





Recommendations for radiotherapy during the novel coronavirus pandemic

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SUMMARY

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The Coronavirus 2019 (COVID-19) pandemic requires swift and assertive health actions. The coronavirus is part of a family of RNA virus common in humans and other animal species. Symptoms include those of common colds but can evolve with complications, such as Severe Acute Respiratory Syndrome (SARS)¹.

Some types of cancer and their respective treatments can weaken the immune system, increasing the risk of infection by COVID-19, especially during chemotherapy or radiotherapy. In addition, this subgroup of patients may develop more severe complications and have a higher risk of respiratory disease that requires hospital admission, treatment in intensive therapy unit with ventilatory support, and a greater probability of unfavorable outcomes².

The first interpersonal transmission in Brasil occurred on 13 March 2020, leading to an exponential spread that has yet to peak. Thus, oncology services have a crucial role in preventing and controlling infection in treatment centers and drawing up a plan to be adopted in this pandemic scenario^{3,4}.

In radiotherapy services, in particular, it is important to consider shorter treatments, as well as avoid interruptions to the greatest extent possible. Given the large volume of publications involving this concerning subject and its many uncertainties, this article compiles information, advice, and experiences from different centers, in addition to suggesting alternative therapies that can be adopted during this period.

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GENERAL RECOMMENDATIONS FOR CANCER PATIENTS

In cancer patients, it is important to strengthen the existing preventive measures to minimize contact with COVID-19. It is important to mention there is a more vulnerable⁵ subgroup comprising:

- Patients under active chemotherapy or radiotherapy treatment.
- Patients with hematological neoplasms, such as leukemia, lymphoma, myeloma, regardless of the treatment stage.
- Patients undergoing immunotherapy or continuous treatment with antibodies.
- Patients undergoing targeted therapy that affects the immune system, such as protein kinase inhibitors or PARP inhibitors.
- Patients who underwent bone marrow or stem cell transplant in the last 6 months or in use of immunosuppressant.
- Patients aged over 60 years.
- Patients with a history of cardiovascular disease.
- Patients with a history of respiratory disease.

Transmission occurs by exhaled droplets and contaminated surfaces, and the preventive measures are the same as those valid for the general population^{3,4,6-8}. Thus, it is key to instruct cancer patients and their medical staff on the following topics:

Preventive Measures

- Avoid social agglomerations and close contact with sick people;
- Avoids interpersonal contact;
- Avoid touching the eyes, nose, and mouth;
- Wash hands often, for at least 20 seconds, especially after using the bathroom, before meals, after blowing the nose, coughing, or sneezing and before contact with other people;
- Clean and disinfect areas often touched daily. If the surface is dirty, use detergent or soap and then disinfect it.
- Get a flu shot;
- Stay home as much as possible;
- Ensure access to medication and supplies for several weeks, in the event it is necessary to self-isolate;
- Avoid traveling longer distances.

Symptoms

- Incubation period: 2 to 15 days after exposure - an average of 5.2 days.

- The most common symptoms are fever, dry cough, and fatigue. Some patients have reported a runny nose, nasal congestion, sore throat, and diarrhea, though the latter is less frequent.
- According to the World Health Organization⁷, based on a study that included 56,000 patients, 81% of those infected develop mild symptoms (fever, cough and, in some cases, pneumonia), 14% severe symptoms (difficulty breathing, shortness of breath), requiring hospitalization for oxygen therapy, and 5% become critically ill (respiratory failure, septic shock, organ failure, and risk of death).
- Symptoms of urgency:
 - Difficulty breathing or shortness of breath.
 - Persistent pain or pressure in the chest.
 - Confusion or inability to remain alert.
 - Bluish lips or face.

SPECIFIC RECOMMENDATIONS³⁻¹⁸ REGARDING TREATMENT

It is critical to categorize patients according to priority levels to assist in the decision-making process, which should always include the entire multidisciplinary team involved in cancer care and be discussed with the patient. The risks/benefits should be weighed in for each case individually⁵.

Priority level 1:

- Patients with tumors of rapid proliferation treated with radio-chemotherapy or radical radiotherapy with curative intent. Intervals with subsequent compensation can be detrimental to the curative outcome.
- Patients with tumors of rapid proliferation whose treatment plan is external radiotherapy combined with brachytherapy and external radiotherapy is already being carried out.
- Patients with tumors of rapid proliferation who have yet to start treatment.

