Oncology Treatments during the COVID-19 Pandemic in Israel: the ONCOR Study

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ABSTRACT **Background:** The increased susceptibility of cancer patients to coronavirus disease-2019 (COVID-19) infections and complications calls for special precautions while treating cancer patients during COVID-19 pandemic. Thus, oncology departments have had to implement a wide array of prevention measures.

Objectives: To address issues associated with cancer care during the COVID-19 pandemic and to assess the implementation of measures aimed at containment of COVID-19 diffusion while allowing continuation of quality cancer care.

Methods: A national survey among oncology departments in Israel was conducted between 12 April 2020 and 14 April 2020. Eighteen heads of hospital-based oncology departments completed a self-report questionnaire regarding their institute's preparedness for treatment of cancer patients during the COVID-19 pandemic.

Results: In this national survey, prevention measures against COVID-19 spread were taken prior to patients' arrival and at arrival or while staying in the departments. Most participants (78–89%) reported using a quick triage of patients and caregivers prior to their entrance to the oncology units, limiting the entrance of caregivers, and reducing unnecessary visits to the clinic. Switching to oral therapies rather than intravenous ones when possible was considered by 82% and shortage in personal protective equipment was reported by five (28%) heads of oncology departments. Some differences between large and small/medium sized medical centers were observed regarding issues related to COVID-19 containment measures and changes in treatment.

Conclusions: Oncology departments in Israel were able to prepare and adapt their services to guidelines and requirements related to the COVID-19 pandemic with little harm to their treatment capacity.

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KEY WORDS: coronavirus disease-2019 (COVID-19), cancer patient management, oncologic treatment, preparation of healthcare system, cancer and COVID-19

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic declared by the World Health Organization in March 2020 challenged healthcare systems and raised concerns for its potential direct and indirect impact on cancer patients. Direct effects included increased susceptibility to coronavirus disease-2019 (COVID-19) infection and worsened clinical outcomes. The indirect effects included delays in diagnosis of cancer and interruptions to the continuity of oncological care (both curative and palliative) [1].

Accumulating data of the current SARS-CoV-2 pandemic indicate that cancer patients are at higher risk of infection as well as complications of this virus. In Wuhan, China, the incidence rate of SARS-CoV-2 infection of cancer patients was 0.79% compared to 0.37% in the general population. In addition, in a meta-analysis of 11 studies from China, the pooled prevalence of cancer in patients with COVID-19 was 2% [2]. In Israel, among 4353 SARS-CoV-2-positive patients from one health maintenance organization (HMO), 4.7% had a history of cancer [3]. This rate is higher than the predicted national prevalence rate of cancer survivors during the same period for 2020 [4]. Cancer patients are also more prone to severe complications including admission to intensive care units and intubation due to SARS-CoV-2 infection and may have higher case fatality rates (13–28%) [5-9].

This increased susceptibility calls for special precautions while treating cancer patients at times of the COVID-19 pandemic. Thus, oncology departments in many countries adjusted their routine activities [10-13]. In a nationwide survey from Italy, 122 oncologic department heads reported the steps taken in their attempts to deal with the new situation, including triage of

patients before entering the hospital, preventive isolation and diagnostic workup, and reducing hospital access of both patients and caregivers [10]. A cancer center in Milan, Italy, used a text message system to screen for symptoms prior to scheduled hospital visits and set up a designated area for patients suspected of SARS-CoV-2 infection [14]. In a cancer center in New York City, USA, the pediatric program established a screening and testing plan that included checking for symptoms or exposure to contacts with confirmed infection and testing SARS-CoV-2 in patients and caregivers [12]. In the Hubei Cancer Hospital in Wuhan, China, several measures were implemented in the radiation-oncology department, including separating the radiotherapy clinic into varying infection control zones, instituting daily symptoms screening for patients, modifying staff schedules, changing radiotherapy workflow and disinfection policies [15].

Despite the implementation of these measures, many oncology departments reduced their activity because of a reduced number of referrals, hesitance of patients to visit hospitals and clinics, or because of re-allocation of resources from the oncology departments [14,16]. For example, 20% of oncology departments in Italy reported significant reduction in activity as 23% of oncologists were redeployed to COVID-19 wards [10]. A study in the United Kingdom and the United States demonstrated that relative to 2019, admissions for chemotherapy and referrals for early cancer diagnosis dropped on average 60% and 76%, respectively. The study estimated that these changes in cancer care would lead to a 1-year excess number of deaths of 6270 in the United Kingdom and 33,890 in the United States [16].

