# The Coronavirus Pandemic in Israel: Implications for Radiation Oncology Departments

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The coronavirus (COVID-19) pandemic has resulted in a global healthcare crisis. It spread fast, affecting all continents, with numbers of infected people increasing daily increasing, and resulting in a high mortality rate, especially in the older and/or co-morbid populations. The number of sick patients requiring respiratory support and intensive care treatment threatens to saturate the capacity of healthcare services. Infection of the medical staff is threatening the capacity of the healthcare system to treat patients presenting with virus, while still providing other routine medical services to the non-infected population.

There are many challenges for the healthcare system to consider during such a crisis, including the ability to address other routine medical needs, such as elective surgeries, heart disease treatments, and diagnostics. Cancer patients are considered a unique population. On the one hand, cancer patients tend to be immunocompromised and have co-morbidities, thus they are at a greater risk for serious disease or even death if infected by the COVID-19 virus [1]. On the other hand, for most cancer patients, delaying cancer treatment to the resolution of COVID-19 pandemic may significantly compromise their prognosis.

Radiation therapy (RT) is an important clinical modality in the treatment of patients with malignancies, and occasionally benign diseases. This treatment is indicated in 50–60% of cancer patients [2]. RT aims to deliver a precise dose of ionizing irradiation to a target volume, which encompasses the tumor volume and potential subclinical spread, while minimizing radiation exposure to the surrounding healthy tissue, resulting in eradication of the tumor cells, prolongation of disease-free survival, and overall survival. In addition to curative indications, RT is a major modality for palliation or symptom control. Palliative RT is applied to control pain and treat luminal patency, for example bronchus in dyspeptic patients, acute cancer-related bleeding, and impending pathological fracture. There are a number of RT techniques (e.g., external beam RT, brachytherapy, intraoperative) and different RT doses and fractionation (i.e., number of daily treatments needed) that are used according to the clinical indication. Most RT is delivered daily for consecutive weeks (5 days per week, 1–7 weeks of therapy) in the RT suites (the dedicated room with an RT machine). In some cases, concomitant treatment of systemic therapy and RT (CRT) is indicated. RT is a complex modality, and a multidisciplinary team of radiation oncologists, nurses, radiation technicians, dosimetrists, and physicists are needed to plan and apply treatments. The teams work physically close together and are in close contact with the patient. Therefore, RT at the time of the COVID-19 pandemic poses new challenges for cancer patients and the RT teams. Especially as there is no evidence for effective anti-viral therapy and the main public health intervention has been social distancing and isolation of infected patients for 14 days, which is not feasible in case of cancer treatments and RT [3].

In this focus article we address the adjustments made in the radiation oncology unit at Sheba Medical Center in preparation of the COVID-19 outbreak with the intent to provide oncological care in the safest conditions for patients and the hospital staff.

In early March 2020, Sheba Medical Center, as a national public hospital, started vigorously preparing for the COVID-19 outbreak and created a facility for the passengers who were quarantined on the Diamond Princess cruise ship and who would continue to be quarantined after disembarking. Following the outbreak news from Wuhan and the subsequent spread to Italy, it became very clear that this disease would present a huge challenge for healthcare systems worldwide. Our team prepared for the management of cancer patients in this pandemic with much uncertainty and with the understanding that rapid changes would require special consideration and preparation.

We identified the following major challenges:

- Many cancer patients are elderly or have co-morbidities
- Patients who are treated with CRT are often immune compromised and thus are at higher risk to develop complications of COVID-19

- Even in patients who receive RT alone, and are not necessarily considered immune compromised, may develop lymphopenia as lymphocytes are extremely sensitive to RT. It is unclear whether these patients are at a greater risk for COVID-19 complications
- Protracted fractionation over a few weeks of treatment may increase the chance for COVID-19 infection compared to short fractionation schemes
- Protracted fractionation over a few weeks of treatment may increase the chances of the RT staff testing positive for COVID-19 infection
- Patients, visitors, and personal touch different surfaces at the RT facility

In early March 2020 we started conducting daily department meetings to address the challenges.

1. Minimizing interpersonal contacts among staff to prevent cross contamination:
   - Ensure rapid transition to treatment preparation processes via electronic workflow (Care Path, Varian, USA)
   - Form teams of physicians and physicists who would work on alternating days to reduce exposure
   - Divide radiation therapists into teams working on the same radiation machine without direct contact with other teams
   - Provide remote access for radiation oncologists and physicists. Deploy and authorize distant access to the electronic medical records, imaging, and treatment planning software
   - Conduct staff meetings, quality assurance meetings, and multidisciplinary tumor boards performed via web-based video conferencing

2. Ensuring patient safely and screening:
   - Intensify general protective measures including the use of surgical masks, gloves, and hand washing
   - Clean public surfaces at short intervals, paying special attention to keyboards, door handles, tables, and treatment couches to avoid touch contamination
   - Screen all individuals for symptoms and fever before entering the clinic
   - Instruct patients to come alone whenever feasible and limit companions to one person
   - Refer any individual with suggestive symptoms to the hospital COVID-19 triage clinic
   - Transform the follow-up clinic for patients to video-based visits with remote access to the patients' current laboratory tests and imaging. Install video cameras and proprietary software protecting patient privacy in the physicians' offices. New patients were still required to come in for the first consult
   - Deploy the infectious disease epidemiology nursing team to recommend requirements for use of gloves, hand washing, and room and couch cleaning before and after each treatment
   - Require all staff and patients to wear surgical masks
   - Extend treatment slots on the radiation machines from 10 minutes to 15 minutes to prevent crowding and to allow for cleaning