Priority level 2:

- Urgent palliative treatment in patients with spinal cord compression with recoverable neurological function.

Priority level 3:

- Radical radiotherapy for patients with less aggressive tumors, with radiotherapy as the first line of radical treatment.

- Postoperative adjuvant radiotherapy with proven residual disease in tumors with aggressive biology.

Priority level 4:

- Palliative radiotherapy when there is a relief of symptoms that may reduce the demand for hospitalization, such as hemostatic radiotherapy in hemoptysis patients.

Priority level 5:

- Adjuvant radiotherapy after complete tumor resection when the risk of recurrence in 10 years is lower than 20%.

REGARDING NEOPLASMS¹⁰⁻¹⁷

Based on the priority levels above, the radio-oncologist can evaluate the interruption of adjuvant therapies with low risk of recurrence, weighing in the risks and benefits, and discussing the situation with the patient, in addition to postponing non-urgent palliative cases and benign cases. In all cases, only hypofractionated schemes of radiotherapy should be considered clinically appropriate.

Breast cancer^{14,15}

In early cases (*in situ neoplasia*, small invasive carcinomas, luminal tumors), the following considerations are possible:

- a. Delay the start of radiotherapy for up to 2 months after the surgery.
- b. If available in the center, consider intra-operative radiotherapy or other forms of accelerated partial breast radiotherapy
- c. If the whole is being treated (with or without lymph nodes), use hypofractionated therapy (3 weeks).
- d. Propose a concomitant boost when there is an indisputable indication for a boost.

In patients with breast cancer and age over 65 years, with T1/T2N0 luminal tumors, who will receive endocrine therapy, depending on the risks and benefits, the omission of adjuvant radiotherapy can be considered.

Patients with a formal indication for lymph node irradiation must have their indication maintained. However, it is important to consider hypofractionated therapy in these patients.

In cases of breast cancer with the possibility of conservative surgery, it is recommended to conduct

a multidisciplinary discussion with the entire medical staff and the patient about the realization of mastectomy, with the purpose of reducing indications for adjuvant radiotherapy in times of pandemic.

Consider hypofractionated therapy for all patients. There are ultra hypofractionation schemes (5 fractions) performed within 1 week that could represent an alternative for the rapid treatment of patients¹⁶.

Patients who underwent chemotherapy before radiation therapy: comply with the interval of up to 8 weeks between the end of the chemotherapy and the start of radiotherapy. Patients who underwent chemotherapy neoadjuvant to surgery should follow the same interval.

Prostate cancer^{17,18}

In patients with low-risk and intermediate-to-low-risk prostate cancer, active surveillance with a follow-up visit in 6 months should be strongly considered.

For those with intermediate-to-high and high risk, postponed neoadjuvant hormone therapy with delayed radiotherapy should be considered. If it is not possible to perform hormone therapy or if the cancer risk is greater than the risk of infection with unfavorable outcomes due to COVID-19, hypofractionated schemes should be strongly considered.

Current level 1 evidence converges to the equivalence of moderate hypofractionation compared to traditional fractioning. Thus, hypofractionation into 20 fractions of 3 Gy is strongly recommended.

If the treatment center has access to the image-guided radiotherapy technology required (*cone-beam* TC or fiducial markers), 7 fractions of 6 Gy, or 6 fractions of 6 Gy, or 5 fractions of 7.25 Gy can also be considered, all in line with the NCCN 2020 Guidelines¹⁹.

Based on the evidence presented recently from RAVES²⁰ and RADICALS²¹, early salvage after prostatectomy should be considered in all cases in the pandemic scenario. Consider postponing the beginning of salvage radiotherapy in up to one month for patients with an indication for such.

For oligometastatic patients (low-volume M1) with an indication for local radiotherapy, consider postponing radiotherapy while the patient is undergoing hormone therapy. If radiotherapy is chosen, consider schemes with 6 fractions of 6 Gy, used in one of the arms of the STAMPEDE²² study, and considered safe and acceptable.

Rectal cancer

Start, if possible, induction chemotherapy. The use of short-course preoperative radiotherapy in 5 fractions of 5 Gy is recommended²³.