The rate of COVID-19 in Israel (as of April 2020) was low compared to the United States and many European countries [17]. Yet, to maintain medical care during the COVID-19 pandemic, medical institutions had to implement a wide array of measures and procedures [18]. The Israeli healthcare system provides universal, socialized healthcare for all citizens with comprehensive reimbursement for all cancer patients. All oncology departments are public, operated either directly by the Ministry of Health (MOH) or by public HMOs. These organizations and the Israeli Society of Clinical Oncology and Radiation Therapy (ISCORT) issued national guidelines and instructions regarding cancer treatment during the pandemic.

The current study addresses issues associated with cancer care during the COVID-19 pandemic and assess the implementation of measures aimed at containment of COVID-19 diffusion while allowing continuation of quality cancer care.

PATIENTS AND METHODS

A national survey among oncology departments in Israel was conducted between 12 April 2020 and 14 April 2020, and reflects the time when a mandatory general public quarantine was in place. This survey was performed by the Cancer and Radiation Epidemiology Unit at the Gertner Institute for Epidemiology and Health Policy Research, in collaboration with the National Council for the Prevention, Diagnosis, and Treatment of Malignant Diseases.

Eighteen heads of hospital-based oncology departments completed a self-report questionnaire regarding the institute's preparedness for treatment of their cancer patients during the COVID-19 pandemic. The survey focused on activities critical for patients currently receiving treatments, those in follow-up (i.e., out of active treatment), medical staff, and caregivers.

The survey included questions on five main topics:

- COVID-19 spread in oncology units (confirmed cases among patients and staff)
- Adoption of specific COVID-19 guidelines to prevent the spread of the virus, including triage (vital signs and fever) and epidemiologic investigation of patients and their caregivers prior to entering the department
- Use of telemedicine
- Case management to maintain continuation of care during the pandemic period
- Activities related to no-show patients

Distribution of answers to the various questions included in the survey is presented for all participating centers [Tables 1 and 2]. The results were stratified according to the size of hospital, expressed by the number of beds, and defined as large when the number of beds exceeded 900.

RESULTS

Overall, 18 out of 19 heads of hospital oncology departments participated in the survey. As of April 2020, six of the oncology departments reported having at least one staff member or patient with COVID-19.

Prevention measures against COVID-19 spread were divided by those taken prior to patient arrival and those taken at arrival or while staying at the departments. In general, most units (89%) instructed patients to inform them if they developed any COVID-19 symptoms or required to be in self-isolation. However, only eight (44%) reported actively approaching patients by phone for triage prior to their visit, with significant differences between large and medium/small size hospitals (80% vs. 31%, respectively, $P = 0.09$) [Table 1].

Regarding measurements taken on arrival, most participants (78–89%) reported using a quick triage of patients and caregivers prior to their entrance to the oncology units (measuring body temperature, questioning patients and caregivers on the presence of symptoms specifically respiratory symptoms, and asking about mandatory self-isolation). All reported on use of facial masks by the patients and their caregivers. Most departments limited the entrance of caregivers; one-third not allowing

