Applications of new irradiation modalities in patients with lymphoma: Promises and uncertainties

Youlia M Kirova, Cyrus Chargari

Youlia M Kirova, Cyrus Chargari, Department of Radiation Oncology, Institut Curie 26, rue d’Ulm, 75248 Paris, Cedex 05, France

Author contributions: Kirova YM designed the study; Kirova YM and Chargari C wrote the paper.

Correspondence to: Youlia M Kirova, MD, Department of Radiation Oncology, Institut Curie 26, rue d’Ulm, 75248 Paris, Cedex 05, France. youlia.kirova@curie.net

Telephone: +33-1-44324193 Fax: +33-1-53102653

Received: January 15, 2011 Revised: March 2, 2011

Accepted: March 9, 2011

Abstract

New highly conformal irradiation modalities have emerged for treatment of Hodgkin lymphoma. Helical Tomotherapy offers both intensity-modulated irradiation and accurate patient positioning and was shown to significantly decrease radiation doses to the critical organs. Here we review some of the most promising applications of helical tomotherapy in Hodgkin disease. By decreasing doses to the heart or the breast, helical tomotherapy might decrease the risk of long-term cardiac toxicity or secondary breast cancers, which are major concerns in patients receiving chest radiotherapy. Other strategies, such as debulking radiotherapy prior to stem cell transplantation or total lymphoid irradiation may be clinically relevant. However, helical tomotherapy may also increase the volume of tissues that receive lower doses, which has been implicated in the carcinogenesis process. Prospective assessments of these new irradiation modalities of helical tomotherapy are required to confirm the potential benefits of highly conformal therapies applied to hematological malignancies.

© 2011 Baishideng. All rights reserved.

Key words: Hodgkin lymphoma; Helical tomotherapy; Cardiac toxicity; Secondary cancers

Peer reviewer: Ying Xiao, PhD, Professor, Director, Medical Physics, Department of Radiation Oncology, Thomas Jefferson University Hospital, Philadelphia, PA 19107-5097, United States

Kirova YM, Chargari C. Applications of new irradiation modalities in patients with lymphoma: Promises and uncertainties. World J Radiol 2011; 3(3): 66-69 Available from: URL: http://www.wjgnet.com/1949-8470/full/v3/i3/66.htm DOI: http://dx.doi.org/10.4329/wjr.v3.i3.66

INTRODUCTION

Radiation therapy still plays a major role in the management of hematological malignancies. Its place and modalities for treatment of lymphoma have evolved over recent decades. First, randomized studies supported reduction of field size and dose radiation in treatment programs for Hodgkin disease[1]. These developments were encouraged by reports that mediastinal radiotherapy was associated with cardiac toxicity and second malignancies, particularly when chemotherapy agents were used concomitantly or sequentially. Second, sophisticated imaging technologies and new radiation delivery techniques have become available[2]. With the recent advances in irradiation devices, new intensity modulated irradiation modalities have emerged. Those offer both increased target dose conformity and improved normal tissue avoidance. Helical tomotherapy combines inversely planned intensity modulated radiotherapy (IMRT) with on-board megavoltage imaging devices[3]. In this way, it has become possible to tailor very sharp dose distributions around the target volumes, close to critical organs[4]. It has emerged as one of the most promising techniques for IMRT delivery.

Here we summarize some of the most promising applications of helical tomotherapy in patients with hematological malignancies.

CLINICAL APPLICATIONS

For lymphoma irradiation, it is now the standard of care
to use involved-field radiotherapy rather than the extended radiation fields of the past. In this setting of volume reduction, implementation of new strategies aimed at further improving target coverage is promising. Helical tomotherapy combines inversely planned IMRT with on-board megavoltage imaging devices. In this way, it has become possible to tailor very sharp dose distributions around the target volumes, close to critical organs. Improving dose conformity around the volumes has become an important end-point for radiation oncologists. Dosimetric results from planning studies of helical tomotherapy have demonstrated its ability in better sparing critical organs from irradiation, in comparison with more conventional irradiation modalities. Helical tomotherapy was shown to provide similar target coverage, and to improve both dose conformity and dose homogeneity within the target volume. This modern irradiation device allows accurate repositioning and critical organs visualization. Tomita et al. compared radiation treatment plans that used IMRT with helical tomotherapy or three-dimensional conformal radiation therapy for nasal natural killer/T-cell lymphoma. Authors found that IMRT achieved significantly better coverage of the planning target volume (PTV), with more than 99% of the PTV receiving 90% of the prescribed dose, whereas 3D-CRT could not provide adequate coverage of the PTV, with only 90.0% receiving 90% (P < 0.0001). These results and others demonstrated that helical tomotherapy could significantly improve target coverage when the PTV was close to critical organs.