Lung cancer

Patients with lung cancer may have a history of pulmonary dysfunction that increases the risk of severe respiratory complications. Thus, this group presents a particularly increased risk for radiotherapy in this pandemic scenario. Consider postponing the treatment:

- Early-stage lung cancer, especially those non-biopsied, with slow growth, advanced age, or comorbidities.
- Oligometastatic patients.
- Consolidation radiotherapy or prophylactic cranial irradiation in patients with small-cell lung cancer with extensive disease.
- Prophylactic cranial irradiation in patients with small-cell lung cancer with limited disease.

Gliomas

Low-grade glioma: postpone the start of radiotherapy as much as possible.

High-grade glioma: treatment should be individualized. Consider hypofractionation using 15 fractions of 2,7Gy or 5 fractions of 5 Gy. If possible, consider using temozolomide with subsequent reassessment for radiotherapy in patients with low-performance status and age over 65 years.

Palliative treatment

In cases of patients with spinal cord compression, metastatic bone pain irresponsive to other treatments (after attempted optimization), or microvascular bleeding, treatment in a single fraction is recommended.

Schemes that may be adopted: 1 fraction of 8 Gy to 10 Gy.

Cancer of the head, neck, anal canal, and cervix

It is not recommended to postpone or change the fractionation scheme.

Others

In sarcomas of the extremities, the hypofractionation is recommended whenever possible, both in neoadjuvant and adjuvant scenarios.

Strongly consider postponing the treatment of benign tumors, such as schwannomas and asymptomatic meningiomas.

Surgeries for keloids with an indication for radiotherapy should be postponed.

RECOMMENDATIONS TO RADIOTHERAPY DEPARTMENTS

- Remote screening (1 to 2 days before the initial consultations and daily before going to the center of treatment) of all patients through a questionnaire, sent by e-mail or phone message, aiming to identify any sign of infection by COVID-19.
- Upon arriving at the radiotherapy center, screen the patient again by measuring their temperature and asking about new symptoms. In case of a positive assessment, isolate the patient in a room reserved for such purposes until the time of treatment; ensure they do not come into contact with other patients and properly sanitize the equipment after the treatment. After the patient treatment is completed, recommend a confirmatory test, and transfer the patient to the last time slots of the day.
- Provide a hydroalcoholic solution for disinfecting hands at the entrance of the sector.
- Arrange treatment schedules in order to increase the interval between treatments and thus reduce the number of patients in waiting rooms.
- Increase the frequency of sanitization of common areas and equipment.
- In case of personnel infection that causes a severe reduction that may affect the functioning of the department, make decisions along with the hospital structure involved if this is the case (consider hiring new employees or contacting other radiotherapy centers; evaluate the use of external professionals).
- For the electronics of the console, it is recommended to often use alcohol wipes or sprays containing at least soft cloth that has been moistened with isopropyl alcohol with a concentration of 70%. To facilitate the cleaning of devices, consider using plastic wrap, which must be changed daily.

RECOMMENDATIONS TO DEPARTMENT EMPLOYEES

- Formally instruct department personnel through a bulletin about the symptoms and prevention of COVID-19.
- Stimulate remote activities, such as design, planning, and clinical meetings.

- Minimum scale of all employees.
- Avoid agglomerations, keeping a one-meter physical distance, if possible.
- Among technicians of radiotherapy, reinforce the need for hand hygiene with soap and water or alcoholic preparations before and after the use of computers and radiotherapy equipment after each application.
- Require the use of surgical masks throughout the working hours for all employees in contact with patients, such as nursing professionals, doctors, and radiotherapy technicians.
- If any staff members present any symptoms, this should be communicated, and they should be forwarded for evaluation and COVID-19 testing. If no test is available, consider a 10-day quarantine from the first day of symptoms.

