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A year of pandemic for European particle radiotherapy: A survey on behalf of EPTN working group

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ABSTRACT

Objectives: To provide an overview of the impact of the pandemic on the clinical activity and take a snapshot of the contingent challenges that European particle therapy centers are called to face, we surveyed the members of the European Particle Therapy Network (EPTN).
Material and methods: A 52-question survey was conducted from 4th April 2021 to 30th July 2021 using the Google Forms platform. Three dedicated sections analysed the clinical context of each participating institution, the staff management, and the clinical changes in the oncological workflow.
Results: Out of the 23 contacted European hubs of particle radiotherapy, a total of 9 (39%) responded to the survey. The number of in-person first evaluations and follow-up visits decreased, but telemedicine was implemented. Multidisciplinary tumour board discussions continued during the outbreak using web-based solutions. A delay in cancer diagnosis and oncological staging leading to an increment in more advanced diseases at first presentation was generally observed. Even if the total number of treatments (photons and particles) in the responding institutions showed a trend of decrease, there was or a stable situation or slight increase in particle treatments. The clinical treatment choices followed the national and international scientific recommendations and were patient/disease-oriented. Hypofractionation and short-schedule of chemotherapy, when applicable, were preferred.
Conclusions: Our findings show a rapid and effective reaction of European particle RT hubs to manage the healthcare crisis. Considering the new waves and virus variants, the vaccination campaign will hopefully reduce the oncological impacts and consequences of the prolonged outbreak.

Introduction

The Coronavirus disease 2019 (Covid-19) [1] outbreak disrupted the health care system worldwide, causing sudden and severe changes in health care attempting to compromise between patient-centred ethics and public health ethics [2]. In this context, radiation oncology also had the challenge to maintain the oncological departments Covid-free and, in the meantime, guarantee a continuum of care. Indeed, if, on the one

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hand, oncological patients are frail and immunocompromised, on the other hand, radiotherapy (RT) is a save-life oncological treatment that must not be postponed or suspended. To drive the clinical practice during the phases of the pandemic [3], a great effort was made by the oncological scientific societies to divulge and continually revise guidance and recommendation documents [4,5]. With this aim also a "Global Coalition" for RT was launched [6]. Several RT and oncological working groups took a snapshot of cancer management during the pandemic also through online surveys [7–17], whereas very little was described about particle RT facilities. For this reason, a survey was administered to particle RT departments or institutions with the endorsement of the European Particle Therapy Network (EPTN). The aim was to portray the strategies or solutions adopted during the pandemic, focused the attention on the RT challenges during two waves of the outbreak (from March 2020 to August 2020 and from September 2020 to February 2021) comparing with the clinical practice of the pre-Covid months (March 2019-February 2020).

Material and methods

Under the supervision of two investigators (*AB and EO*), the leading research center (CNAO) designed an online survey (Supplement 1) to assess the change and the challenges in particle therapy during the pandemic. The Checklist for Reporting Results of Internet E-Surveys (CHERRIES)[18] was followed. The initial version of the survey was pretested by the leading research center, along with two of the researchers (*FDM and MM*), to ensure its usability and technical functionality. As recommended by the CHERRIES checklist, validation and approval were sought from the EPTN Directorship and the leading research center sent an email to each EPTN hub (investigator centers) allocating a survey link, permitting to complete the investigation only once using the Google Forms platform. The survey was an open survey written in English and remained available from April 4th, 2021 to July 30th, 2021; the research center sent four individualized reminder emails to non-respondents before the closure of the survey. The participation was voluntary, and no incentives were offered to the responding centers to provide results. The platform checked the completeness of the questionnaire before the submission of the results. To avoid potential duplicates, any responder was identified by his institutional e-mail address. The data were stored by the leading center scientific directorship until the closure of the survey in order to protect any unauthorized accesses

Questions were set up in three main parts:

1) *Particle therapy hub characteristics* (type of institution, type of radiotherapy techniques available, number of health care providers): six questions;
2) *Workforce planning for risk mitigation* (management of personnel): fifteen questions;
3) *Management of patients and clinical practice* with three subsections considering "first evaluation", "treatment", and "follow-up" considering the two waves of the outbreak separately (from March 2020 to August 2020 and from September 2020 to February 2021): thirty-one questions. Considering the above reported international and national recommendations, specific questions were addressed regarding treatment approaches in different clinical settings.

