

ILROG emergency guidelines for radiation therapy of hematological malignancies during the COVID-19 pandemic

Joachim Yahalom,¹ Bouthaina Shbib Dabaja,² Umberto Ricardi,³ Andrea Ng,⁴ N. George Mikhaeel,⁵ Ivan R. Vogelius,⁶ Tim Illidge,⁷ Shunan Qi,⁸ Andrew Wirth,⁹ and Lena Specht,⁶ on behalf of the International Lymphoma Radiation Oncology Group (ILROG)

¹Memorial Sloan Kettering Cancer Center, New York, NY; ²MD Anderson Cancer Center, Houston, TX; ³Department of Oncology, University of Turin, Turin, Italy; ⁴Dana-Farber Cancer Institute, Boston, MA; ⁵Guy's & St Thomas' Hospital, London, United Kingdom; ⁶Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ⁷National Institute for Health Research (NIHR) Manchester Biomedical Research Centre, The University of Manchester, Christie National Health Service (NHS) Foundation Trust, Manchester, United Kingdom; ⁸National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China; and ⁹Peter MacCallum Cancer Institute, Melbourne, VIC, Australia

The International Lymphoma Radiation Oncology Group (ILROG) guidelines for using radiation therapy (RT) 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. (*Blood*. 2020;135(21):1829-1832)

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, including 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 organizations. However, special considerations are pertinent for RT of hematological malignancies. The International Lymphoma Radiation Oncology Group (ILROG) is a well-recognized worldwide organization of radiation oncologists with a record of producing guidelines for modern RT of these diseases that have become standard.³⁻¹³ With the present guidelines, ILROG aims to help radiation oncologists treating hematological malignancies make rational choices regarding possible changes to reduce the pressure on RT institutions in the current emergency situation. With regard to treatment techniques, keeping those with which the staff is familiar is recommended. 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 in which RT can be used

as a bridging measure, resulting in rapid and effective tumor control, delaying the need to initiate systemic therapy. To decide on the most appropriate action in patients with hematologic malignancies, 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).

Omitting RT

When the risk of severe outcomes from COVID-19 infection (for those aged ≥ 60 years and/or with serious underlying health conditions) outweighs the benefit of RT, omitting RT is to be considered in the following situations^{14,15}:

- in a palliative setting, where alternatives can be offered (eg, optimizing pain control);
- for localized low-grade lymphomas if completely excised (eg, follicular lymphoma, marginal zone lymphoma, cutaneous B-cell lymphoma)¹³;
- for localized nodular lymphocyte-predominant Hodgkin lymphoma if completely excised¹⁶; and
- in consolidation RT for diffuse large B-cell lymphoma/aggressive non-Hodgkin lymphoma (NHL) in patients who have completed a full chemotherapy course and achieved a complete remission.

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

	Standard		Emergency COVID-19 crisis alternative dose fractionation			BED calculations, Gy		
	Total dose, Gy	No. of fractions	Comments	Total dose, Gy	No. of fractions	Dose/Fraction, Gy*	EQD2 $\alpha/\beta = 3$ Gy	EQD2 $\alpha/\beta = 10$ Gy
Curative								
HL favorable, chemosensitive	20	10	Consider hypo-fractionation only in a critical resource shortage situation	18	6	3	22	20
HL unfavorable, chemosensitive NLPHL RT alone	30.6	17	Consider hypo-fractionation only in a critical resource shortage situation	27	9	3	32	29
HL, chemorefractory	40	20	Consider hypo-fractionation only in a critical resource shortage situation	36-39	12-13	3	43-47	39-42
Aggressive NHL, chemosensitive	30	15	No significant cardiac and/or lung exposure and no overlapping critical organs	25	5	5	40	32
			Some cardiac/lung exposure or overlapping critical organs	27	9	3	32	29
Aggressive NHL, chemorefractory disease Localized aggressive NHL, primary RT alone (not chemo candidate)	40-50	20-25	No significant cardiac and/or lung exposure and no overlapping critical organs	30	6	5	48	38
			Some cardiac/lung exposure or overlapping critical organs	36-39	12-13	3	43-47	39-42
Indolent lymphoma, limited stage	24	12	Start with 4 Gy $\times 1$, reevaluate after 2-3 mo \rightarrow	4	1	4	6	5
			If insufficient response, proceed to definitive RT	20	5	4	28	23
NK-/T-cell lymphoma	45†	25	In patients treated with effective chemotherapy regimen‡	36	9	4	50	42
Cutaneous T-cell lymphoma, TSEBT	10-12	6-10	Give 2-3 treatments, 1 per week, evaluate response after each	8-12	2-3	4	11-17	9-14
Solitary bone plasmacytoma or solitary extramedullary plasmacytoma	40-45	20-25	Nonspine, non-H&N sites	30	6	5	48	38
			Spine or H&N sites	36	12	3	43	39

BED, biological equivalent dose; chemo, chemotherapy; CNS, central nervous system; EQD2, equivalent dose in 2-Gy fractions; H&N, head and neck; HL, Hodgkin lymphoma; NK, natural killer; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; TSEBT, total skin electron beam therapy.

*When using 5 Gy per fraction to 25 to 30 Gy or 4 Gy per fraction to 36 Gy, we recommend keeping the maximum dose (Dmax) to ≤ 25 Gy for retina, optic nerves, optic chiasm, cochlea, brainstem, brachial plexus, spinal cord, and cauda; V25 (the volume of the organ receiving 25 Gy) < 5 cc for stomach, duodenum, and other small bowel; mean liver dose < 20 Gy; and mean dose < 6 Gy for kidney (bilateral, but optimal if 1 kidney can be spared). If these dose constraints cannot be met, we recommend using 3 Gy per fraction to 27 Gy for chemosensitive disease and 36 Gy for chemorefractory disease.

