



Impact of the SARS-CoV2 pandemic dissemination on the management of neuroendocrine neoplasia in Italy: a report from the Italian Association for Neuroendocrine Tumors (Itanet)

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Abstract

Introduction The organization of the healthcare system has significantly changed after the recent COVID-19 outbreak, with a negative impact on the management of oncological patients. The present survey reports data collected by the Italian Association for Neuroendocrine Tumors on the management of patients with neuroendocrine neoplasia (NEN) during the pandemic dissemination.

Methods A survey with 57 questions was sent to NEN-dedicated Italian centers regarding the management of patients in the period March 9, 2020, to May 9, 2020

Results The main modification in the centers' activity consisted of decreases in newly diagnosed NEN patients (– 76.8%), decreases in performed surgical procedures (– 58%), delays to starting peptide receptor radionuclide therapy (45.5%), postponed/canceled follow-up examinations (26%), and canceled multidisciplinary teams' activity (20.8%). A low proportion of centers (< 10%) reported having to withdraw systemic anti-tumor medical treatment due to concerns about the pandemic situation, whereas PRRT was withdrawn from no patients.

Conclusion Although the COVID-19 outbreak induced the centers to reduce some important activities in the management of NEN patients, the Italian network was able to provide continuity in care without withdrawing anti-tumor treatment for the majority of patients.

Keywords COVID-19 · SARS-CoV2 · Pandemic · Neuroendocrine tumors · Multidisciplinary team · Management · Peptide receptors radionuclide therapy

Introduction

Following the spread of the COVID-19 outbreak in Italy in February 2020 induced by the novel SARS-CoV2 virus, strict measures have been implemented by the national government, including restricting movement and recommendations to go to hospitals only in cases of absolute necessity.

The healthcare system has suffered from the increasing numbers of infected persons requiring intensive care, and hospitals' activities have been modified to satisfy the novel emerging need [1–3]. Oncological patients have been reported to be at higher risk of being affected by COVID-19, with an increased risk of severe illness and mortality [4, 5]. Several reports have been produced evaluating the potential impact of the SARS-CoV2 pandemic dissemination on the management of patients with different kinds of tumors, including colon, breast, and lung cancers [6–8]. However, no data are available for neuroendocrine neoplasia (NENs). Given the rarity of these diseases and the need for dedicated specialized centers to care for NEN patients, collecting data in this specific patient population may be challenging.

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The aim of this study was to understand how the pandemic dissemination of SARS-CoV2 infection has modified the clinical management of NEN patients in Italy.

Methods

An invitation to participate in an online survey (COVINET survey) by the SurveyMonkey® platform (<https://it.surveymonkey.com/>) was sent to the members of the Italian Association for Neuroendocrine Tumours (Itanet) (www.ita-net.org) using email distribution. Itanet is a national multidisciplinary NEN-dedicated scientific association comprised of approximately 200 physicians, including virtually all of the Italian specialists involved in the management of NEN patients. The questionnaire for the online survey had been prepared by a team including oncologists (SP, FS), gastroenterologists (FP, SM), an endocrinologist (AF), an internal medicine physician (DC), a surgeon (MF) and a nuclear medicine (MM) physician on behalf of Itanet, and was sent to the Society's members with specific instructions on how to answer.

A single member of each receiving center was identified as the referral survey sender to avoid the risk of potential duplicates. Specifically, each sender was required to collect data from the center after involving the components of the NEN dedicated team. The median number of physicians working in each NEN dedicated multidisciplinary teams was 6, thus resulting in an overall amount of physicians involved in the survey of approximately 140 specialists. The final analysis of collected data was performed by the study coordinator (FP), and shared with the member of the Itanet board (MF, SP, FS, SM, AF, DC) who reviewed and approved the results. The survey consisted of 57 questions related to the clinical management of NEN patients during the 2 months from March 9, 2020 (the beginning of the "lock-down" period in Italy in accordance with the national legislation), to May 9, 2020 (defined as the observation period) (supplementary file 1). It included three main sections: (i) features and standard activity of the center before the SARS-CoV2 dissemination; (ii) modality used by the center to follow NEN patients during the reference period; (iii) estimation of the modification/delay/reduction of the planned clinical activity, with particular effects on patients' treatment. Data were collected by the SurveyMonkey® platform. This study was notified to the Ethics Committee of the coordinating center (Sant'Andrea University Hospital, ref. CE 7023_2020) and was carried out according to the Declaration of Helsinki.

Results

Centers features and standard activity

A total of 24 centers participated in the COVINET survey, including 6 Centers of Excellence for NEN management certified by the European Neuroendocrine Tumors Society (ENETS). Of these, 15 (62.5%) were located in northern Italy, which was the area with a higher SARS-CoV2 incidence. The majority of the participating centers ($n=20$, 83.3%) were in hospitals that were included in the national network for COVID-19 management. As far as the volume of activity is concerned, 5 centers (20.8%) were considered "low-activity centers" with < 100 NEN patients in follow-up, 10 centers (41.7%) had "mid-activity" with 100–300 NEN patients in active follow-up and the remaining 9 centers (37.5%) were "high-activity centers" with > 300 NEN patients followed. The mean reported number of planned visits to be performed for NEN outpatients during the observation period was 84. All centers had a multidisciplinary team dedicated to the management of the NEN patients.