For some queries, multiple-choice answers were allowed, with encouragement to add clarifying items. The answers were collected by the scientific directorship of the leading research center, then critically validated by two researchers of the same institute (*AB and EO)*, and independently revised by two external reviewers (*FDM and MM*). Firstly, the answers were evaluated, hiding the submitting author/center identity. Only after the first blinded analysis, the submitting author could be contacted to investigate eventual inconsistencies or to complete missing data.

Statistical analysis

Given the limited sample, basic descriptive analyses were performed to analyze the results that are reported as frequencies, means, standard deviation (SD), or percentages when appropriate.

Results

Out of the 23 contacted European particle hubs, a total of 9 (39%) centers responded to the survey. The median time for the questionnaire competition was 30 min. Even if, according to CHEERIES checklist, respondents were able to review and change their answers, among the respondents, three centers were later contacted to solve inconsistencies. There were no incomplete questionnaires.

Particle therapy hub characteristics

Responding Particle RT facilities were from Italy (2), France (2), Netherlands (1), Belgium (1), Germany (1), Denmark (1), and Austria (1) and included six university hospitals (66.6%), two research and monothematic institutes (22.2 %), and one general hospital (11.2%). Five centers (55.5%) had available only particle therapy (with two of them having both carbon ion radiotherapy -CIRT- and proton beam RT-PBT), while the remaining ones were able also to deliver photon beam RT (X-RT) and to administer brachytherapy (BT). During the outbreak, the staff was composed of (mean $\pm$ SD) 13.7 $\pm$ 8.31 radiation oncologists, 43.8 $\pm$ 40.1 radiation therapists, 10.6 $\pm$ 18.3 nurses, 15.5 $\pm$ 6.9 medical physics for every center.

Workforce planning for pandemic risk mitigation

Triage methods for "patient-facing" health care professionals consisting of periodically swab tests with or without serological analysis in four (44.4%) hubs associated with swab analysis, performed in each center (100%), in case of close contact with Covid-19 positives. To limit the epidemic impact, two different RT teams ("patient-facing" and "not patient-facing") were implemented in six centers in both waves, guaranteeing a turnover of health care staff. Hubs that did not implement this solution in the first waves did not use it in the second one; a monothematic institution, considering the increment of Covid-19 swab tests (administered to the staff every 15 days) was able to reduce this measure during the second wave. To note that, during the first wave, five centers extended remote working solutions to radiation oncologists, but only one center did not offer this option during the second wave. The department meetings, normally held in person, virtualized at most in all the responding centers during the first wave, and this choice was mainly maintained during the second wave, with 8 out of 9 centers employing such a solution. Also, in this case, a slackening was applied in the center that increased the staff screening procedures. While eight institutions did not change their clinical activities during the waves, only one became a Covid-19-Oncological hub receiving positive-tested cancer patients. Moreover, radiation oncologists of three hubs were involved in shifts in dedicated Covid-19 departments during both waves.

With regards to multidisciplinary tumour boards (MTB), they were performed mainly virtually and only partially in person. In this context, even if the experts of each field were present in the discussions, all participant hubs experienced the absence of MTB clinical professionals because deployed elsewhere (e.g. supporting colleagues in Covid-19 wards) to cope with the emergency or on sick leave due to quarantine procedures.

Management of patients and clinical practice

First evaluation

Compared to the pre-Covid-19 period (from March 2019 to February 2020), the number of the first clinical evaluations in each institution

decreased during the two waves of the pandemic (March 2020- February 2021), recording, for most cases, a reduction greater than 6% (6–10% in 44%, 11–20% in 33%, >21% in 11%). Only one center experienced a reduction lower than 5%. The reasons for the decrease in clinical activities were due to:

- Independent choice of the patients to postpone the first evaluation (recorded in 7 centers);
- Decreased referral from other institutions (recorded in 7 centers);
- Cancellation of the appointment by the institution according to national/regional emergency directives and regulations (recorded in 4 centers).

