

Advantages of proton therapy in the treatment of lymphomas are confirmed by the data from international centres as well as data from the Proton Therapy Center in Prague - sparing of vital organs and risk reduction are unquestionable

The latest version of the NCCN treatment protocols created by globally recognized experts in the treatment of cancer has extended the general recommendations for the proton therapy in the treatment of all types of lymphomas.

News in the proton radiotherapy of malignant lymphomas

Radiotherapy (RT) is still an important therapeutic modality in the treatment of lymphomas. The combination of system therapy with radiation therapy will provide a high probability of cure in the majority of patients with Hodgkin's lymphoma (HL) and some patients with non-Hodgkin's lymphoma (NHL). However, RT is considered a modality associated with increased risk of late and very late toxicity. RT may increase the risk of severe illness and death

from non-lymphoma diseases several years or even decades after a successful treatment of lymphoma. This risk must be taken into account particularly in patients with long estimated survival. Therefore, we are witnessing efforts for either complete omission of RT from the treatment regimen for certain types and stages of lymphoma, or for the reduction of target tissue volume (a change from high-volume irradiation to the irradiation of the initially affected lymph nodes or regions), often with the reduction of the radiation load for the surrounding healthy tissues (modern RT techniques, including proton RT).

RT techniques in the treatment of lymphomas

Lymphoma RT is associated with certain specificities compared with RT of most solid (non-haematological) tumours. Lymphoma, as a radiosensitive disease, usually does not require the use of a total radiation dose exceeding the limits of the surrounding tissues. However, minimizing of exposure of surrounding healthy tissues is essential. Their irradiation is associated with significant limitations for the patient, as the development of acute postradiation toxicity, but may also pose a risk of late and very late toxicity. Therefore, classical dose limits for risk organs cannot be used in lymphomas as in the RT of the majority of solid tumours.

In the last decade, we have seen the spectrum of available RT techniques significantly extended. In the field of photon RT techniques, 3D conformal RT (3D-RT) is commonly available. Advanced techniques include intensity modulated RT (IMRT), volumetric arc RT (VMAT) and helical tomotherapy. As for RT techniques using another source of ionizing radiation, proton RT is available (pencil beam scanning technique).



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Photon techniques

However, photon techniques (IMRT, VMAT, tomotherapy) are considered less useful when compared with the benefits for other malignancies. In addition, the older 3D-CRT still maintains its position. The use of modern techniques should be individualized after considering the potential benefits and risks. The benefits of these highly conformal techniques primarily include the reduction of the volume of tissue exposed to high doses of radiation (i.e. a dose close to the prescribed dose for the target volume). The disadvantages of these techniques include mainly low-dose bath (i.e. a large volume of tissue irradiated with middle and low doses of radiation, possibly increasing the risk of induction of secondary malignancies and late functional impairment) and a theoretical risk of target volume underdosing in the irradiation of moving targets without the possibility of fixation or tracking (e.g. mediastinal irradiation without gating).

Mediastinal irradiation in the maximum inspiration (deep inspiration breath-hold DIBH)

DIBH in mediastinal lymphoma RT is currently a debated and topical subject. This technique is relatively simple and feasible in most patients with mediastinal lymphomas. It uses active control of the patient's breathing. Hence, irradiation is active only in deep inspiration (patients are usually able to maintain this position for 15 to 20 seconds). Centres using DIBH must have the equipment necessary to capture the spirometry curves and must be able to synchronize irradiation with the specified respiratory phase of the patient (irradiation is shut down at the beginning of the patient's exhalation). Active breathing control increases the sparing of lung tissue, the heart, and coronary arteries, primarily in upper mediastinal tumours RT. Moreover, it reliably ensures a total fixation of the mediastinum during RT and reduces the risk of missing the target volume.

