The evolving scenario of cancer care provision across the COVID-19 pandemic in Europe

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Purpose of review
Over the past 2 years, the COVID-19 pandemic has had short-term and long-term effects on the delivery of cancer care. Some European countries faced an unprecedented widespread crisis during the first year of the SARS-CoV-2 pandemic, only being able afterwards to gradually recover, thanks to the improvement in preventive measures, changes in public health and reactive processes in cancer care and a better understanding of the ongoing heath emergency.

Recent findings
The development of SARS-CoV-2 vaccines and COVID-19 specific treatments, the growing testing and tracking capability to limit virus diffusion, and research efforts to better define areas of action have all greatly limited the negative impact of the health emergency on routine cancer care.
The need to protect those more vulnerable and to ensure continuity of care for oncology patients has been balanced across the pandemic, with the aim to guarantee an optimal standard of care.

Summary
This article aims to provide an overview on the evolving scenario of cancer care throughout the COVID-19 pandemic in Europe, focusing on the particular features that characterized the pandemic course as well as the main differences that were observed across it.

Keywords
cancer care, COVID-19, Europe, oncology, SARS-CoV-2

INTRODUCTION

From the beginning of the health emergency related to SARS-CoV-2 infection, cancer care has been severely impacted worldwide [1–3]. Patients with cancer are particularly prone to experience severe COVID-19 outcomes, due to their intrinsic frailty, with a short-term case fatality rate estimated between 25% and 30% in the prevaccination phase [4▪,5,6▪▪,7,8,9▪]. Several attempts have been made to assess the prognostic weight of a previous history of cancer on COVID-19 outcomes. Overall, different outcomes were observed across cancer types, also according to the treatment setting, the class of ongoing oncological treatments, as well as the patient characteristics and biological features [5,10–15]. In addition, it has become rapidly noticeable that COVID-19 caused long-term implications, not only at patient level, but also in terms of the structural organization of cancer care delivery [3,6▪▪,15–17].

This article aims to provide an overview on the evolving scenario of cancer care across the COVID-19 pandemic in Europe, focusing on the particular features that characterized the pandemic course, as well as the main differences that were observed across it.

PLASTICITY OF CANCER CARE SYSTEM DURING AN UNPRECEDENTED SITUATION: VOICES FROM THE FIRST COVID-19 WAVE

As a response to the COVID-19 pandemic, cancer care faced the challenge of having to make significant changes to withstand this problematic situation and maintain care. Following the initial outbreak in China in early 2020, European countries

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KEY POINTS

- Cancer care in Europe faced challenging adjustments during the COVID-19 pandemic, from screening to treatment scheduling.
- The different pandemic waves have been characterized by better understanding of the mechanisms of SARS-CoV-2 infection as well as the development of vaccines and anti-COVID-19 therapies.
- Developing preventive measures for the infection was found to be crucial for many oncology patients, due to their intrinsic vulnerability.
- A radical drop in the rate of COVID-19 infection was reported after vaccination, and an increasing seroconversion rate was observed with the booster strategy.
- Oncologists should encourage their patients and caregivers to complete the full course of vaccination.

experienced an increasing healthcare emergency, with geographical and temporal heterogeneity. Staff redeployment and the need to reduce outpatient and visitor access to hospitals resulted in a forced reorganization of many clinical processes, at different levels.

National and international surveys as well as observational transversal studies conducted among the oncology community represented an immediate way to capture the ongoing evolving situation [18–20]. All procedures related to the management of patients with cancer were affected, with no exception, in order to limit the exposure of frail patients and the healthcare system to SARS-CoV-2 infection. On the basis of a case-by-case evaluation, telemedicine was encouraged instead of face-to-face consultations for patients not strictly in need of active or in-person care and followed-up in an outpatient setting. Overall, this approach was observed to be positively accepted and appreciated by patients during the acute phase of the pandemic [21]. Nevertheless, it should also be acknowledged that some aspects of healthcare reorganization had a negative psychological impact on patients and their families. Concern about having the treatment plan interrupted because of the health emergency has been captured by several surveys conducted among patients with cancer, and this feeling was more pronounced among those patients on active treatment [22,23]. The oncological disease itself appeared to remain the main source of apprehension for patients during the COVID-19 wave, while SARS-CoV-2-related aspects (e.g. fear of getting infected, emotional burden due to restriction on visitors and reduced social contact) had a lower impact than cancer-associated anxiety [24,25]. On the contrary, few studies have investigated how caregivers and relatives of patients with cancer dealt with restrictions imposed to social contacts and access to hospitals and facilities. A dedicated analysis conducted in this sense found that caregivers were strongly impacted in the affective sphere by forced social distancing. Restoring physical and social support to their assisted were seen to be the main needs. Lack in structural social policies to support patients and their families on an emotional level has probably revealed a vulnerability of the healthcare systems towards this aspect [26].

