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COVID-19 Rapid Letter

Practical indications for management of patients candidate to Interventional and Intraoperative Radiotherapy (Brachytherapy, IORT) during COVID-19 pandemic – A document endorsed by AIRO (Italian Association of Radiotherapy and Clinical Oncology) Interventional Radiotherapy Working Group [☆]



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In the contest of COVID-19 rapid spread in Italy, the Italian Government in March 2020 released an official recommendation statement indicating [1].

Regarding oncological patients, the statement indicates to regional health authorities to identify and implement as quickly as possible the arrangements necessary to ensure oncological treatments, in order not to influence disease prognosis.

The Italian Association of Radiotherapy and Clinical Oncology (AIRO) released an orientation paper in order to assure homoge-

neous working procedures during the COVID-19 pandemic emergency [2].

Interventional Radiation Therapy (IRT, Brachytherapy, BT) and IntraOperative Radiotherapy (IORT) represent potentially life-saving treatment options in different oncological clinical settings with indications shared in multidisciplinary contexts following international guidelines or trial protocols [3]. Delaying radiation treatments could worsen the overall prognosis of the disease, so that it seems to be essential to ensure radiation treatments delivery even at the time of COVID-19 emergency, fully guaranteeing health professionals, patients, and caregivers safety [4,5].

Current evidences review on “COVID-19 disease” and “Radiation Oncology” was performed, then a multicenter team composed by all members of current AIRO-IRT/IORT-Working Group (WG), an infectious disease expert working in a COVID-19 Hospital, the past chair and deputy chair of AIRO-IRT/IORT-WG, members of AIRO committee, the chair of the Scientific Committee and the president of AIRO wrote this document.

To enable the regular conduct of clinical activity and the reduction of the risk of COVID-19 diffusion in the radiation oncology departments, it is essential to identify patients and operators with suspected or proven infection performing triage at the hospital and/or departments entrance (Table 1).

It is strongly recommended the identification of dedicated team members to manage COVID-19 cases. As a general rule, the RADS

Abbreviations: ASAP, as soon as possible; EBRT, External Beam Radiation Therapy; SBRT, Stereotactic Body Radiation Therapy; SIB, Simultaneous Integrated Boost; IORT, Intraoperative Radiotherapy; IRT, Interventional Radiotherapy; HDR, High Dose Rate; PDR, Pulsed Dose Rate; HT, Hormone Therapy; CT, Chemotherapy.

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Table 1
Suspected or positive COVID-19 patient management in Radiation Oncology Departments.

Triage	General recommendations	Radiation treatment recommendations
<u>Patient at home</u>	Physiological anamnesis through telephone or videoconference contact in order to limit suspicious patient access to Radiation Oncology Departments Consider link suspicious patients to Local Public Health Institution Agency or General practitioner for domiciliary COVID-19 screening	Postpone and/or convert follow-up evaluations to telephone/videoconference contact in case of negative COVID-19 patients without referred post-treatment symptoms Plan follow-up evaluations in COVID-19 negative patients but with referred symptoms related to radiation treatments according to the clinical case presentation verified telephone/videoconference contact
<u>Asymptomatic patient</u>	Imperative wearing of mask (according to internal recommendation). Assure recommended inter-personal distance Body temperature check at Department main entrance Physiological anamnesis and patient self-declaration of health. Consider COVID-19 testing for inpatient treatments (according to internal recommendation)	Follow treatment program Healthcare workers wear surgical mask and follow hands hygiene protocols
<u>Suspicious patient</u> with typical symptoms (cough and/or fever and/or dyspnea and/or conjunctivitis unrelated to oncological disease)	Imperative wearing of mask (according to internal recommendation). Assure recommended inter-personal distance Address patient the hospital dedicated COVID-19 way Official notification to Institutional Direction Consider COVID-19 testing Investigate contact with COVID-19 positive or suspected people	Postpone the start or interrupt ongoing treatments according to personalized clinical judgment If treatment cannot be postponed, assure the respect of local protocols for the Infection Control in patients with COVID-19 or suspected COVID-19 Healthcare workers wear surgical mask and follow hands hygiene protocols
<u>COVID-19 + patient</u> (symptomatic or asymptomatic)	Imperative wearing of mask (according to internal recommendation). Assure recommended inter-personal distance Address patient the hospital dedicated COVID-19 way Official notification to Institutional Direction Consider COVID-19 testing Investigate contact with COVID-19 positive or suspected people Consider symptoms-based hospitalization	Postpone the start or interrupt ongoing treatments according to personalized clinical judgment Healthcare workers wear surgical mask (consider FFP2/FFP3 in case of aerosol-generating procedures) and follow hands hygiene protocols
<u>Previous COVID19+</u> patient confirmed healed	Imperative wearing of mask (according to internal recommendation). Assure recommended inter-personal distance Consider quarantine with ward and referent clinicians	Start or continue ongoing treatment Healthcare workers wear surgical mask and follow hands hygiene protocols