Proton therapy and current data

Proton radiotherapy is the next logical step in the evolution of radiotherapy, as the standard photon RT has reached its physical limits. Data on the safety of proton RT are long-term, e.g. in paediatric cancer patients. Currently, there are new results of 2 clinical studies of treatment outcomes and toxicity of proton RT in mediastinal lymphomas. The first study by Hoppe et al. published in August 2014 dealing with involved node proton RT in the treatment of Hodgkin lymphoma reports the prospective phase II study results. The available results indicate that it is a safe treatment as regards the undesirable side effects and the treatment outcomes. The study was performed in a cohort of 22 patients with a newly diagnosed Hodgkin's lymphoma in the period from June 2009 to June 2013. The patients were in the stages I-III. 3 irradiation plans were performed after the completion of chemotherapy - one plan for proton irradiation and 2 plans for photon radiotherapy (3D conformal radiotherapy, IMRT). The optimal chosen plan was the one associated with the dose of 4 Gy and higher in the lowest body volume. 15 patients underwent proton RT. Median follow-up of patients after proton RT was 37 months (26-55 months). The evaluated data indicate 93% survival without a relapse of the disease 3 years after the treatment. None of the patients suffered from a severe acute or late adverse effect (grade III and higher).

The second study from Massachusetts General Hospital at Harvard Medical School by Winkfield et al. published in October 2015 deals with the evaluation of the 8-year results of proton RT in mediastinal lymphomas. This is the largest study evaluating the

outcomes in 46 patients with HL and NHL (34 HL, 12 NHL). Proton RT significantly reduces the dose for cardiac structures, lungs, spinal cord and the integral dose. It is a very well-tolerated treatment that also provides excellent local control (5-year OS of 98%, 5-year PFS 80%, 5-year TFS 78%).

It has been repeatedly demonstrated that proton RT reduces the exposure of healthy surrounding organs (high, medium and low doses) and minimizes the total radiation load of the patient. The use of the proton RT reduces the risk of acute pulmonary toxicity (a significant reduction of the risk of radiation pneumonitis, particularly in large-scale or repeated irradiation of the lymph system over the diaphragm), the incidence of spinal cord lesions (especially of Lhermitte's syndrome), sometimes also the incidence of dysphagia and odynophagia, xerostomia, nausea, diarrhoea and fatigue. The reduction of the risk of late and very late toxicity has already been mentioned. Moreover, proton RT often allows repeated irradiation in chemoresistant lymphomas with the possibility of dose escalation (repeated irradiation after TBI, repeated irradiation of the mediastinum or an affection under the diaphragm).

3 years ago, prestigious treatment protocols of the American organization the National Comprehensive Cancer Network (NCCN) included a reference to the possible use of proton RT in all the types of lymphomas. The latest version of these prestigious protocols created by globally recognized experts in the treatment of cancer has extended the general recommendations for the proton therapy in the treatment of all types of lymphomas. Proton RT is

now considered an advanced RT technique in lymphomas that may offer a clinically significant and substantial advantage in the form of sparing of important high-risk organs. Moreover, these protocols negate the requirement for randomized clinical trials for the proton RT (as a technique with a potential to reduce late and very late toxicity) to be included in the clinical practice. A technique that is associated with clinically significant minimization of the risk of organ exposure, still with maintained irradiation of the target volume, should be considered, regardless of the availability of the randomized clinical trials results. It is very unlikely that we will soon have data that would enable us to quantify the risk of late toxicity after individual advanced RT techniques, since a minimum of 10 years and longer is necessary to evaluate these results. Therefore, the theoretical assumption of surrounding tissue sparing and of good irradiation of the target volume is sufficient for the indication of proton RT.

Experience of experts from the Proton Center in Prague

A total of 38 patients with a lymphoma were treated in the Proton Therapy Center from 4/2013 to 10/2015. 4 further patients with a mediastinal affection are being prepared. In the above stated group of patients, 35 patients (29 with HL, 6 with NHL) underwent proton RT of an affection located over the diaphragm including the mediastinum, 3 patients (all of them with HL) were irradiated in another area affected by lymphoma (axillary lymph nodes, neck and supraclavicular lymph nodes lymph after previous irradiation, spine). The IS-RT definition of the target volume has been used since 3/2015 (12 patients). Since 4/2015, the maximum inspiration technique (DIBH) has been used in most patients - a total of 10 patients. The proton RT technique used in these patients was pencil beam scanning (PBS). To our knowledge, this is the first publication of patients who received the PBS radiotherapy in deep inspiration (DIBH). None of the patients developed clinically significant toxicity associated with the radiotherapy. None of the 18 evaluable patients (3 years or more after the end of irradiation) suffered from recurrences in the irradiated area or severe postradiation toxicity (grade II and higher).

Conclusion

Proton RT, in the Czech Republic also available in its most advanced form (pencil beam scanning with DIBH RT), should always be considered in patients requiring mediastinal RT or repeated irradiation.

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