Follow-up of NEN patients during the SARS-CoV2 pandemic dissemination

Most centers ($n=17$, 70.8%) modified patients' follow-up modality due to the pandemic dissemination. Specifically, in one center, both outpatients' visits and hospitalizations were stopped, whereas in 16 (66.7%), they were reduced and limited to urgent clinical conditions. No change in the standard activity was reported by the remaining 7 centers (29.2%). Multidisciplinary teams' activity was maintained in 19 centers (79.2%); however, in 12 centers (50%) the modality of discussion was modified by avoiding physical meetings in favor of web-based virtual meetings. In 5 centers (20.8%), MDT activity was suspended, and meetings were not held. A significant decrease in ambulatory activity was reported during the observation period, with the mean number of visits for NEN outpatients being 30 (vs 84 planned before the COVID-19 outbreak, – 64.3%). Most centers ($n=21$, 87.5%) used telemedicine to follow-up NEN patients during the observation period, either by phone, video calls, email or instant messaging.

A large proportion of centers ($n=22$, 91.7%) reported that planned imaging follow-up procedures were rescheduled, and in 59% of patients, they were performed outside the center, where the patients were usually followed.

Modification of center activity during the SARS-CoV2 pandemic dissemination

There was a dramatic reduction in the centers' clinical activity (Table 1). The number of surgical procedures for

Table 1 Consequences of COVID-19 dissemination on NENs management reported by the centers

Activity	Reported change (%)
Decrease in newly diagnosed NEN	- 76.8
Suspended MDT activity	20.8
Decrease in surgical procedures	- 58
Delay to initiate PRRT	45.5
Delayed/cancelled follow-up examinations	26

NEN patients fell from 69 planned operations to 29 performed procedures (- 58%). A total of 109 NEN patients were newly diagnosed in the 24 participating centers during the observation period, again confirming a decrease of 76.8% compared with standard activity, during which the usual overall reported number of newly diagnosed patients by the centers was 235/month. Among the newly diagnosed patients, 85.1% had non-functioning tumors and 56.4% had advanced metastatic disease.

When asking the center to estimate what was the percentage of reduction in clinical activity for NEN patients, 15 centers (62.5%) reported a 25–50% reduction, and 7 centers (29.2%) a decrease > 75%. Only 2 centers (8.3%) reported no significant decrease in clinical activity for NEN patients.

As far as medical treatments were concerned, the management of patients varied depending on the specific therapy. Specifically, somatostatin analogs therapy was maintained unchanged for all patients. Everolimus, sunitinib and chemotherapy were continued for 90.9%, 95.2%, and 90.9% of patients, respectively.

As far as peptide receptor radionuclide therapy (PRRT) was concerned, 10 out of 24 participating centers (41.7%) were qualified to perform PRRT by the National Health System. Overall, 45.5% of centers reported a delay in the initiation of PRRT for new candidates for treatment due to the pandemic situation. In those patients who had already started PRRT before the SARS-CoV2 dissemination, the administration schedule was not modified in 85% of cases, whereas in the remaining 15% of patients, it was delayed. However, PRRT was withdrawn from no patients. A proportion of 23.8% of centers reported concerns expressed by patients receiving PRRT regarding the safety of the treatment; however, only one single center asserted that patients decided not to initiate PRRT due to safety reasons.

Almost ¼ of centers (21.7%) referred patients who were candidates to begin PRRT to other centers, due to the limitations/patients' concerns due to the pandemic dissemination. A total of 13% of centers reported having referred to other centers patients who had already started PRRT.

A total of 12 centers (50%) reported having stopped patients' enrollment in clinical trials or having experienced delays in activating new planned clinical trials.

When asked what was the most frequent general consequence of the pandemic dissemination on the management of NEN patients, the first three answers reported by the centers were: delay of diagnosing new NEN patients (50%), delay of beginning previously planned treatment (37.7%), and delay of performing planned follow-up examinations (26%).

Discussion

In recent months, the COVID-19 pandemic dissemination has had a significant impact on hospital activity and organization, with several departments involved in the management of COVID-19 patients, including those usually dedicated to NEN patients.

Recently, suggestions on how health care providers might make modifications to their care of NEN patients has been proposed by the North American Neuroendocrine Tumor Society [9]. Furthermore, several studies performed on different kinds of cancers have clearly shown that this unexpected condition has negatively modified the level of caring for oncological patients [6–8]. To the best of our knowledge, this is the first report from a multidisciplinary community of physicians dedicated to caring for NEN patients evaluating the impact of the COVID-19 pandemic dissemination on the management of these patients.