(Remote visits, Avoidance of treatment if little to no benefit or if an alternative treatment is available, Deferment of treatment if clinically appropriate, and Shortening of radiotherapy if treatment is unavoidable) principle is recommended to plan each individual patient treatment [6].

For new outpatients' appointments it is recommended, if possible, to contact patients the day before the start of treatment (or any fraction if once weekly) whereas any new patient who has to undergo inpatient therapy should be contacted the day before hospitalization or any preoperative anesthesiologic assessment. According to national, regional or institutional recommendation, consider nasopharyngeal swab for SARS-CoV-2 in people who has to undergo inpatient therapy.

In case of suspected or positive patients, starting or continuing treatments should be allowed by local health authorities and carried out under condition of maximum safety for health professionals, with dedicated routes and facilities, dedicated treatment schedules and appropriate sanitization of treatment areas and equipment [7].

It is also recommended to limit access to patients and their relatives or accompanying persons:

- offering IRT or IORT, if available and whenever possible,
- encouraging high hypofractionation, where indicated,
- postponing treatments of certain oncological diseases according to clinical judgement,
- in palliative setting it might be useful to optimize medical symptomatic treatments, if judged to be of similar efficacy,
- postponing treatment for benign diseases,

- considering hormonal or cytotoxic therapy in selected cases for further deferral of radiotherapy,
- allowing only one accompanying person per patient, whenever possible,
- considering dedicated “COVID+ interventional radiotherapy pathway”.

Follow-up evaluations should be:

- postponed until proven healing in COVID-19 positive patients,
- postponed and/or converted to telephone contact in case of negative COVID-19 patients without referred post-treatment symptoms,
- planned according to the clinical case presentation verified by telephone contact, in COVID-19 negative patients but with referred symptoms related to radiation treatments.

According to institutional recommendations, the use of specific Personal Protective Equipment is indicated during treatments with an aerosol generating procedure such as intubation, open suctioning of the respiratory tract, endoluminal IRT with bronchoscopy or upper gastrointestinal endoscopy and IRT for some intrabuccal lesions [1,8].

In these cases, it is suggested to wear disposable gloves, FFP2/FFP3 mask and fluid resistant surgical mask, eye/face protection, disposable fluid repellent gown, disposable caps and shoe covers.

The surgical room for IORT and the IRT dedicated room should have an area for donning and doffing of personal protective equipment and exchange of material and medications for the procedure.

Table 2

Relevant clinical indications for COVID-19 negative or positive patients eligible for IRT or IORT treatments. The indications should be decided on an individual basis.