This tendency echoed in the implementation of telemedicine during the outbreak (6 cases, 66.6%).

Treatments

Compared to the pre-Covid-19 period, considering all the techniques available in the analyzed institutions, the number of treated patients decreased in most of the cases (6 departments, 66.6%), overall more than 6% (6–10% in 4 cases, 11–20% in 1 case, >21% in 1 case), whereas three institutions experienced an increase up to more than 10%. To note that the reasons for this reduction were various: from the patient's refusal to start an RT treatment (observed in 5 of the 6 institutions), to the delay of the staging procedures and diagnosis, which led to the dropping of the indication of RT (spotted in 4 of the 6 institutions), from the Covid-19 infection that stalled the staging procedures or the start of the oncological treatments (noticed in 5 of the 6 hubs) to the change of indication (reported by 2 of the 6 departments) after an MTB discussion (i.e. palliation or low-risk cancers referred to traditional RT).

Figs. 1 and 2 describe the differences of PBT and CIRT in the respective institutions in the analysed periods; the graphs did not include the overall treatment (BT, x-Ray) delivered in these hubs or the mixed beam approach. We can notice that in 4 centers the increase of PBT appears evident, whereas a stable tendency can be observed in the other institutions. To note that the #2 Center and the #7 Center were in the ramp-up phase of PBT, but the investigators reported a significantly slower accrual than expected in the second phase. Fig. 3 shows the average number of patients treated during the two waves; overall, only two centers recorded a mean daily reduction of treatments.

Both the CIRT facilities experienced an increase in the number of treated patients, but in one case it was due to the current phase of the institution (ramp-up phase), in the other one this increase was consequent to the delay of staging procedures and surgeries (considering that most referral hospitals were occupied with coping the healthcare crisis) that brought a greater number of patients, for the local extension of the disease, to be unfit for surgery or conventional RT. The same experience was described also by hub # 4 in Fig. 1.

During the pandemic, all the institutions had continued to treat also positive patients who needed a curative RT, changing the RT fractionation in 3 cases. The same approach was mainly observed for the palliative treatments and, only in one center, the patients, who were a candidate for palliative RT, were sent to another institution. Age did not impact, more than the pre-Covid-19 era, the treatment decision as well as comorbidities (that only in 1 hub affect the clinical decision).

Moreover, compared to the previous practice (considering the period between March 2019 and February 2020), the treatment approach remained unchanged in neoadjuvant RT (100%), induction chemotherapy (100%) and adjuvant RT (8 hubs, 88.8%) settings with only one case of decrease of the numbers of adjuvant RT. Also the radical upfront RT approach, overall, was mainly unchanged (7 centers, 77.7%), decreased in one center and increased in the remaining one.

Although the sample size is limited, when taking into account the different histologies and tumours, the different flow of patients and the different treatments, it can be observed that, where treated, the RT was sometimes postponed for low-risk tumours (i.e. low-grade meningiomas). It was also reported an increased number of very locally advanced head and neck tumours that lead to radical RT instead of surgery, as well as unresectable pancreatic cancers.

Follow-up

Mainly during the pandemic, 8 centers reported a deferral in the follow-up schedules decided by the centers themselves (according to the national/regional emergency directives and/or the recommendations of national/international RT scientific societies) or independently postponed by the patients. Compared to the pre-Covid-19 era, overall, the number of clinical evaluations decreased less than 5% in one case, between 5 and 10% in five institutions, between 10 and 20% in one center and two hubs described a reduction greater than 20%. In each center, telemedicine was implemented for the follow-up evaluation. Despite the change in the follow-up schedules or the patient's postponement, there was not a significant delay in the diagnosis of progression of the disease, reported only by 5 institutions in which was described as anecdotal (<5%) in 4 centers and more sizeable (between 10 and 20%) in only one respondent.