Prospective data with long-term follow-up evidenced that heart dose exposure may cause cardiac disease and adversely affect quality of life, particularly in young patients with mediastinal radiotherapy for Hodgkin lymphoma. Hudson et al. assessed the impact of treatment toxicity on long-term survival in pediatric Hodgkin's disease, and reported an excess mortality from cardiac disease, and reported an excess mortality from cardiac disease and reported an excess mortality from cardiac disease and incidence of second malignancies. This risk becomes significantly elevated 5 to 10 years after irradiation for Hodgkin's lymphoma and the incidence of breast cancer risk, and suggested significant relative risk reduction for second cancers with involved field radiotherapy. In other malignancies, our retrospective data in patients with solitary plasmacytoma demonstrated that doses to critical organs, including the heart, lungs, or kidneys could be decreased. This may be clinically relevant in heavily pretreated patients who are at risk for subsequent treatment-related cardiac toxicity. High response rates were also reported and encouraged further prospective assessment, and most patients experienced a complete response prior to stem cell allograft.

An increased risk of secondary malignancies has been reported after radiotherapy for lymphoma. In particular, young patients have a high risk of developing breast cancer in their life after mediastinal radiotherapy for a lymphoma. The improved outcome among patients with Hodgkin's lymphoma has been associated with increased incidence of second malignancies. This risk becomes significantly elevated 5 to 10 years after irradiation for Hodgkin lymphoma and the incidence of breast cancer has been reported to increase by a factor of 4.3 (95% CI: 2.0-8.4) for patients treated with mantle irradiation. Koh et al. quantified the reduction in radiation dose to normal tissues and modeled the reduction in secondary breast cancer risk, and suggested significant relative risk reduction for second cancers with involved field radiotherapy. While the dose response for radiation dose above 10 Gy remains uncertain, carcinogenesis after radiation is exacerbated by the large dose gradient across the breast and treatment field position. Although helical tomotherapy might significantly decrease high doses delivered to the breast, it increases the volume that receives lower doses, which has also been implicated in the carcinogenesis process. For that reason, intensity-modulated irradiation should not be delivered in children outside of a clinical trial.
Finally, preliminary results suggested that helical tomotherapy could be employed for total lymphoid irradiation in the preparative regimens for allogeneic bone marrow and chronic graft-versus-host disease. When using conventional irradiation devices, extended source-to-skin patient setup and/or field matching are required, and all critical organs are within the beam coverage. Treatment planning with helical tomotherapy for total lymphoid irradiation in adults demonstrated that the dose to the spinal cord, kidneys, intestinal compartment, and lungs could be decreased\cite{21,22}.

**ALTERNATIVE IRRADIATION MODALITIES**

We have pointed out the potential of helical tomotherapy in the light of our institutional experience. Actually, helical tomotherapy is not the only solution to improve both dose conformity and dose homogeneity within the target volume, and its availability remains rather limited (low number of helical tomotherapy devices). Other IMRT techniques could also be applied for delivering highly conformal irradiation. In 2005, Goodman et al.\cite{23} assessed the feasibility and potential advantages of linear accelerator based IMRT in the treatment of lymphoma involving large mediastinal disease volumes or requiring reirradiation. Compared to conventional parallel-opposed plans and conformal radiotherapy plans, IMRT could decrease the dose delivered to the lung by 12% and 14%, respectively. The PTV coverage was also improved, compared with conventional RT\cite{23}. Recent dosimetric data demonstrated that the forward planned IMRT technique could be easily used for improving PTV conformity while sparing normal tissue in Hodgkin’s lymphoma\cite{24}.