Site	Patient setting	Interruption impact	COVID– patients	COVID+ patients	Notes
Breast [21–23]	Low-risk Adjuvant	Medium-low	Consider treatment omission in selected cases (age \geq 70 years, invasive Luminal A, \leq 2 cm, cN0, planned for endocrine therapy) Postpone	Postpone after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider exclusive IORT (if available)
	High-risk Adjuvant	Medium-high	Postpone limiting the time gap	Start after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider IORT or perioperative IRT anticipated boost (if available) in particular for young patients (age \leq 40 years as per EORTC trial). Evaluate concomitant boost if indicated (e.g. age \leq 40 years, as per EORTC trial, or positive margins)
	Adjuvant salvage treatment for relapse	High	Start ASAP	Postpone after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider exclusive IORT or perioperative IRT (if available) Alternative EBRT or IRT (local anesthesia) with consequent no start-time limitation
Vulva-vagina [24]	Adjuvant	Low	Postpone if negative resection margins and cN0 Consider omitting CT on case by case and resources	Postpone after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	-
	Curative	High	Start ASAP Consider omitting CT on case by case and resources	Start after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider EBRT if IRT requires major anesthesia
Uterine cervix [24]	Adjuvant	Low	Postpone	Postpone	-
	Curative	Very high	Start ASAP Consider selected early stages that would normally undergo radical hysterectomy Consider omitting CT on case by case and resources	Start ASAP if safety – guaranteed Start after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider PDR or HDR IRT with bifractionated schemes to reduce hospitalization Consider to treat IR-CTV using EBRT in order to reduce the PDR time or the HDR fractions Consider smaller diameter applicators for better patient compliance and avoidance of anesthesia In experienced centres consider SBRT boost or SIB if IRT requires major anesthesia. Referral to another centre for IRT is generally preferred to using EBRT Consider strong hypofractionation Consider IRT only also in high-risk group on case by case
Endometrium [24]	Adjuvant	Intermediate-low	Observation alone Postpone if high-risk up to 3 months from surgery unless residual disease, positive resection margins or aggressive histological subtype	Observation alone Postpone after confirmed healing if high-risk Consider dedicated COVID19+ Interventional Radiotherapy Pathway	
	Exclusive	Intermediate-high	Start ASAP If surgery is not possible consider HT or CT (if locally advanced) on individualised situation. Consider EBRT and/or IRT in selected cases that would normally undergo radical hysterectomy	Postpone after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider strong hypofractionation
Prostate [6]	Low risk	Very low	Consider Surveillance or postponed treatment	Consider Surveillance or postponed treatment	Consider ultra-hypofractionated EBRT
	Intermediate/ High risk	High	Consider hypo fractionated EBRT	Postpone decision after confirmed healing considering HT	Consider EBRT boost instead of IRT boost Consider IRT only if resources are available
Penis	Curative	Medium-high	Start ASAP	Start ASAP if safety – guaranteed Start after confirmed healing Consider dedicated COVID19+ Radiotherapy Pathway	Consider contact IRT
Urethra	Palliative	Medium-high	Start ASAP	Start ASAP if safety – guaranteed Start after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider endoscopic desobstruction Consider single fraction HDR IRT
Trachea and main	Palliative	High	Start ASAP	Start ASAP if safety – guaranteed Start after confirmed healing	Consider endoscopic desobstruction Consider single fraction HDR IRT or

(continued on next page)

Table 2 (continued)