The delivery of oncology treatment was modified during the most critical months whenever possible and indicated, by choosing schedules, formulations and modality of administration that were able to guarantee a lower number of visits to the hospital [27]. Overall, treatment adherence seemed not to be particularly affected during the pandemic and was not strictly associated with the degree of perception or knowledge about COVID-19 [28,29]. Moreover, specialized COVID-19 facilities and cancer care units were separated, in order to reduce the risk of virus diffusion among patients and healthcare workers. Patients could be admitted to hospitals only when asymptomatic and with a negative test for SARS-CoV-2 [20,27]. Screening programmes were delayed and suspended in many European countries in March and April 2020, and patients also became more cautious accessing healthcare facilities because of the perceived risk of virus exposure [30–32]. Inclusion of patients in clinical trials was greatly impacted, as many trials were suspended in 2020, with a consequent drop of enrolment rates [33]. In parallel, there was a decrease in oncology trials launched during the pandemic period [34,35]. Criteria for the management of patients with COVID-19 have been widely included in protocols of oncology trials.

Several surveys were promoted to investigate the point of view of stakeholders towards the impact of SARS-CoV-2 infection. The majority of oncologists reported concerns mostly about the indirect burden of the pandemic (e.g. leading to potential reduced quality of cancer care) than on the intrinsic risk of COVID-19 disease in oncology patients [3]. National and international societies published dedicated guidelines and expert consensus to inform the use of systemic anticancer treatments and the provision of cancer care during the pandemic [36].

Some useful ideas emerged from these surveys, to be implemented in the postpandemic era: the adoption of virtual congresses or of hybrid models for oncology meetings, the possibility for patients based in nonmetropolitan settings to access clinical trials through telemedicine consultation, the use of home delivery of oral treatments, and in general, the optimization of procedural and organization aspects, which affect the everyday quality of life of patients with cancer [37–39].

ONCOLOGY CARE ACROSS DIFFERENT COVID-19 WAVES

The COVID-19 pandemic has been characterized by three main waves so far, based on epidemiological notions, the emergence of SARS-CoV-2 variants and the introduction of the vaccination on a large scale [40]. Each wave has been characterized by different incidence and mortality rates, symptoms related to the circulation of virus variants, as well as by tailored precautionary measures that have been adopted over time (Table 1). Italy was the original epicentre of the pandemic, with a subsequent spread in Western Europe. As of fall 2020, following a decrease in the number of COVID-19 cases, the re-emerging wave in western countries was accompanied by an increase in cases in eastern European countries [41]. The continuity of cancer care and the administration of anticancer therapies were defined as priorities by oncological societies during all the pandemic phases [36,42,43], and different approaches were implemented according to specific situations.

Major improvements have been observed across the pandemic waves, likely due to increased testing and tracking capability, better understanding of physio-pathological mechanisms of SARS-CoV-2 infection and development of vaccines and anti-COVID-19 therapies. Specifically, with regard to patients with cancer, data derived from 2634 patients with SARS-CoV-2 infection included in the European OnCovid registry reported a significant downtrend in mortality in the Delta and Omicron phases compared with the first pandemic wave [6▪▪].

Lee *et al.* reported results from a cohort of 285 oncology patients who were infected by the Omicron variant, of whom 72% were fully vaccinated [44]. A case fatality rate of 4.9% and around one-third of asymptomatic infections were observed. Advanced age, metastatic tumours and increased comorbidities were the main risk factors for worse outcomes [44].

