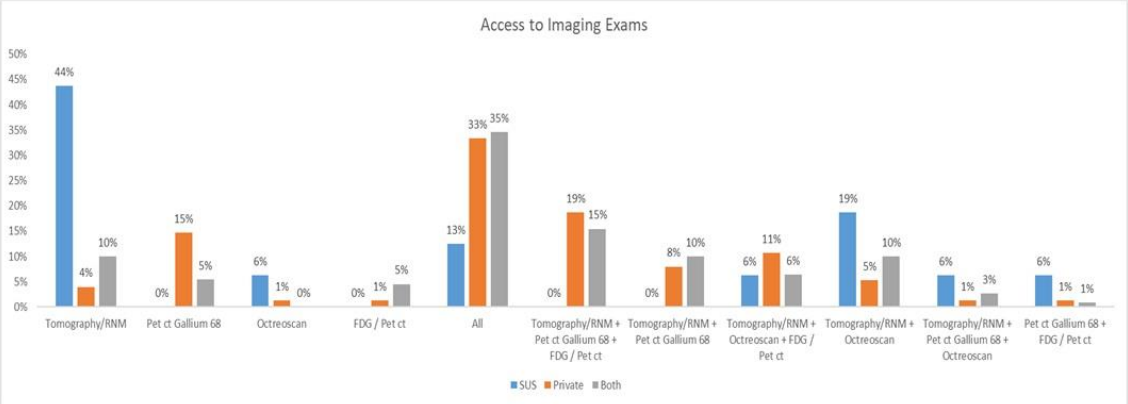
Regarding Oral Therapy (mTOR); Everolimus and Sunitinib are both available in the Public Health Care (19%), but in the Private Health Care, it is a widely applicable therapy with greater availability (71%) compared to Everolimus and (63%) Sunitinib.

Intravenous Chemotherapy is a therapy that has been widely used in the Public Health Care, representing (63%) of availability. On the other hand, Oral Chemotherapy, such as therapy (CapTem) in the Private Health Care, has been used (39%) of the cases according to the participants' reports, whereas, we present the availability in the Public Health Care (38%), impacting the response rate, with at least one line of treatment.

Interferon Alpha has been used in current clinical practice a little, representing 61% in the Private Health Care, and 44% in the Public Health Care, which also involves using

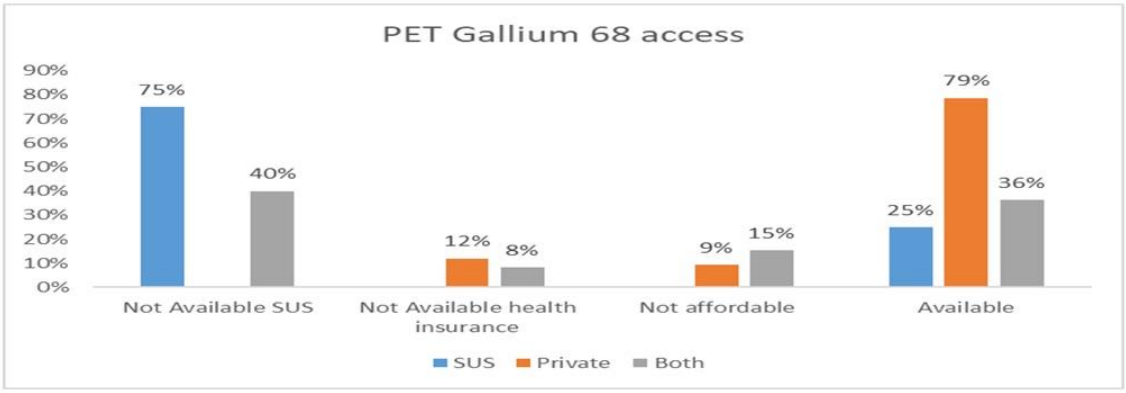
procedure/surgery combined to a line of treatment; Chemoembolization and Metastectomy. We have representative data (94%) Metastectomy as an option available in the Public Health Care, and in the Private Health Care(89%) and in relation to Chemoembolization (69%) availability in the Private Health Care and (63%) in the Public Health Care Systems.

Graph 5: Access to imaging exams



Source: Own Authorship (2021)

Accesses of diagnostic and follow-up exams, such as Tomography and Resonance, present a prominent percentage with (44%) available in the Private Health Care and only (4%) in the Public Health Care. Among the PET CT we can observe the availability of the PET Scan with Gallium 68, (15%) in relation to the Octreoscan, and (1%) for the pet FDG in the Private Health Care, in relation to the Public Health Care only (5%) has access. The percentage in relation to access to the Public Health Care, specifically in the PET Scan with Gallium 68, a large portion of patients has access, but through the Private Health Care, represented (Graph 6).