Site	Patient setting	Interruption impact	COVID- patients	COVID+ patients	Notes
bronchus [25]				Consider dedicated COVID19+ Radiotherapy Pathway	hypofractionated EBRT
Esophagus [26]	Curative	High	Start ASAP	Start ASAP after confirmed healing	Consider EBRT without IRT boost+/- CT If not suitable for concomitant CT, consider hypofractionated EBRT alone Consider stenting desobstruction Consider IRT or EBRT with single fraction or hypofractionated approaches Consider stenting or external-drainage desobstruction
	Palliative	High	Start ASAP	Start ASAP only if safety-guaranteed Start after confirmed healing	
Biliary duct	Palliative	High	Start ASAP	Start after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider stenting or external-drainage desobstruction
Anal canal – Lower Rectum [27]	Curative	Medium-high	Start ASAP CT according to age, comorbidities and tumor biology	Start after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider EBRT if IRT requires major anesthesia Consider IORT anticipated boost (if available) If surgery not available, consider Short/ Long course EBRT, on case by case
	Palliative	High	Start ASAP	Start ASAP only if safety-guaranteed Start after confirmed healing	Consider strong hypofractionation Consider IORT anticipated boost (if available)
Skin [28]	Adjuvant	Low/medium	Choice based on patient's prognosis, age, comorbidities and the location Consider postpone in case of basal cell carcinoma (outside face) even with closely excised margins Priority in case of squamous cell carcinoma and/or face location	Postpone after confirmed healing	Consider hypofractionated regimens
	Curative	High/ Medium	SCC: No postponed, especially for large lesion or/and face lesion BCC: discuss in multidisciplinary board to postpone or contact ipofractionated radiotherapy based on lesion size and location (priority for face lesion)	Discuss in multidisciplinary board if postpone or Contact ipofractionated radiotherapy Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider hypofractionated regimens Consider no biopsy but only clinical diagnosis) Consider in selected cases systemic therapy Priority in case of squamous cell carcinoma and/or palliative setting and/ or face location
Soft tissues – Sarcomas [29]	Adjuvant	Intermediate -High	Postpone on an individual patient basis	Postpone after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider IORT or perioperative IRT (if available) In selected cases, consider preoperative hypofractionated EBRT Consider hypofractionated IRT or EBRT with no start-time limitation IRT (local-anesthesia)
Lips – Oral mucosa	Curative	Medium-high	Start ASAP	Start ASAP only if safety – guaranteed. Start after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	
Tongue [30]	Curative	High	Start ASAP	Start ASAP only if safety – guaranteed. Start after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider switch to hypofractionated EBRT in order to avoid IRT with anesthesiologic involvement for bleeding risk
Nasopharynx	Curative	High	Start ASAP	Start ASAP only if safety – guaranteed. Start after confirmed healing Consider dedicated COVID19+ Interventional Radiotherapy Pathway	Consider hypo fractionated HDR IRT or EBRT
Keloids	Adjuvant	Very Low	Observation alone Postpone Consider no surgery for benign disease	Observation alone Postpone Consider no surgery for benign disease	

In case of endocavitary and/or interstitial IRT requiring major anesthesia the definitive indication should be made considering the expected need for intensive therapy unit and its availability.

As long as IORT is concerned, cases should be prioritized by the Operating team and coordinated centrally [9].

We suggest to shortening the case duration of surgery, discussing in advance every potential scenarios with the referring surgeons (e.g. treatment volume and doses according to site, histology

and resection margins) and assigning the docking procedure to an expert team.

Optionally discuss treatment options in multidisciplinary boards with consultants from Anesthesia and Intensive Care and Infectious Diseases.

Patients should be adequately informed.

There are few evidences on the management of radiation treatments' long-term interruptions, due to large-scale emergencies

[10,11]. It is indicated to avoid or in any case limit delaying treatments that could negatively affect the disease control and/or the related symptoms, evaluating comorbidities and balancing the cost/benefit ratio related to infection or contamination risk and the risk of cancer not being treated optimally [3,12–20].

Whenever possible and clinically indicated, providing radiotherapy and/or systemic therapy and/or targeted treatments would potentially reduce the impact on need for level 2/3 hospital beds for elective surgery. Patients over 70, especially with co-morbidities, are at highest risk of death from coronavirus and ideally, they should be seen once the pandemic is over, unless clinically urgent [9].

Table 2 summarizes relevant clinical suggestions for COVID-19 negative or positive patients eligible for IRT treatments in relation to oncological disease.

By adopting these practical suggestions we will protect ourselves and the patients from the risk of infection, respecting oncological outcomes and reducing the workload in any Radiotherapy Service.

The indications reported in this orientation paper cannot leave aside the careful evaluation of the proposed treatment setting, the clinical case and the life expectancy of each patient also taking into account any concomitant or alternative valid therapy.

Conflicts of interest

All the authors have declared no conflict of interest.

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