The turnaround in mortality rates reflects the widespread diffusion of routine testing to capture early uncomplicated disease as well as the improved ability to manage the pandemic itself, including the use of specific treatments.

Cancer care in Europe has gradually recovered its standards through the second wave, up to the present time. Despite expected long-term impact on some aspects, for example related to temporary discontinuation of screening programmes, research and clinical trials activities, and the psychological burden on patients, families and healthcare workers [39,45,46], a steady state has been obtained between the application of measures to prevent SARS-CoV-2

Table 1. Characteristics of the main pandemic phases

Characteristic	First wave	Second wave	Third wave	Present
Main SARS-CoV-2 VOC	/	B.1.1.7 [Alpha] B.1.351 [Beta] P.1 [Gamma]	B.1.617.2 [Delta]	B.1.1.5.29 [Omicron]
Period	March 2020–August 2020	From fall 2020	From March 2021	From November 2021
Typical clinical spectrum	Fever, cough, dyspnoea, anosmia, ageusia, chest and muscle pain, fatigue, gastrointestinal symptoms	Fever, cough, dyspnoea, anosmia, ageusia, chest and muscle pain, fatigue, gastrointestinal symptoms	Fever, dyspnoea and cough, headache	Flu, sore throat
Social precautions	Mandatory	Mandatory	Mandatory	Not always mandatory
SARS-CoV-2 vaccination	Not available	Available for frail populations	Progressively available for anyone	Available for anyone
Testing capability	Low (only suspected cases)	Increased (contact tracing)	Routinely	Routinely

VOC, variant of concern.

transmission and the imperative to pursue active cancer care in all its parts.

SPECIFIC MANAGEMENT OF SARS-COV-2 INFECTION IN PATIENTS WITH CANCER: FROM AN EMPIRIC TO AN EVIDENCE-BASED APPROACH

From the beginning of the COVID-19 pandemic in March 2020, more than two million deaths were reported in Europe [47]. During the first 2 years of the pandemic, strategies were implemented to combat the infection, thanks to the attempts of several international registries collecting data on oncology patients who became infected with COVID-19 and to prospective and randomized trials with COVID-19 specific treatments and vaccines, increasing our collective understanding of SARS-CoV-2 disease and filling unmet medical needs in this population [48–50].

During the first wave, many drugs were used as empirical therapy for SARS-CoV-2 infection: among patients included in the European multicentre study from Pinato *et al.* [5], it was observed that broad-spectrum antibiotics and cloroquine/hydroxicloroquine were administered to more than half of patients, while antivirals (remdesivir, lopinavir, ritonavir) were used less frequently. Other therapies included corticosteroids, heparin and mAbs.

Gradually, data from randomized controlled trials have modified the landscape of COVID-19 treatment, by reducing the use of antimalarial drugs and of some less effective mAbs, by defining specific indications for administering antibiotics and antivirals, and by implementing the use of steroids [51]. Regarding the use of mAbs in the management of patients with malignancies and COVID-19 infection, a recent real-word retrospective study conducted in 395 patients found significant reduced need for hospitalization due to COVID-19 with the use of casirivimab-imdevimab [52].

In view of the potential limitations related to the use of mAbs, including the in-hospital administration, the need for posttreatment monitoring and the reducing efficacy against emerging SARS-CoV-2 variants, many oral antiviral agents were developed. The use of nirmatrelvir as well as ritonavir within 3 days after the onset of COVID-19 symptoms was associated with an 89% relative risk reduction of COVID-19 related hospitalization or death by day 28 among nonhospitalized adults at a high risk for progression to severe disease (including patients with malignancies receiving chemotherapy within 90 days prior to study entry as well as individuals with active cancer) [53]. Due to potential drug-drug interactions and overlapping toxicities between anticancer and anti-COVID-19 agents, a multidisciplinary management involving oncologists and infectious disease specialists is strongly recommended for COVID-19 infected oncology patients undergoing treatment. Notably, the trial was restricted to unvaccinated persons, although a separate, ongoing trial (ClinicalTrials.gov Identifier: NCT05011513) of nirmatrelvir and ritonavir is including only vaccinated people with high-risk features.

