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ILROG Emergency Guidelines for Radiation Therapy of Hematological Malignancies During the COVID-19 Pandemic

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Abstract:
The ILROG guidelines for using radiation therapy in hematological malignancies are widely used in many countries. The emergency situation created by the COVID-19 pandemic may result in limitations of treatment resources. Furthermore, in recognition of the need to also reduce the exposure of patients and staff to potential infection with COVID-19, the ILROG task force has made recommendations for alternative radiation treatment schemes. The emphasis is on maintaining clinical efficacy and safety by increasing the dose per fraction while reducing the number of daily treatments. The guidance is informed by adhering to acceptable radiobiological parameters and clinical tolerability. The options for delaying or omitting RT in some hematological categories are also discussed.

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The ILROG guidelines for using radiation therapy in hematological malignancies are widely used in many countries. The emergency situation created by the COVID-19 pandemic may result in limitations of treatment resources. Furthermore, in recognition of the need to also reduce the exposure of patients and staff to potential infection with COVID-19, the ILROG task force has made recommendations for alternative radiation treatment schemes. The emphasis is on maintaining clinical efficacy and safety by increasing the dose per fraction while reducing the number of daily treatments. The guidance is informed by adhering to acceptable radiobiological parameters and clinical tolerability. The options for delaying or omitting RT in some hematological categories are also discussed.

Background

The COVID-19 pandemic has created an unprecedented challenge for health care systems worldwide (1,2). Radiation therapy (RT), is regarded as essential in many clinical circumstances and must be provided even during these difficult times. Yet, limitations in resources of space, equipment and staff may result in reduction of treatment capacity. Furthermore, exposure of high-risk patients should be minimized by limiting the number of visits for RT.

General guidelines on RT under these conditions have been issued by several organisations. However, special considerations are pertinent for RT of hematological malignancies. The International Lymphoma Radiation Oncology Group (ILROG) is a well-recognized world-wide organization of radiation oncologists with a record of producing guidelines for modern RT of these diseases which have become standard (3-13). With the present guidelines ILROG aims to help radiation oncologists treating hematological malignancies in making rational choices regarding possible changes to reduce the pressure on the RT institutions in the present emergency situation. With regard to treatment techniques, it is recommended to keep techniques that the staff is familiar with. Simpler techniques are encouraged when resources are limited.

Strategies

There are 3 potential strategies to reduce the demand for RT during the pandemic: omitting, delaying and shortening the RT course. There are also clinical situations where RT can be used as bridging measure resulting in rapid and effective tumor control delaying the need to initiate systemic therapy. Clinicians need to carefully assess disease factors (indication for radiotherapy, expected benefit and natural history of disease) and patients' individual risk in case of COVID-19

infection (age, comorbidities and expected case-fatality rate) to decide on the most appropriate action in patients with hematologic malignancies.

Omitting RT: *when the risk of severe outcomes from COVID-19 infection (aged ≥60 years and/or presence of serious underlying health conditions) outweigh the benefit of RT.*

To be considered in the following situations (14,15):

- Palliative setting, where alternatives can be offered e.g. optimizing pain control
- Localized low-grade lymphomas if completely excised (e.g., follicular lymphoma, marginal zone lymphoma, cutaneous B-cell lymphoma) (13)
- Localised Nodular Lymphocyte Predominant Hodgkin lymphoma if completely excised (16)
- Consolidation RT for DLBCL / aggressive NHL in patients who completed full chemotherapy course and achieved a complete remission

However, if more chemotherapy needs to be given in order to omit RT, this may induce prolonged immunosuppression which may in many clinical situations not be the best decision during a pandemic. Multidisciplinary discussion of each individual case is important.

Delaying RT: *when there is no or little expected adverse effect on outcome from the delay*.