†With optimal chemotherapy.

‡In patients who are not treated with chemotherapy, or in those treated with nonoptimal regimens, a higher effective dose is needed, and use of the standard fractionation should be considered if at all possible.

Table 1. (continued)

	Standard		Emergency COVID-19 crisis alternative dose fractionation				BED calculations, Gy	
	Total dose, Gy	No. of fractions	Comments	Total dose, Gy	No. of fractions	Dose/Fraction, Gy*	EQD2 $\alpha/\beta = 3$ Gy	EQD2 $\alpha/\beta = 10$ Gy
Palliative								
Symptomatic aggressive NHL (no chemo options)	30	10	Life expectancy ≥ 3 mo	25	5	5	40	31
			Life expectancy < 3 mo	8	1	8	18	12
Symptomatic multiple myeloma	20	5	No cord compression	8	1	8	18	12
			Cord compression	20	5	4	28	23
Symptomatic indolent lymphoma	4	2	No cord compression	4	1	4	6	5
			Cord compression	20	5	4	28	23
Myeloid sarcoma/ leukemia	24	12	Cranial leptomeningeal disease	8	2	4	11	9
			Focal leptomeningeal spine disease, and symptomatic chloroma outside the CNS	12	3	4	17	14

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†With optimal chemotherapy.

‡In patients who are not treated with chemotherapy, or in those treated with nonoptimal regimens, a higher effective dose is needed, and use of the standard fractionation should be considered if at all possible.

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, delaying RT is to be considered in the following situations:

- for asymptomatic localized low-grade lymphomas;
- for localized nodular lymphocyte-predominant Hodgkin lymphoma;
- in a palliative setting for low-grade lymphomas in stable patients; and
- for 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 cannot be omitted or delayed is 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 experiences 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 underreported 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 fraction 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 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 only to the emergency situation of the COVID-19 pandemic. 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.

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REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention [published online ahead of print 24 February 2020]. *JAMA*. doi:10.1001/jama.2020.2648.
2. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337.
3. Constine LS, Yahalom J, Ng AK, et al. The role of radiation therapy in patients with relapsed or refractory Hodgkin lymphoma: guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2018;100(5):1100-1118.
4. Dabaja BS, Hoppe BS, Plastaras JP, et al. Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines [published correction appears in *Blood*. 2019; 133(12):1384-1385]. *Blood*. 2018;132(16):1635-1646.
5. Dabaja BS, Specht L, Yahalom J. Lymphoblastic lymphoma: guidelines from the International Lymphoma Radiation Oncology Group (ILROG). *Int J Radiat Oncol Biol Phys*. 2018;102(3):508-514.
6. Illidge T, Specht L, Yahalom J, et al; International Lymphoma Radiation Oncology Group. Modern radiation therapy for nodal non-Hodgkin lymphoma—target definition and dose guidelines from the International

- Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2014;89(1):49-58.
7. Ng AK, Yahalom J, Goda JS, et al. Role of radiation therapy in patients with relapsed/refractory diffuse large B-cell lymphoma: guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2018;100(3):652-669.
8. Specht L, Yahalom J, Illidge T, et al; ILROG. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the International Lymphoma Radiation Oncology Group (ILROG). *Int J Radiat Oncol Biol Phys*. 2014;89(4):854-862.
9. Tsang RW, Campbell BA, Goda JS, et al. Radiation therapy for solitary plasmacytoma and multiple myeloma: guidelines from the International Lymphoma Radiation Oncology Group [published correction appears in *Int J Radiat Oncol Biol Phys*. 2018;102(5):1602]. *Int J Radiat Oncol Biol Phys*. 2018;101(4):794-808.
10. Yahalom J, Illidge T, Specht L, et al; International Lymphoma Radiation Oncology Group. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2015;92(1):11-31.
11. Bakst RL, Dabaja BS, Specht LK, Yahalom J. Use of radiation in extramedullary leukemia/chloroma: guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2018;102(2):314-319.

12. Pinnix CC, Yahalom J, Specht L, Dabaja BS. Radiation in central nervous system leukemia: guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2018;102(1):53-58.
13. Specht L, Dabaja B, Illidge T, Wilson LD, Hoppe RT; International Lymphoma Radiation Oncology Group. Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2015;92(1):32-39.
14. National Comprehensive Cancer Network (NCCN). B-cell lymphomas. 2020. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 2 January 2020.
15. National Comprehensive Cancer Network (NCCN). Primary cutaneous lymphoma. 2020. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 2 January 2020.
16. Appel BE, Chen L, Buxton AB, et al. Minimal treatment of low-risk, pediatric lymphocyte-predominant Hodgkin lymphoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2016;34(20):2372-2379.
17. Aldridge DR, Radford IR. Explaining differences in sensitivity to killing by ionizing radiation between human lymphoid cell lines. *Cancer Res*. 1998;58(13):2817-2824.
18. Bentzen SM, Dörr W, Gahbauer R, et al. Bioeffect modeling and equieffective dose concepts in radiation oncology—terminology, quantities and units. *Radiother Oncol*. 2012; 105(2):266-268.

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A list of members of the International Lymphoma Radiation Oncology Group (ILROG) steering committee appears in the supplemental appendix.

ORCID profiles: N.G.M., 0000-0003-0359-0328; I.R.V., 0000-0002-8877-1218; L.S., 0000-0002-6902-2190.

Correspondence: Joachim Yahalom, C/O Beatrice Fregonese, ILROG Central Office, Memorial Sloan Kettering Cancer Center, Koch Building, Room 20-193D, 530 East 74th St, New York, NY, 10021; e-mail: yahalomj@mskcc.org.

Footnotes

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