68Gallium-labeled PET-CT with Somatostatin Analogues (such as DOTATATE) is a functional method with high resolution and high accuracy in the identification and follow-up

of Neuroendocrine Tumors. Different studies attribute to the Pet ScanGalio 68 an accuracy greater than 95% in the detection of NENs, a result far superior to those obtained through scintigraphy with Somatostatin Analogues (58%) or Computed Tomography (63%).

4 DISCUSSION

In the present study, we can conclude important differences in the approach to treatment in relation to the limitations of access in the Systems (Public Health Care, Private Health Care and Health Insurance Plan). The survey had the participation of 201 Medical Oncologists, of which (31.8%) responded that they have been trained for more than 15 years and practice clinical practice within the scope of the Brazilian Public Health System and/or Private. For follow-up, the most requested marker was Chromogranin A (39%). Regarding diagnosis, 35.8% of the 201 participants claim to ask for a slide review in their clinical practice, and their access to tomography and resonance covers (58%). When contextualizing the performance of Pet Scan with Gallium 68, it is available in (15%), but a significant percentage did not have access to the Public Health Care Service, corresponding to (95%). Subgroup analysis revealed statistically significant differences in the availability of Somatostatin Analogue, being offered in 56% in the Public Health Care and 84% in the Private Health Care ($p < 0.05$).

It is noteworthy the availability of Somatostatin Analogue in 56% in the Public Health Care, where according to the two placebo-controlled phase III studies, antitumor effects in Gastroenteropancreatic NENs (GEP) were demonstrated, regardless of the functionality of the NEN. Where we contemplate similar safety and efficacy in clinical practice in the use of Octreotide or Lanreotide. 11.12

According to the Guidelines of the Brazilian Gastrointestinal Tumor Group, it is important to emphasize the use of the Somatostatin Analogue as a standard treatment in the first line, presenting symptom control, and Carcinoid Syndrome, leading to a better quality of life, prevention and eventual complications, such as Carcinoid Heart Disease and Retroperitoneal Fibrosis.

Another relevant point in the study is the Oral Systemic Therapy, the mTOR inhibitor, Everolimus is used in the treatment of functioning Pancreatic, Gastrointestinal or Pulmonary Neuroendocrine Tumors, being associated with Octreotide, represented in the RADIANT-4 study that showed a survival of 11 months, compared with placebo 3.9 months.13 This highlights the importance of the availability of Everolimus in the Public Health Care System for better clinical management. Emphasizing the data from our work, more than 70% still do not use this Oral Systemic Therapy, due to the lack of access to it.

We can also use the Octreoscan or Pet Scan tools with Gallium 68 to confirm the expression of SSTR2 Somatostatin Receptors 2 and to assess advanced disease, although this is not mandatory for starting therapy.14 We found a disproportionate use of 6% in the Public Health System , with agreement at 15%. The Pet Scan exam with Galio 68 is extremely important for the staging of advanced NEN, and can often help in the indication of surgery in the curative background, Liver Transplantation, thus modifying their prognosis. Also useful in the indication of treatment such as Lutetium 177, through the uptake of Somatostatin Receptors captured in the exams, according to the NETTER-1 study, phase III, previously treated Midgut patients, submitted to 177 Lu-DOTATATE for 4 cycles, versus Octreotide LAR every 4 weeks, had a median progression-free survival of 40 months for the lutetium arm versus 8.4 months for Octreotide.

Our study has some limitations. In the questionnaire sent to the Medical Oncologists, the distinction by state was not proposed, making the discussion unfeasible from the perspective of the financial deficit of the States, which could help to explain the data for the unavailability of access in imaging exams such as in the Pet Scan with gallium68 (85 %), and in treatment, as is the case for the Analogue of Somatostatin 44%.

Furthermore, we had an extension of non-responders. Considering that in Brazil we have 3,583 Medical Oncologists registered with the Federal Council of Medicine-CFM, according to the last update in 2018, of which 1,037 Oncologists work in Greater São Paulo, we obtained only 201 answered questionnaires, which may limit the generalization of our results.

The present study provided important data for the establishment of future research and new articles on Neuroendocrine Tumors, with priority being given to new inclusions of treatment protocols, for greater control of symptoms and increased disease-free survival, such as mTOR, Oral and Incorporation of Somatostatin Analogues into the Public Health Care System.

5 CONCLUSION

The following research is different because it has been the first Brazilian research focused on a comparison of treatment lines in patients with Neuroendocrine Tumor, together with the limitations of financial resources in the Private and Public Health Care Systems sphere, which can have impacts on the follow-up and treatment of patients.

The Neuroendocrine Tumor can be described as a rare disease, for which few studies have been developed so far, which highlights the importance of shared therapeutic decision-making among the specialists and the establishment of protocols.

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