Volumetric modulated arc therapy (VMAT) has also demonstrated its ability in tailoring accurate dose distributions around the target volumes. Weber et al.\cite{25} compared VMAT to conventional fixed beam IMRT in ten patients with early Hodgkin disease. They found no difference in levels of dose homogeneity. However, for involved node radiotherapy, doses to the PTV and OAR were higher and lower with VMAT when compared to IMRT, respectively.

Finally, the dosimetric advantages of proton therapy could also be used for reducing the risk of late radiation-induced toxicity related to low-to-moderate doses in critical organs. Chera et al.\cite{26} compared the dose distribution in Hodgkin’s lymphoma patients using conventional radiotherapy, IMRT, and 3D proton therapy in Hodgkin’s lymphoma patients with stage II disease. Authors found that 3D proton therapy could reduce the dose to the breast, lung, and total body. However, the availability of...
proton therapy is very low and only a few patients could benefit from this highly conformal irradiation modulation.

CONCLUSION

There is growing dosimetric evidence that highly conformal irradiation modalities may improve critical organs sparing, with clinically relevant consequences. Prospective clinical evaluation of helical tomotherapy modalities is required to confirm the potential benefits of highly conformal therapies applied to hematological malignancies.

REFERENCES

1. Yahalom J. Transformation in the use of radiation therapy of Hodgkin lymphoma: new concepts and indications lead to modern field design and are assisted by PET imaging and intensity modulated radiation therapy (IMRT). Eur J Haematol Suppl 2005: 90-97

2. Girinsky T, Ghalibafian M. Radiotherapy of hodgkin lymphoma: indications, new fields, and techniques. Semin Radiat Oncol 2007; 17: 206-222

3. Walsh JS, Patel RR, Ritter MA, Harari PM, Mackie TR, Mehta MP. Helical tomotherapy: an innovative technology and approach to radiation therapy. Technol Cancer Res Treat 2002; 1: 311-316

4. Beavis AW. Is tomotherapy the future of IMRT? Br J Radiol 2004; 77: 285-295

5. Ferme C, Eghbali H, Meerwaldt JH, Rieux C, Bosq J, Berger F, Girinsky T, Brice P, van't Veer MB, Waley MS, Jaubert J, Henry-Amar M. Chemo-therapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 2007; 357: 1916-1927

6. Tomita N, Kodaira T, Tachibana H, Nakamura T, Nakahara R, Inokuchi H, Mizoguchi N, Takada A. A comparison of radiation treatment plans using IMRT with helical tomotherapy and 3D conformal radiotherapy for nasal natural killer/T-cell lymphoma. Br J Radiol 2009; 82: 756-763

7. Hudson MM, Poquette CA, Lee J, Greenwald CA, Shah A, Luo X, Thompson EL, Willimas JA, Kun LE, Crist WM. Increased mortality after successful treatment for Hodgkin's disease. J Clin Oncol 1998; 16: 3592-3600

8. Prosnitz RG, Chen YH, Marks LB. Cardiac toxicity following thoracic radiation. Semin Oncol 2005; 32: 571-580

9. Vlachaki MT, Kumar S. Helical tomotherapy in the radiotherapy treatment of Hodgkin's disease - a feasibility study. J Appl Clin Med Phys 2010; 11: 3042

10. Gagliardi G, Constone LS, Moiseenko V, Correa C, Pierce LJ, Allen AM, Marks LB. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys 2010; 76: 577-585

11. Chargari C, Vernant JP, Tamberini J, Zelfiki S, Fayolle M, Campana F, Fourquet A, Kirova YM. Feasibility of Helical Tomotherapy for Debulking Irradiation Before Stem Cell Transplantation in Malignant Lymphoma. Int J Radiat Oncol Biol Phys 2010; Epub ahead of print

12. Chargari C, Zelfiki S, Kirova YM. Potential of helical tomotherapy for sparing critical organs in a patient with AIDS who was treated for Hodgkin lymphoma. Clin Infect Dis 2009; 48: 687-689