Given the rarity and the peculiar indolent behavior of the majority of NENs, specific challenging issues need to be addressed by physicians dealing with these diseases, including (i) to maintain active MDT, which is well known to be a key factor in the effective care of NEN patients [10, 11]; (ii) to avoid delays in initial NEN diagnosis, which is frequently reported in real-world practice even before the pandemic dissemination [12]; (iii) to evaluate the potential increased risk of severe illness in NEN patients with COVID-19 receiving targeted agents with immunomodulatory activity such as everolimus and sunitinib; (iv) to maintain the scheduled workflow for patients on treatment or who are candidates for PRRT, which requires specific logistic organization in terms of timing of hospitalization; and (v) to carry out planned surgical procedures, which may provide definitive disease cures in NEN patients with localized or locally advanced diseases, as well as in selected cases of metastatic patients [13].

The main figures reported by the present survey confirm that a significant proportion of Italian NEN-dedicated centers experienced difficulties when facing these issues. The number of new diagnoses decreased by 76.8%, resulting in a significant number of patients with undiagnosed NEN who will receive a delayed diagnosis after the emergency status

resolves. This delay will have a negative impact by reducing their probability of receiving curative surgery for early-stage disease and by delaying the initiation of an effective anti-tumor medical therapy in those patients with more advanced disease. The significant decrease in newly diagnosed NEN patients may be related to several factors: (i) Refusal or delay of patients to come to hospitals, which is reasonable given the usual clinically indolent course of most non-functioning NENs, particularly in the early stage disease (notably, 56.4% of newly diagnosed patients were reported to have advanced metastatic disease when referring to the center, and 85.1% were non-functioning); (ii) Reduction of the overall numbers of radiological procedures performed during the observation period, which might explain the decrease in number of incidentally found NEN that represent a consistent proportion of newly diagnosed NEN in general [14]; (iii) A general decrease in all cancer-related patients encounters which has recently been observed as a result of pandemic in other oncological settings [15].

Approximately $\frac{1}{4}$ of participating centers (26%) reported the need to postpone or cancel planned follow-up examinations. This figure is quite expected, given the reasonable need to minimize patients' access to the hospitals, a suggestion proposed by the oncologist community as a part of the specific care of oncological patients during the COVID-19 pandemic [16].

As far as PRRT is concerned, it was observed that the modality and timing of the treatment was maintained by almost all centers (85%) despite the COVID-19 pandemic, suggesting that centers with more experience and with a dedicated nuclear medicine department performing PRRT were able to promptly adapt to the new indications and restrictions imposed by the extraordinary situation. Conversely, almost half of centers (45.5%) reported that PRRT initiation was postponed in candidate patients who had not yet received their first dose of lutetium-177-DOTA-octreotate. This apparent discrepancy may be explained by the need to conserve health system resources for those patients who had already started PRRT to ensure treatment completion by deciding to delay treatment initiation in some patients, a figure that has recently been reported for other oncological diseases by the nuclear medicine community [17]. However, PRRT was withdrawn from no patients.

A significant decrease in NEN dedicated surgical procedures was reported (– 58%) in the survey. Deferring surgery for oncological disease may be a difficult choice for physicians, given the potential risk of tumor progression. However, in the era of COVID-19 that we are experiencing, this risk needs to be balanced with the potential increased risk of infection and severe illness that may occur as a consequence of immunodepression induced by the cancer itself and by surgical procedures [5]. Since

most NEN are slow-growing, it seems reasonable to defer major surgical procedures with the intent to offer patients effective and safe management, as proposed for other non-endocrine early-stage cancers [18]. This may explain the choice of the majority of centers to defer planned surgery in a significant proportion of NEN patients.

An additional finding reported by the present survey was the low proportion of patients receiving medical treatments for whom a schedule modification was proposed. Although this is highly expected for SSAs, which have a negligible impact on the immune system, it seems less obvious for everolimus, sunitinib, and chemotherapy, which were maintained in 90.9%, 95.2%, and 90.9% of cases. Regarding everolimus and sunitinib, to date there is no available scientific data to compare this figure with other reports even outside the setting of NEN patients. As far as chemotherapy is concerned, other surveys performed of nonendocrine cancers have reported a low proportion of oncologists who changed treatment plans in their clinical practice [19, 20]. This figure is in agreement with data reported by the present survey, confirming the ability of the NEN dedicated teams to continue to provide optimal care to their patients.

Conclusion

The spread of the COVID-19 pandemic had a significant impact on the management of NEN patients, reducing the number of newly diagnosed patients, deferring a significant proportion of surgical procedures, and delaying the beginning of PRRT in a consistent proportion of candidate patients.

However, the network of NEN dedicated Italian centers was able to provide continuity in care without withdrawing medical treatments or PRRT for the majority of patients. A better understanding of the real consequences of the COVID-19 pandemic on the care of NEN patients will be feasible once the emergency resolves.

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Compliance with ethical standards

Conflict of interest Authors have no conflict of interest to declare.

Ethical approval All procedures were approved by the Coordinating Center (Sant'Andrea University Hospital of Rome).

Informed consent All participant members provided consent prior to their participation.

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