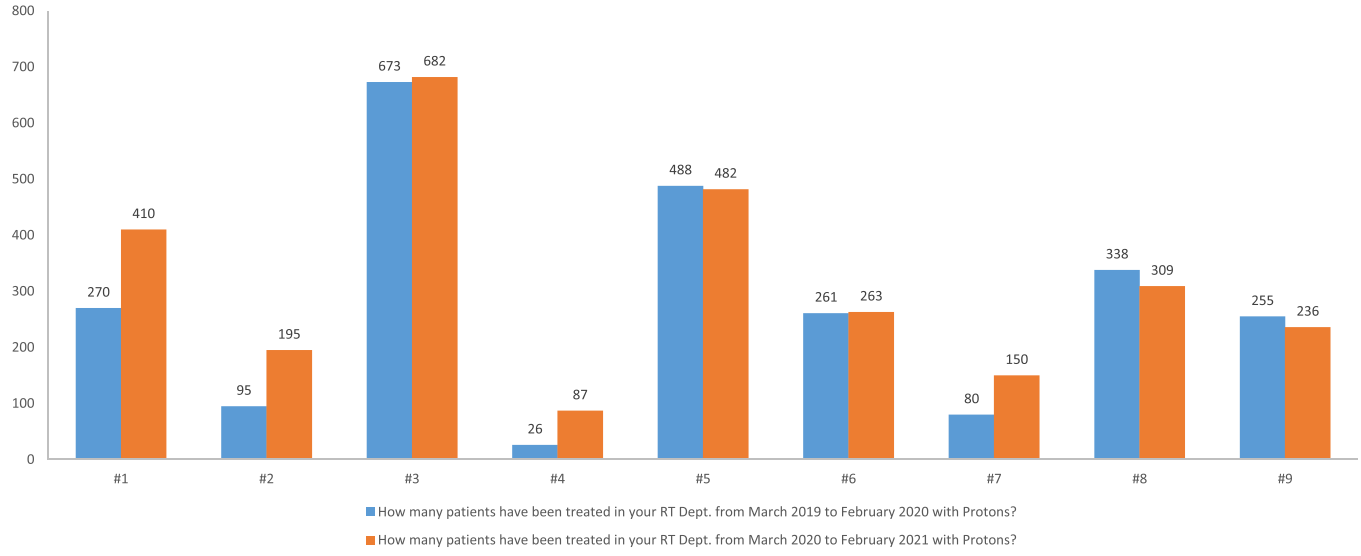

Fig. 1. Comparison between pre-Covid and outbreak period for PBT treatments.

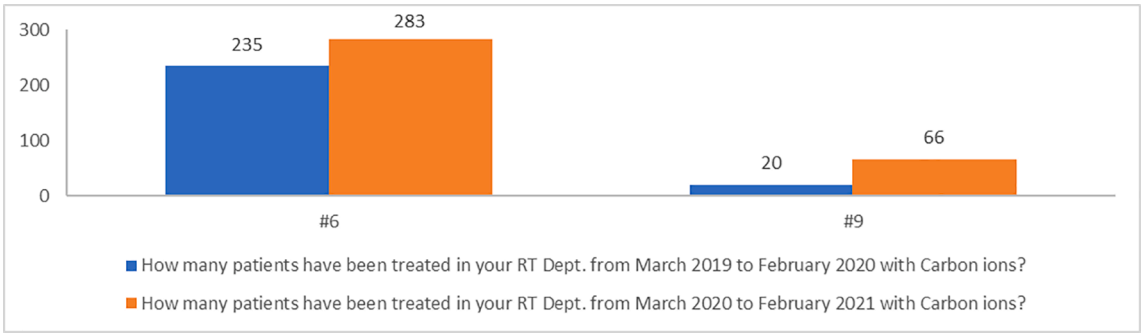

Fig. 2. Comparison between pre-Covid and outbreak period for CIRT treatments.