RECOMMENDATIONS FOR CANCER PATIENTS UNDERGOING TREATMENT WITH SUSPECTED OR CONFIRMED INFECTION

- Assess the cancer risk involved in treatment interruption.
- The interruption of treatment has a greater impact on tumors of high cell replication, in which the total time of treatment has an impact on oncologic outcomes.
- The decision regarding the interruption must be made by the radio-oncologist along with the multidisciplinary team involved in patient care by weighing in the risks and benefits of this strategy.
- If it is impossible to interrupt the treatment, wait for clinical recovery and the mandatory quarantine of 10 to 14 days before restarting the treatment. Ideally, two tests performed 24 hours apart should come back negative.
- If the patient discontinues treatment, it is recommended to follow the unplanned interruption guide available on https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfco191_radiotherapy-treatment-interruptions.pdf
- If it is impossible to interrupt treatment, organize the time of treatment in order to isolate cases, preferably in the last time slot of the day, grouping them.
- The infected patient should remain, from their arrival at the hospital or clinic, wearing a surgical mask, replacing it after two hours of use or when it becomes moist.
- During the patient treatment, the entire team in contact with them should wear N95 masks, gloves, eye protection, and a disposable protective apron. Everyone should be trained on the correct way to put on and take off the protective gear. If no N95 masks are available, the use of a surgical mask is recommended.
- Clean the room and treatment table after the treatment. The cleaning must be done wearing disposable gloves, and hands must be washed immediately after the procedure. If the surface was already dirty, use detergent or soapy water before disinfecting it.
- Never dry sweep surfaces because this favors the spread of micro-organisms transported by dust particles. Instead, wet sweep them with a mop or squeegee and cleaning cloths.
- For cleaning the floors, techniques of wet sweeping, lather, rinse, and dry should be used. Potential disinfectants for cleaning surfaces include those made of chlorine, alcohols, some phenols, and iodophors and quaternary ammonium compounds.
- All equipment should be cleaned at the end of the treatment of each patient with a suspected or confirmed case, even with the professionals are wearing PPE and avoiding contact with infected material.
- The use of kits for cleaning and disinfecting surfaces specific for patients in isolation is recommended.

REVIEW AND RETURN CONSULTATIONS

- For review consultations, telemedicine or consultations by phone are recommended. If a physical examination is necessary, it should be brief.
- Postpone return consultations and non-urgent follow-ups.

RECOMMENDATIONS FOR CANCER PATIENTS UNDERGOING TREATMENT

- Instruct patients that the oncologic treatment must not be interrupted.
- Patients undergoing treatment, at the first sign of respiratory infection, should contact their doctor for further instructions.
- It is recommended that an informed consent form is drafted for all patients informing about the

possibility of contamination during treatment.

- Patients must be instructed on handwashing, general hygiene, and preventive measures.
- Instruct patients to avoid physical contact with people who have influenza symptoms such as dry cough, shortness of breath, fever, or runny nose, as well as those with suspected infection by COVID-19.
- Encourage patients not to arrive early for their radiotherapy sessions.
- Restrict the number of companions, allowing them only in cases in which the patient is unable to go to the treatment center alone.
- Recommendations for the use of masks are the same as those valid for the general population^{4,6}.
 - Healthy individuals: no recommendation for the use of masks, except if:
 - Living with a sick individual who cannot wear a mask.
 - Is caring for a sick individual or suspects an infection by COVID-19.
 - Masks are only effective if used in combination with frequent hand washing using soap and water or alcohol gel.
 - People with symptoms or confirmed cases: wear a surgical mask, following the guidelines:
 - Before putting on the mask, sanitize hands properly.
 - Cover the mouth and nose, leaving no space between the face and the mask.
 - Avoid touching the mask during use.
 - Replace the mask when it gets moist and do not reuse single-use masks.
 - Remove the mask from the back to the front and

discard it immediately in a closed bin. Sanitize hands afterward.

RECOMMENDATIONS FOR PATIENTS WHO HAVE ALREADY COMPLETED THEIR TREATMENT

- The same preventive measures that are valid for the general population apply to these patients and close contacts.
- Routine examinations should be avoided.
- Follow-up examinations should be conducted at the discretion of the clinical oncologist and radio-oncologist, but if possible and not detrimental to the patient, they should be postponed.

CONCLUSION

Hippocrates' principle of *primum non nocere* is of paramount importance in the global pandemic scenario, with a high risk of health care collapse in the Brazilian context. Flattening the curve of dissemination of COVID-19 by implementing the various measures mentioned above is fundamental for departments of radiotherapy to minimize disruptions to treatment without impacting the oncological outcomes of patients.

Always considering the risks and benefits for each individual cancer patient, the current scenario demands such interventions.

Contribution of the authors

MTMS; ARNSS; APAP; DRFEN; FCFR; LHB; TYTS - drafting of the text, literature review. SAH – text supervision and revision, literature review.

PALAVRAS-CHAVE: Radioterapia. Neoplasias. Coronavírus. COVID-19. SARS-CoV-2. Pandemias.

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