Table 1. Prevention measures

	Medical center size					
	Total		Large		Medium/Small	
Questions	**n=18**	**%**	**n=5**	**%**	**n=13**	**%**
Have the patient been asked to inform the clinic on COVID-19 symptoms or isolation?						
No	2	11.1	0	-	2	15.4
Yes	16	88.9	5	100.0	11	84.6
Have you approached patients to inquire them on COVID-19 symptoms or isolation?						
No	10	55.6	1	20.0	9	69.2
Yes, partially	8	44.4	4	80.0	4	30.8
Is there a triage* process in place for patients accessing oncology center?						
No	2	11.1	1	20.0	1	7.7
Yes	16	88.9	4	80.0	12	92.3
Is there a triage* process for caregivers accessing oncology services?						
No	4	22.2	1	20.0	3	23.1
Yes	14	77.8	4	80.0	10	76.9
Are you measuring body temperature of the patients?						
No	2	11.1	1	20.0	1	7.7
Yes	16	88.9	4	80.0	12	92.3
Are you measuring body temperature of the caregivers?						
No	2	11.1	1	20.0	1	7.7
Yes	16	88.9	4	80.0	12	92.3
Are you testing a-symptomatic patients for COVID-19?						
No	18	100.0	5	100.0	13	100.0
Yes	0	0	0	0	0	0C
Do you have security enforcing restrictions at the entrance to the clinic?						
No	10	55.6	1	20.0	9	69.2
Yes	8	44.4	4	80.0	4	30.8
What number of caregivers are allowed to access the clinic?						
0	6	33.3	1	20.0	5	38.5
1	10	55.6	3	60.0	7	53.8
>1	2	11.1	1	20.0	1	7.7
What is your policy for a patient who is in isolation but is not a confirmed for COVID-19?						
No treatment while isolated	16	88.9	4	80.0	12	92.3
Treatment in isolation conditions**	2	11.1	1	20.0	1	7.7
When do you use N95 facial masks?						
No use	10	58.8	1	20.0	9	75.0
In suspected or confirmed cases only	7	41.2	4	80.0	3	25.0
Unknown	1				1	
Was there an option for the senior staff or staff at high-risk to work from home?						
No	7	38.9	0	-	7	53.8
Yes	11	61.1	5	100.0	6	46.2
Do patients wear a protective facemask?						
No	0	0	0	0	0	0
Some	0	0	0	0	0	0
All	18	100.0	5	100.0	13	100.0
Does the staff wear a protective facemask?						
No	0	0	0	0	0	0
Yes	18	100.0	5	100.0	13	100.0
Do visitors wear a protective facemask?						
No	0	0	0	0	0	0
Some	3	16.7	2	40.0	1	7.7
All	15	83.3	3	60.0	12	92.3

*Triage: COVID-19 signs, isolation, being at high risk areas
**Conditions: separated spaces, different clinic's hours

entrance of any caregivers (except for cases needing direct assistance) and more than half allowing entrance of only one caregiver. However, while most (80%) of the large hospitals used a dedicated guard, this procedure was conducted by only 31% of the smaller hospitals ($P = 0.09$) [Table 1].

Most departments (72.2%) adjusted their facilities to reduce possibility of cross-infections either among the visitors (patients and caregivers) and/or among visitors and personnel. These measurements were site-dependent and included converting waiting rooms to allow distancing of at least two meters from each visitor to another and at the front desk, installing barriers, limiting the numbers of patients visiting the clinic simultaneously, or implementing policies to reduce the time spent in the waiting area. These policies were based on separating patients by either space or time and included increasing intervals between visits, assigning patients to different shifts, setting up a waiting area outside of the clinic, or preparing the medications in advance [Table 2].

As shown in Table 2, half of the departments reported a reduction in their working personnel (physicians, nurses, and paramedical staff). A shortage in personal protective equipment was reported by five (28%) heads of oncology departments, mostly medium/ small hospitals.

Most departments implemented steps aimed at reducing unnecessary visits to the clinic. These included a shift to telephone interactions or telemedicine (78%) and switching to oral therapies rather than intravenous ones when possible. This approach was taken mostly by the medium/small hospitals compared to large hospitals (60% vs. 92%, $P = 0.11$). Only 31% of participants reported postponement of radiotherapy; all of these patients were from departments that do not have an in-house radiotherapy facility. Delaying radiotherapy was also more common among the smaller hospitals (45% vs. 0%, $P = 0.1$). Seventy-one percent reported intentionally postponing visits, but this delay was intended mostly for patients in follow-up (i.e., cancer patients in remission) and not patients with active treatment. About 40% of the departments postponed imaging tests such as computed tomography or positron-emission tomography/ computed tomography. Of these, 57.1% reported that they preferred to make their decisions based on clinical or laboratory examinations. Importantly, most departments reported using an alternative way to be in touch with patients who cancelled their appointment, such as a telephonic follow-up interview conducted by the clinical staff [Table 3].