3. Modifying radiation protocols:
   - Conduct daily web-based meetings with updates of measures taken at different centers worldwide
   - Adopt different protocols that do not compromise oncological treatment yet still reduce potential risk for infection. Elderly population with low-risk breast cancer can start adjuvant endocrine therapy and RT can be delayed or omitted (depending on the risk)
   - Postpone radiotherapy for low and intermediate prostate cancer patients who are treated with endocrine therapy
   - Shorten radiation regimens, such as using a single 8 Gy fraction for palliation instead of a 5 to 10 fraction course
   - Offer extreme hypo-fractionation, such as five treatments for breast and prostate cancer, rather than longer regimens

**Table 1.** Similarities among COVID-19, pneumonia, and oncologic treatment-related effects on the lung

| | COVID-19 pneumonia | Immunotherapy-related pneumonitis [6,7] | Radiation pneumonitis [8] | Infectious (non-COVID-19) pneumonia |
|---|---|---|---|---|
| Chest X-ray | Diffuse bilateral opacities | Many possible patterns, including diffuse bilateral opacities | Confined to region of treatment unilateral, diffuse if large volume of radiation used | Usually unilateral, confined to specific lobes |
| Fever | High | Low | Low | High |
| Dyspnea onset | Acute | Acute or slowly progressive | Slowly progressive | Acute |
| White blood cell count | Lymphopenia, neutrophilia | Variable | Lymphopania | Leukocytosis |
| Medical treatment | Not proven | Steroids, hold immunotherapy | Steroids, prolonged | Anti-bacterial or anti-viral mediations |

## SPECIAL CONSIDERATIONS FOR ONCOLOGIC POPULATIONS

*Differential diagnosis of COVID-19 in cancer patients*

Cancer patients receiving RT to the lung or mediastinum are potentially the most difficult patients to manage during the COVID-19 outbreak period. These patients present with overlapping symptoms of fever, cough, and dyspnea with hypoxemina that may be clinically difficult to distinguish from COVID-19. RT, chemotherapy, or immunotherapy and cancer itself may be associated with pneumonitis and fever similar to symptoms of the COVID-19 disease [Table 1]. Other causes such as, pulmonary embolism, lung atelectasis, tumor progres-

sion, aspiration as well as and bacterial or other viral pneumonia may cause dyspnea as well and should be kept in mind. Although evidence is limited, patients with lung cancer may be at high risk of sever pneumonia if they are contaminated [4,5].

Hypersalivation occurs in head and neck patients early in the course of radiotherapy before xerostomia occurs and requires extra caution by the staff. Daily contact with the immobilization masks that are contaminated by oral secretions may further increase the risk for the staff.

Active screening of cancer patients for infection should be conducted prior to treatment. If a patient tests positive, treatment should be postponed until the infection has subsided. Once treatment has started, meticulous monitoring of these patients is required to discern treatment effects from infection.

Consider delay of treatments if it does not compromise oncological outcome, especially for the geriatric patients.

## CONCLUSIONS

We are currently in the acceleration phase of the COVID-19 pandemic and the future regarding effective treatment and vaccination is uncertain. As caregivers for cancer patients, we are obliged to remember that aggressive cancer does not wait for resolution of COVID-19 infection and we will need to carefully evaluate risks and benefits of initializing or delaying treatment for our patients. We need to be flexible and nimble to optimize cancer care in the context of this corona tsunami.

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Capsule

### Cells gone rogue

Autoantibodies are proteins produced by the immune system that attack a person's own tissues and organs, leading to autoimmune disease. Autoantibodies can be present in the serum years before the clinical onset of autoimmunity, but it is not understood how they cause disease. **Singh** et al. used multi-omics single-cell technology to trace the evolution of rogue cell clones responsible for producing pathogenic autoantibodies in the blood of patients with the autoimmune disease cryoglobulinemic vasculitis. The researchers found that a benign antibody can transform into one that causes inflammation of blood vessels in the skin, kidney, nerves, and joints. The gene mutations that accumulate in the rogue cells during the early stages of autoimmune disease have also been identified in cancer cells from patients with lymphoma.

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Capsule

### Structure of the nCoV trimeric spike

The World Health Organization has declared the outbreak of a novel coronavirus (2019-nCoV) to be a public health emergency of international concern. The virus binds to host cells through its trimeric spike glycoprotein, making this protein a key target for potential therapies and diagnostics. **Wrapp** and colleagues determined a 3.5-angstrom-resolution structure of the 2019-nCoV trimeric spike protein by cryo-electron microscopy. Using biophysical assays, the authors showed that this protein binds at least 10 times more tightly than the corresponding spike protein of severe acute respiratory syndrome (SARS)-CoV to their common host cell receptor. They also tested three antibodies known to bind to the SARS-CoV spike protein but did not detect binding to the 2019-nCoV spike protein. These studies provide valuable information to guide the development of medical countermeasures for 2019-nCoV.

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