SARS-COV-2 VACCINATION: THE TURNING POINT

Due to the higher risk of patients with cancer to develop complications from SARS-CoV-2 infection, preventive measures are considered a key strategy to contain the spread and risk of infection [43]. The vaccination campaign was launched in many European countries between December 2020 and January 2021. The start was less functioning than expected, slowed down by vaccines manufacturing delays as well as supply shortages. By contrast, country like Israel proceeded with fast decision making and extraordinary logistical organization. Similarly, the rate of vaccination in USA was at first three times higher than the European average. The most important players that contributed to a successful beginning of the campaign in these countries were the application of less restrictive priorities for vaccination access, and the presence of vaccines manufactures in the country [54]. However, within a few months, EU led the immunization marathon on a global scale reverting the trend, reaching the target of administering one dose to 70% of adults by July 2021, the same percentage secured in the USA, confirming once again the responsiveness of European countries to the many obstacles that came on the way. Different organizational models were adopted across EU, but all of them were characterized by similar policies and system of prioritization according to scales of target population risk and need [54,55]. The availability of effective vaccines has reduced the burden of COVID-19 disease [56,57]. Patients with cancer have been prioritized for vaccination, although some concerns about the efficacy and safety of the vaccines in this population have been raised due to their exclusion from key trials [58,59].

A French survey delivered among patients with cancer before the beginning of the vaccination campaign reported a rate of reticence against SARS-CoV-2 vaccines of 16.6%, with efficacy (59.4%), safety (50.3%) and the type of vaccine administered (35.2%) as the most frequent reasons for concern [60]. Nevertheless, only 5.6% of 522 French patients who were retrospectively evaluated after the introduction of the vaccination effectively refused it,

while the reported rate of denial was 11.2% in an Italian cohort, mostly driven by apprehension toward the occurrence of potential vaccine-related adverse events. This rate raised to 19.7% after the announce of AZD1222 suspension in March 2021 [61]. The administration of the second dose was received with significantly less distrust [62]. Overall, these observations highlighted the need to ensure an adequate broadcast of medical information [62].

Immunization following SARS-CoV-2 vaccination in frail populations has been a matter of several analyses. A meta-analysis evaluating 35 studies demonstrated a suboptimal immunologic response after complete immunization amongst the oncological population, especially for patients with haematological malignancies as compared to patients with solid tumours (65 vs. 94%; $P < 0.0001$) [63▪]. However, a radical drop in the rate of COVID-19 infection was reported after vaccination, and an increasing seroconversion rate was observed with a booster strategy [63▪]. Risk factors for a reduced seroconversion in patients with cancer overlap with those of the general population, including male sex, older age, chronic use of corticosteroids and type of vaccine [64]. Another issue was the optimal timing of administration of the vaccine with regard to the schedule of anticancer treatments, although the timing does not seem to influence the seroconversion [65]. Due to the suboptimal immunologic response and the emergence of new immune-escaping variants, booster doses have been strongly recommended by European health authorities for frail populations including patients with cancer. The benefit of a third dose in a cohort of patients with active cancer was higher in those who did not develop an antibody response after the second dose, and it was not influenced by an active anticancer treatment [66].

As vaccination is the most effective strategy for controlling the pandemic, oncologists should encourage their patients and caregivers to complete the full course of vaccination as well as to promote and populate dedicated registries to