To be considered in the following situations:

- Asymptomatic localised low-grade lymphomas
- Localised Nodular Lymphocyte Predominant Hodgkin lymphoma
- Palliative setting for low-grade lymphomas in stable patients

- Patients who develop COVID-19 infection prior to commencing RT, until the infection is clear, provided the malignancy is not progressing

Shortening RT Course: *using alternative hypofractionation RT regimens when RT could not be omitted or delayed.*

To be considered with the aim of maintaining high cure / palliation rates without undue toxicity. Hypofractionation will always influence the effective dose for late effects, so risks need to be carefully weighed. Radiobiological considerations and clinical experience were used by the ILROG task force to generate the suggested altered dose and fractionation schedules described in Table 1:

- The fractionation sensitivity of hematologic malignancies is under reported in clinical series. However, laboratory data suggest little to no shoulder on the linear-quadratic model of cell survival, leading to a large value of α/β. (17) We therefore expect the biological effect of radiation on lymphoma cells, measured as equivalent dose in 2 Gy fractions, EQD2 (18), to lie between EQD2 using $\alpha/\beta = 10$ Gy and EQD2 = total dose.
- The suggested hypofractionated schemes have little reduction of the total dose aiming to maintain the same level of tumor control. The risks of acute and late toxicity to normal tissues associated with large dose per faction and higher EQD2 for $\alpha/\beta = 3$ Gy are currently mitigated by the use of modern conformal RT techniques. Modern technology offers steep dose gradients around the target tumor with most of the surrounding normal tissues in the low dose volume. Hence, if possible, using technology that provides optimal conformality is even more important here, including good quality control and daily image guidance. The risks are also mitigated by the low RT doses used in hematological malignancies, particularly the indolent types.

- The accuracy of the of the prediction of the α/β model may be less for the larger fraction sizes. Therefore, to mitigate clinical risk we have used dose per fractionation regimens that many in the clinical community are already familiar with and know are well tolerated.
- Hypofractionation has, however, not been rigorously tested in prospective randomized trials in the curative treatment of hematologic malignancies, and therefore the treatment schedules proposed are recommended to apply for the emergency situation of the COVID-19 pandemic only. For patients with substantial cardiac or lung exposure, standard (2 Gy) fractionation should be used if at all possible.

In Table 1 we present guidelines for possible abbreviated fractionation schemes for different clinical presentations that could be used in an emergency like the present COVID-19 pandemic. Other fractionation schemes could also be appropriate, depending on clinical circumstances, if the EQD2 is equivalent to curative standard treatment regimens. We have included guidance for constraints for doses to normal tissues, but it is important to note that the proposed abbreviated treatments should always be used with due consideration and clinical judgement in individual cases.

Author Contributions:

All authors contributed equally. We formed a task force that met daily through the web ex, divided the work to all authors, and over six days we came to an agreement on the document.

Conflicts:

None of the authors has a relevant conflict of interest.

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CURATIVE

Table 1. Standard and proposed emergency fractionation schemes for curative and palliative radiation therapy for hematologic malignancies.