DISCUSSION

The current survey demonstrated that most oncology institutions in Israel implemented many of the measures recommended by local authorities (MOH, ISCORT) and international profession-

Table 2. Facilities and staff preparedness

	Medical center size					
	Total		Large		Medium/Small	
Questions	n=18	%	n=5	%	n=13	%
Have the clinic been adjusted to enable distancing of at least 2 meters from one patient to another?						
No	5	27.8	2	40.0	3	23.1
Yes	13	72.2	3	60.0	10	76.9
Have the clinic been adjusted to enable distancing of at least 2 meters or installed a barrier between patients and the reception desk?						
No	5	27.8	1	20.0	4	30.8
Yes	13	72.2	4	80.0	9	69.2
Do you use measures to limit the number of patients at the clinic at any given time?						
No	7	38.9	2	40.0	5	38.5
Yes	11	61.1	3	60.0	8	61.5
Do you use measures to reduce the time spent by patients in the clinic?						
No	11	64.7	3	75.0	8	61.5
Yes	6	35.3	1	25.0	5	38.5
Unknown	1		1			
Was there a reduction in the number of physicians per shift?						
No	9	50.0	2	40.0	7	53.8
Yes	9	50.0	3	60.0	6	46.2
Was there a reduction in the number of nurses per shift?						
No	8	44.4	2	40.0	6	46.2
Yes	10	55.6	3	60.0	7	53.8
Was there a reduction in paramedical staff per shift?						
No	8	44.4	2	40.0	6	46.2
Yes	10	56.6	3	60.0	7	53.8

Table 3. Steps for continuation of cancer treatment

	Medical center size					
	Total		Large		Medium/Small	
Questions	n=18	%	n=5	%	n=13	%
Is there enough protective equipment for the health staff?						
No	3	16.7	0	-	3	23.1
Yes	13	72.2	4	80.0	9	69.2
Sometimes	2	11.1	1	20.0	1	7.7
Was remote work considered?						
No	5	27.8	1	20.0	4	30.8
Yes	13	72.2	4	80.0	9	69.2
Have you incorporated telephonic and telehealth interactions with patient rather than face-to-face visit?						
No	4	22.2	1	20.0	3	23.1
Yes	14	77.8	4	80.0	10	76.9
Did you give instructions to patients regarding the use of telemedicine?						
No	6	35.3	1	25.0	5	38.5
Yes	11	64.7	3	75.0	8	61.5
Unknown	1		1			
Have you discussed treatment options during the COVID-19 period with the patients?						
No	1	5.9	0	-	1	8.3
Yes	16	94.1	5	100.0	11	91.7
Unknown	1				1	
Are high-risk groups (such as lung cancer patients, hematologic patients after transplant) getting special attention?						
No	9	56.3	4	80.0	5	45.5
Yes	7	43.8	1	20.0	6	54.5
Unknown	2				2	
Is there a reduction or postponement of radiotherapy treatments?						
No	11	68.8	5	100.0	6	54.5
Yes	5	31.3	0	-	5	45.5
Unknown	2				2	
Have you considered reducing the frequency of intravenous treatments or replacing intravenous by oral treatments?						
No	3	17.6	2	40.0	1	8.3
Yes	14	82.4	3	60.0	11	91.7
Unknown	1				1	
Was there a postponement of imaging tests such as computed tomography or positron-emission tomography/computed tomography?						
No	10	58.8	3	75.0	7	53.8
Yes	7	41.2	1	25.0	6	46.2
Unknown	1		1			
Was there a postponement of visits of patients not on active cancer treatment?						
No	5	29.4	1	25.0	4	30.8
Yes	12	70.6	3	75.0	9	69.2
Unknown	1		1			
Is there a policy for patients who cancel their appointments due to infection concern?						
No	3	17.6	1	25.0	2	15.4
Yes	14	82.4	3	75.0	11	84.6
Unknown	1		1			
Is there a protocol for the institute staff to address no-show patients?						
No	2	11.8	1	25.0	1	7.7
Yes	15	88.2	3	75.0	12	92.3
Unknown	1		1			

al societies (ASCO, ESMO, NHS) [19-21] regarding oncology service preparedness during the COVID-19 pandemic. Prevention measures against COVID-19 spread were taken prior to patient arrival, at arrival, or while staying in the departments. Most departments reported using a quick triage of patients and caregivers, limiting the entrance of caregivers, implementing steps aimed at reducing unnecessary visits to the clinic by shifting to telephone interactions, and switching to oral therapies rather than intravenous ones, when possible.

Maintaining continuity of care for cancer patients amid the COVID-19 pandemic has been challenging in many countries due to the reallocation of staff and other resources, staff on sick leave or mandatory isolation, appointment cancellations by concerned patients, and financial burden of the pandemic on the healthcare systems [10]. Observations from the current survey suggest that oncology institutions in Israel had a similar challenge in attempting to maintain level of care under changes to resource availability such as reductions in staff size, separation of staff to pre-defined shifts, and partial shortage of personal protective equipment. Continuity of care in oncology departments in Israel was supported by the MOH, which excluded cancer care from the guidelines to halt all elective treatments.