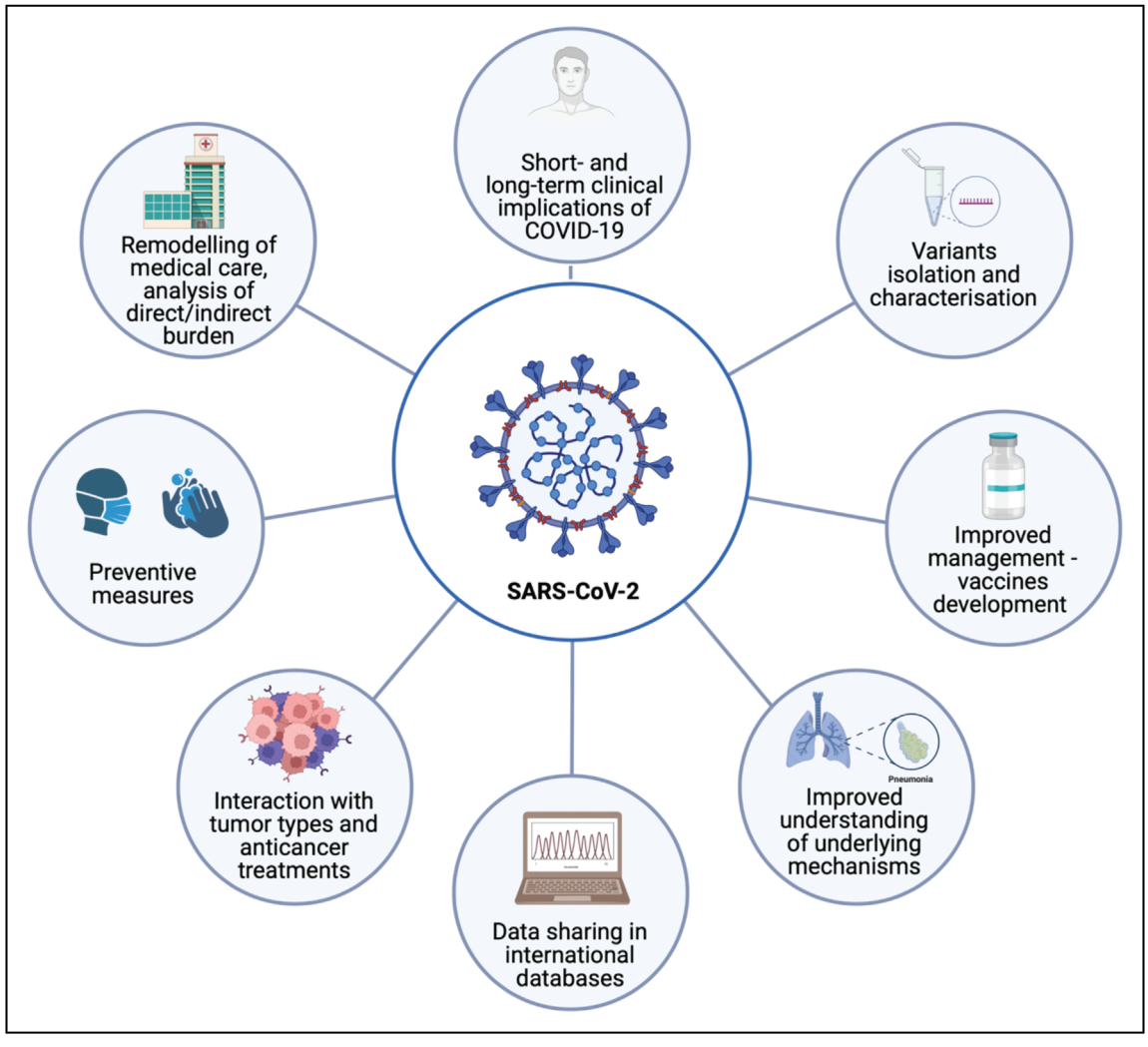

FIGURE 1. Key factors in the management of the COVID-19 pandemic in oncology.

increase the available evidence on this relevant topic.

CONCLUSION

The COVID-19 pandemic represents an unprecedented crisis, which has led to major changes in the organization of cancer care, as patients with malignancies are recognized as vulnerable, with a need to be particularly protected. Figure 1 depicts the most important topics and steps related to the pandemic and its effects on cancer care.

Italy was the first country to face the SARS-CoV-2 spread and to declare a public confinement in the first months of 2020. Starting from then, an escalated epidemiological scenario disrupted the capability of different affected countries to manage the emergent situation without impacting their healthcare. Two years later, a forced cohabitation with a circulating virus has reshaped some aspects of oncological care. Nonetheless, the threats posed by COVID-19 have resulted in several multidisciplinary efforts to mitigate the detrimental effect of the pandemic on cancer care. These have led to positive learnings and actions to help recover from pandemic disruptions as much as possible, highlighting the rapid global cooperation to help the world facing this challenging situation.

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Conflicts of interest

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