13. Kirova YM, Chargari C, Amessis M, Vernant JP, Dhedin N. Concurrent involved field radiation therapy and temsylomulinus in refractory mantle cell lymphoma (MCL). Am J Hematol 2010; 85: 892

14. Chargari C, Kirova YM, Zelfiki S, Cauza L, Amessis M, Dendere R, Campana F, Fourquet A. Solitary plasmocytoma: improvement in critical organs sparing by means of helical tomotherapy. Eur J Haematol 2009; 83: 66-71

15. Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP, Diller LR, Constine LS, Smith RA, Mahoney MC, Morris EA, Montgomery LL, Landier W, Smith SM, Robison LL, Oeffinger KC. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. Ann Intern Med 2010; 152: 444-455; W114-W154

16. Alm El-Din MA, El-Badawy SA, Taghian AG. Breast cancer after treatment of Hodgkin's lymphoma: general review. Int J Radiat Oncol Biol Phys 2008; 72: 1291-1297

17. Metayer C, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, Joensuu T, van Leeuwen FE, van't Veer MB, Curtis RE, Holowaty EJ, Andersons M, Wiklund T, Gospodarowicz M, Travis LB. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol 2000; 18: 2435-2443

18. Zellmer DL, Wilson JF, Janjan NA. Dosimetry of the breast for determining carcinogenic risk in mantle irradiation. Int J Radiat Oncol Biol Phys 1991; 21: 1343-1351

19. Koh ES, Tran TH, Heydarian M, Sachs RK, Tsang RW, Brenner DJ, Pintille M, Xu T, Chung J, Paul N, Hodgson DC. A comparison of mantle versus involved-field radiotherapy for Hodgkin's lymphoma: reduction in normal tissue dose and second cancer risk. Radiat Oncol 2007; 2: 13

20. Hodgson DC, Koh ES, Tran TH, Heydarian M, Tsang R, Pintille M, Xu T, Huang L, Sachs RK, Brenner DJ. Individualized estimates of second cancer risks after contemporary radiation therapy for Hodgkin lymphoma. Cancer 2007; 110: 2576-2586

21. McCutchen KW, Watkins JM, Eberts P, Terwilliger LE, Ashenafi MS, Jenrette JM 3rd. Helical tomotherapy for total lymphoid irradiation. Radiat Med 2008; 26: 622-626

22. Wong JY, Liu A, Schultheiss T, Popplewell L, Stein A, Rosenthal J, Issenhal M, Forman S, Solmon C. Targeted total marrow irradiation using three-dimensional image-guided tomographic intensity-modulated radiation therapy: an alternative to standard total body irradiation. Biol Blood Marrow Transplant 2006; 12: 306-315

23. Goodman KA, Toner S, Hunt M, Wu EJ, Yahalom J. Intensity-modulated radiotherapy for lymphoma involving the mediastinum. Int J Radiat Oncol Biol Phys 2005; 62: 198-206

24. Cella L, Liuazzi R, Magliulo M, Conson M, Camera L, Salvatore M, Pacelli R. Radiotherapy of large target volumes in Hodgkin's lymphoma: normal tissue sparing capability of forward IMRT versus conventional techniques. Radiat Oncol 2010; 5: 33

25. Weber DC, Poguet N, dipasquale G, Cozzi L. Involved-node and involved-field volumetric modulated arc vs. fixed beam intensity-modulated radiotherapy for female patients with early-stage supra-diaphragmatic Hodgkin lymphoma: a comparative planning study. Int J Radiat Oncol Biol Phys 2009; 75: 1578-1586

26. Chera BS, Rodriguez C, Morris KG, Louis D, Yeung D, Li Z, Mendenhall NP. Dosimetric comparison of three different involved nodal irradiation techniques for stage II Hodgkin's lymphoma patients: conventional radiotherapy, intensity-modulated radiotherapy, and three-dimensional proton radiotherapy. Int J Radiat Oncol Biol Phys 2009; 75: 1173-1180

S-Editor Cheng JX L-Editor O'Neill M E-Editor Zheng XM