Appointment cancellations by concerned patients were reported by some of the oncology departments. Thus, to encourage patients to continue active treatment as scheduled, the MOH, as well as major hospitals launched campaigns on television and electronic and social media platforms. ISCORT issued recommendations to its members [22] and the Israel Cancer Association issued recommendations for the patients and opened a web-based forum to answer patient questions and concerns [23]. This coordination emphasizes the strength of the Israeli oncology healthcare system, which is universal, public, and free of charge to all patients.

Reports from the United States and the United Kingdom indicate large drops in cancer screening [11], diagnosis, and early treatment [16]. The current survey focused only on diagnosed and treated oncology patients. The effect of the pandemic on earlier stages in the cancer patient's journey, from screening to diagnosis and surgical treatments may indeed be major and need to be assessed.

Some of the practices adopted by the oncology departments in Israel included changes in procedures, for example switching patients to oral medications or to regimens requiring fewer hospital visits. Importantly, in case of a subsequent wave or a similar pandemic, these operating procedures could be rapidly disseminated and implemented in all departments. However, some of the most effective anti-infective measures required additional resources.

In this national survey, we observed some differences between large and small/medium sized medical centers:

- Issues related to COVID-19 containment measures, such as dedicating special staff to contact each patient before the visit regarding safety measures and employing a dedicated guard and availability of personal protective equipment that were less common in small/medium hospitals
- Changes in treatment such as switching from intravenous to oral therapies were more common in small/medium size hospitals.

To maintain a uniform and equal cancer care system during crisis, there is a need to adjust cancer care on a national level and assist all centers to overcome shortage in resources during the ongoing COVID-19 pandemic and in similar future events.

Strategies that should be considered in case of future similar pandemic include better allocation of national resources toward all departments and separation of cancer patients from sources of possible infection. This change may include strengthening the services delivered to cancer patients in the community such as home based blood testing, home visits, use of telemedicine and extended after-hours phone consultation services, or generation of cancer hubs to treat all cancer patients. Indeed, such measures were taken in several countries. In the Lombardy region in Italy, a cancer-dedicated medical center became the cancer hub for hospitals in Milan. In the United Kingdom, cancer services were moved to centralized hubs, and in Australia community centers for oncology are being developed [14,24,25].

CONCLUSIONS

Oncology departments in Israel were able to prepare and adapt their services to guidelines and requirements related to the COVID-19 pandemic with little harm to their treatment capacity. The dynamic nature of the pandemic requires continued consideration of local resources and patient conditions and preferences to tailor the ideal treatment plan in light of changing circumstances.

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Capsule

Stem cells remember

Tissue stem cells sense their surroundings, and this perception influences subsequent fate and function. **Gonzales** and co-authors observed that stem cells accumulate epigenetic memories of diverse environmental. By wounding skin and monitoring the temporal steps involved in mobilizing stem cells of the hair follicle to repair the epidermis, the authors found that stem cells bear memories of their original niche, migration, encounters with inflammation, and adaptation to the new fate and tasks. During homeostasis, immigrant stem cells are functionally and transcriptionally analogous to native cells, but upon future assaults, they unleash discrete epigenetic memories to heighten physiological response and affect tissue fitness.

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Capsule

Skin inflammation a proinflammatory TWEAK for skin

Although biologic therapies that target the proinflammatory cytokines interleukin-17 (IL-17), IL-23, and tumor necrosis factor (TNF) are established approaches for treating human psoriasis, other cytokine-signaling pathways may participate in psoriatic skin inflammation. **Gupta** and co-authors analyzed the ability of the TNF superfamily cytokine TWEAK to induce expression of psoriasis-associated genes in cultured human keratinocytes and contribute to psoriasis-like skin changes in mice after treatment with the Toll-like receptor 7 agonist imiquimod. Genes induced by TWEAK stimulation of human keratinocytes heavily overlapped with those induced by IL-17 and TNF. Conditional deletion of the TWEAK receptor Fn14 in mouse keratinocytes reduced skin inflammation elicited by imiquimod. These findings suggest that therapeutics targeting the TWEAK-Fn14 axis may provide an additional means to calm the dysregulated cytokine circuits that drive psoriasis.

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