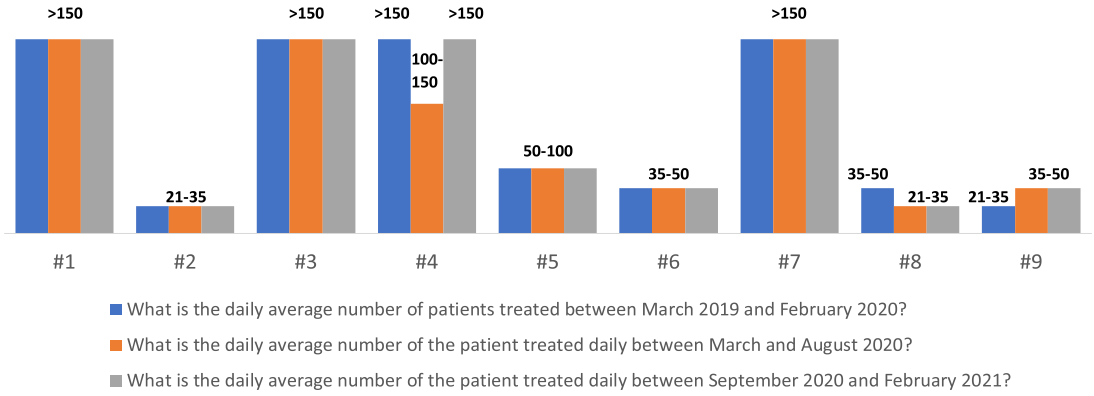

Fig. 3. Daily average number of the patients treated in each institution comparing three periods (pre-Covid vs March-August 2020 and September-February 2021).

Clinical trials

In comparison with the pre-Covid-19 clinical practice, the pandemic impacted the conduction of clinical trials in seven institutions (77.7%). The reasons were summarized as follows:

- Reduction in available staff (86%).
- Halted enrolment (71%).
- Ceased opening new clinical trials (57%).
- Limited available screening services necessary for the enrolment (57%).
- Prioritized enrolment for certain clinical trials (i.e. hypofractionation, shorter chemotherapy schedule, safety profiles) (29%).
- Decrease in eligible patients (29%).
- Remote monitoring by sponsors (14%).
- Hospital directors' decision (14%).

Discussion

Despite the limited number of respondents to the survey among the invited institutions, several valuable points arose, describing the impact of Covid-19 on particle RT practice and opening up to possible future suggestions.

Our survey highlighted that to avoid the crowd and ensure social distancing, remote working solutions and staff turnover ("patient-facing" and "not patient-facing" personnel) were carried out in several departments. The routine swab or serological tests were executed in order to reduce the epidemic impact leading, in one center, also to slacken the measures during the second wave.

Physical meetings are of utmost importance in oncology but, during the outbreak, the e-meeting platform allowed to maintain stimulating and lively the clinical debate in department meetings, as well as MTB, guaranteeing a continuum of care.

Another point deserving attention is that in all institutions the volume of first clinical visits and routine follow-up decreased, but the consultations were mainly assured online implementing telemedicine solutions, which turned out as valuable tools [19], with a mild delay in diagnosis of the progression of the disease during the follow-up. Considering that the web tool appeared as a contingent but effective solution both for MTB and remote clinical evaluation, in the post-Covid-19 era, it might be refiled especially to endorse discussions among clinicians from different institutions, but also to provide second opinions for patients, saving time and travel expenses.

Interestingly enough, the main reasons for the reduction of the ambulatory's clinical activities were due to an independent patients' decision, in addition to the decreased referral of the external institutions. In four centers, according to the national/international directives, visits had to be postponed if not clinically urgent.

The anxiety and fears of oncological patients that had been judged to be at high death risk from Covid-19 had, therefore, a dramatic effect also on the start of treatment that was often autonomously postponed by the patients even with the reassurance of the oncological staff [20–22]. This might represent a serious collateral effect of Covid-19, considering the prolongation of the pandemic and require urgent intervention in order to promote mental oncological well-being ventures also through virtual communities. In this scenario co-production between clinicians, psychologists, patients, patient associations might be a successful option [23].