	Standard		Emergency COVID-19 Crisis Alternative Dose-Fractionation				BED Calculations	
	Total Dose	No. Fractions	Comments	Total Dose	No. Fractions	Dose/ Fraction*	*EQD2 α/β = 3 Gy*	*EQD2 α/β = 10 Gy*
HL favorable, chemosensitive	20 Gy	10	Consider hypofractionation only in critical resource shortage situation	18 Gy	6	3 Gy	*22 Gy*	*20 Gy*
HL unfavorable, chemosensitive **NLPHL RT alone**	30.6	17	Consider hypofractionation only in critical resource shortage situation	27 Gy	9	3 Gy	*32 Gy*	*29 Gy*
HL, chemorefractory	40 Gy	20	Consider hypofractionation only in critical resource shortage situation	36-39 Gy	12-13	3 Gy	*43-47 Gy*	*39-42 Gy*
Aggressive NHL, chemosensitive	30 Gy	15	No significant cardiac and/or lung exposure and no overlapping critical organs	25 Gy	5	5 Gy	*40 Gy*	*32 Gy*
			Some cardiac/ lung exposure or overlapping critical organs	27 Gy	9	3 Gy	*32 Gy*	*29 Gy*
Aggressive NHL, chemorefractory disease **Localized aggressive NHL, primary RT alone (not chemo candidate)**	40-50 Gy	20-25	No significant cardiac and/or lung exposure and no overlapping critical organs	30 Gy	6	5 Gy	*48 Gy*	*38 Gy*
			Some cardiac/ lung exposure or overlapping critical organs	36-39 Gy	12-13	3 Gy	*43 -47 Gy*	*39-42 Gy*
Indolent lymphoma, limited stage	24 Gy	12	Start with 4 Gy x1, reevaluate after 2-3 months→ If insufficient response, proceed to definitive RT	4 Gy 20 Gy	1 5	4 Gy 4 Gy	*6 Gy* *28 Gy*	*5 Gy* *23 Gy*
NK/T-cell lymphoma	45 Gy#	25	In patients treated with effective chemotherapy regimen¤	36 Gy	9	4 Gy	*50 Gy*	*42 Gy*
Cutaneous T-cell lymphoma, TSEBT	10-12 Gy	6-10	Give 2-3 treatments, 1 per week, evaluate response after each	8-12 Gy	2-3	4 Gy	*11-17 Gy*	*9—14 Gy*
Solitary bone plasmacytoma or Solitary extramedullary plasmacytoma	40-45 Gy	20-25	Non-spine, non-H&N sites	30 Gy	6	5 Gy	*48 Gy*	*38 Gy*
			Spine or H&N sites	36 Gy	12	3 Gy	*43 Gy*	*39 Gy*
PALLIATIVE								
Symptomatic aggressive	30 Gy	10	Life expectancy ≥ 3 months	25 Gy	5	5 Gy	*40 Gy*	*31 Gy*

NHL (no chemo options)			Life expectancy < 3 months	8 Gy	1	8 Gy	*18 Gy*	*12 Gy*
Symptomatic multiple myeloma	20 Gy	5	No cord compression	8 Gy	1	8 Gy	*18 Gy*	*12 Gy*
			Cord compression	20 Gy	5	4 Gy	*28 Gy*	*23 Gy*
Symptomatic indolent lymphoma	4 Gy	2	No cord compression	4 Gy	1	4 Gy	*6 Gy*	*5 Gy*
			Cord compression	20 Gy	5	4 Gy	*28 Gy*	*23 Gy*
Myeloid sarcoma/leukemia	24 Gy	12	Cranial leptomeningeal disease	8 Gy	2	4 Gy	*11 Gy*	*9 Gy*
			Focal leptomeningeal spine disease, and symptomatic chloroma outside the CNS	12 Gy	3	4 Gy	*17 Gy*	*14 Gy*

Abbreviations: BED, biological equivalent dose; EQD2, equivalent dose in 2-Gy fractions; HL, Hodgkin lymphoma; NLPHL, nodular lymphocyte predominant, Hodgkin lymphoma; RT, radiation therapy; NHL, non-Hodgkin lymphoma; CR, complete response; PR, partial response; PET, positron emission tomography; TSEBT, total skin electron beam therapy; H&N, head and neck; CNS, central nervous system

*When using 5 Gy per fraction to 25-30 Gy or 4 Gy per fraction to 36 Gy, we recommend keeping Dmax to $\leq$ 25 Gy for retina, optic nerves, optic chiasm, cochlea, brainstem, brachial plexus, spinal cord and cauda; V25< 5cc for stomach, duodenum, and other small bowel; mean liver dose < 20 Gy; and mean dose < 6 Gy for kidney (bilateral, but optimal if one kidney can be spared). If these dose constraints cannot be met, we recommend using 3 Gy per fraction to 30 Gy if CR, 33 Gy if PR, 36 Gy if refractory.

#With optimal chemotherapy.

¤ In patients who are not treated with chemotherapy or treated with non-optimal regimens a higher effective dose is needed, and it should be considered to use the standard fractionation if at all possible.