In the present analysis, the reduction in the number of the first clinical evaluations had repercussions also in the numbers of delivered treatments during the two waves, which showed a decreasing trend in 66.6% of the institutions, for all the RT techniques. Consistent with recent literature [22,24–26], it leaps out that the diagnostic and staging delay during the pandemic caused an increment in the progression of the disease, such as making patients unfit for surgery or other oncological treatments. Moreover, the reduction of cancer diagnosis during the pandemic experienced by several European countries suggested not only

an increase of advanced and difficult-to-treat disease but also of cancer deaths[27–29]. Alarming is the result of a national population-based modelling study that estimated an increase (between 4.8 and 16.6%) in the number of cancer deaths (from breast, colorectal, lung and esophageal tumors) up to 5 years after diagnosis due to the diagnostic delay during the outbreak [30].

In this scenario, in our survey, the MTB discussions influenced the clinical decision, opting for other RT techniques or oncological treatments considering the risk/benefit ratio. However, treatment decisions were always disease and patient-oriented. As supported by the national and international guidelines driving the oncological management during the outbreak [4,5], short-course chemotherapy, as well as hypofractionated schedules, also in particle treatments, were preferred when applicable.

However, extracting only the data on particle RT treatments, this reduction was not so considerable but actually, the number of treatments was stable or slightly increased. These findings were to ascribe to the main indications of particle therapy recommended in difficult-to-cure and more aggressive tumours. It should be highlighted that CIRT hubs experienced an increase in treatments. While this result was due to the ramp-up phase of #9 center, in the #6 center the increased referral of very locally advanced diseases was the primary cause. Moreover, the short schedules of CIRT treatments are in step with the international recommendation to reduce patient's time spent in hospitals [31,32].

As happened in other clinical contexts [33,34], also in particle RT the clinical research had to readapt to the contingent situation preferring, according to the national and international oncological recommendations, short schedules of medical and RT treatments. Considering the prolonged pandemic, the "new normality" should consider in all studies contingency plans and ethical amendments[35].

Potential bias

This study has several limitations. Among these, we should mention the accrual of the centers (only 39% participated in this survey), the limited time span (one year before the outbreak for comparison), and the difference of types of tumours treated in each institution. Moreover, three of the responding hubs are currently in their ramp-up phase.

The belated time frame, considering the COVID situation as of the beginning of 2022, may also appear as a limitation. Still, this may represent an opportunity to collect data about the following waves and compare results.

Moreover, considering the different spread of the pandemic in Europe also the geographic location of responding institutions might have biased the interpretation of results.

Lastly, no IP check nor log file analysis (recommended by CHEERIES checklist) were perfomed, but in order to avoid duplicate answers, the responder was identified by a unique institutional e-mail address.

Conclusions

Due to the pandemic, the particle RT hubs observed a delay in cancer diagnosis and staging, leading to an increment in more advanced diseases at first presentation in RT departments. The number of in-person first evaluations and follow-up visits decreased, but telemedicine was mainly implemented. Even if the total number of total treatments in the responding institutions showed a trend of decrease, there was a stable or slight increase of numbers of treatments with particles. The clinical treatment choices followed the indication of MTB discussions, national/international scientific recommendations but were always patient/disease-oriented with an increment, where and when applicable, of short schedule of RT. If telemedicine options did help to replace physical visits, the spontaneous decision of patients to postpone treatment, if not supported by dedicated psychological services, could represent a serious collateral effect of Covid-19, considering the prolongation of the pandemic. Despite the limitations of this survey, our findings showed a rapid, effective, and resilient reaction of European particle RT hubs to the healthcare crisis. Considering the likely upcoming waves and virus variants that can be expected in the "new normal," the ongoing vaccination campaign and the "lessons learned" will hopefully limit further oncological impacts and consequences.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J. A. Langendijk is member of International Advisory Board of IBA and RaySearch and honorarium is paid to UMCG Research BV; the department of Radiation Oncology of UMCG has research collaborations with IBA, RaySearch, Siemens, Mirada, Leonie and Elekta. The other authors declare no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.02.004.

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