Dosimetric comparison of intensity modulated proton therapy and intensity modulated radiotherapy in primary mediastinal B-cell lymphoma

การศึกษาเพื่อประเมินปริมาณรังสีของการวางแผนการรักษาโดยเทคนิคการฉายรังสีปรับความเข้มด้วย โปรตอน (IMPT) และเทคนิคการฉายรังสีปรับความเข้มด้วยโฟตอน (IMRT) ในมะเร็งต่อมน้ำเหลืองบริเวณทรวงอกระยะต้น

Sompat Vatanasuvran[1] ,Tassapong Raiyawa[2]

[1]Division of Therapeutic Radiology and Oncology, Department of Radiology, Faculty of Medicine, Chulalongkorn University

[2]Division of Therapeutic Radiology and Oncology, Department of Radiology, King Chulalongkorn Memorial Hospital, The Thai Red Cross Society

Corresponding author

Sompat Vatanasuvran

Division of Therapeutic Radiology and Oncology, Department of Radiology, Faculty of Medicine, Chulalongkorn University

1873 Rama IV Road, Pratumwan, Bangkok, 10330

E-mail: sompat.v20@chula.md

สมภัทร วัฒนาสุวรรณ[1], ทัศน์พงศ์ รายยวา[2]

[1]สาขารังสีรักษาและมะเร็งวิทยา ฝ่ายรังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

[2]สาขารังสีรักษาและมะเร็งวิทยา ฝ่ายรังสีวิทยา โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย

ผู้นิพนธ์ประสานงาน

สมภัทร วัฒนาสุวรรณ

สาขารังสีรักษาและมะเร็งวิทยา ฝ่ายรังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

1873 ถนน พระราม 4 แขวงปทุมวัน เขตปทุมวัน กรุงเทพมหานคร10330

อีเมล: sompat.v20@chula.md

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บทคัดย่อ

หลักการและเหตุผล: มะเร็งต่อมน้ำเหลืองชนิดที่ไม่ใช่ฮอดจ์กิน เป็นมะเร็งในระบบโลหิตที่มีการพยากรณ์โรคที่ดีมากหลังจากได้รับการรักษาด้วยเคมีบำบัดและการฉายรังสี อย่างไรก็ตามผู้ป่วยที่ได้รับการฉายรังสีโดยเฉพาะที่ทรวงอกอาจมีโอกาสเกิดผลข้างเคียงในระยะยาว เช่น กล้ามเนื้อหัวใจขาดเลือด ภาวะหัวใจล้มเหลว และ การอักเสบของปอดจากการฉายรังสีเป็นต้น ซึ่งโอกาสในการเกิดผลข้างเคียงดังกล่าว พบว่าแปรผันตามปริมาณรังสีที่อวัยวะดังกล่าวได้รับ งานวิจัยนี้เป็นงานวิจัยเพื่อเปรียบเทียบปริมาณรังสีระหว่างการฉายรังสีปรับความเข้มด้วยรังสีโปรตอน (IMPT) และการฉายรังสีปรับความเข้มด้วยรังสีโฟตอน (IMRT)

วัตถุประสงค์: เพื่อเปรียบเทียบปริมาณรังสีระหว่างการฉายรังสีปรับความเข้มด้วยรังสีโปรตอน (IMPT) และการฉายรังสีปรับความเข้มด้วยรังสีโฟตอน (IMRT) ในผู้ป่วยมะเร็งต่อมน้ำเหลืองบริเวณทรวงอกระยะต้น

วัสดุและวิธีการ: การศึกษานี้ได้นำภาพถ่ายเอ็กซ์เรย์คอมพิวเตอร์ของผู้ป่วยมะเร็งต่อมน้ำเหลืองบริเวณทรวงอกระยะต้นจำนวน 12 คน มาวางแผนการฉายรังสีแบบ IMPT และ IMRT โดยกำหนดปริมาณรังสีที่ครอบคลุมขอบเขตของก้อนมะเร็ง (98% CTV สำหรับเทคนิค IMPT และ 95% PTV สำหรับเทคนิค IMRT) ให้อยู่ที่ 45 เกรย์ต่อการฉายรังสี 25 ครั้ง จากนั้นจึงทำการเปรียบเทียบค่าตัวแปรเชิงรังสีคณิตของทั้งสองแผนการรักษา

ผลการศึกษา: ทั้งสองเทคนิคการฉายรังสีสามารถครอบคลุมขอบเขตก้อนมะเร็งได้ตามเป้าหมาย การฉายรังสีด้วยเทคนิค IMPT สามารถลดปริมาณรังสีโดยเฉลี่ยที่หัวใจ ปอด และ หลอดอาหารได้รับเมื่อเทียบกับการฉายรังสีด้วยเทคนิค IMRT นอกจากนี้การฉายรังสีด้วยเทคนิค IMPT ยังมีค่าความสม่ำเสมอของรังสี (heterogeneity index) ที่ดีกว่า แต่มีค่าดัชนีความเข้ารูป (conformity number) ที่ด้อยกว่าการฉายรังสีด้วยเทคนิค IMRT อย่างมีนัยสำคัญทางสถิติ

ข้อสรุป: การฉายรังสีด้วยเทคนิค IMPT สามารถลดปริมาณรังสีที่อวัยวะข้างเคียงได้รับ ซึ่งอาจส่งผลให้ผลข้างเคียงเฉียบพลันและผลข้างเคียงระยะยาวลดลงได้

คำสำคัญ: ตัวแปรเชิงรังสีคณิต, มะเร็งต่อมน้ำเหลืองชนิดที่ไม่ใช่ฮอดจ์กิน, การรักษาด้วยรังสีโปรตอน, IMPT

Abstract

Backgrounds: Non-Hodgkin lymphoma is a hematologic disease with excellent outcome after chemotherapy and radiotherapy. However, a patient undergoing radiotherapy is at risk of developing late toxicities such as myocardial infraction, congestive heart failure and radiation pneumonitis which varies according to radiation doses to organs at risk. This study compares the dosimetry of intensity modulated proton therapy (IMPT) with the intensity modulated radiation therapy (IMRT).

Objective: To compare the dosimetry between IMPT and IMRT in patients with primary mediastinal B-cell lymphoma (PMBCL) and measure the difference in target dose coverage, heterogeneity, conformity, and doses to organs at risks.

Material and Methods: Computed tomography (CT) of 12 patients with PMBCL were re-planned with IMRT and IMPT techniques with the prescribed dose of 45 Gy in 25 fractions, which required to covered 95% of PTV in IMRT and 98% of CTV in IMPT. Both plans were compared and evaluated.

Result: Both plans achieved adequate target coverage (98% of CTV for IMPT and 95% of PTV for IMRT). IMPT minimized mean heart, lung, and esophagus doses, with the mean heart and lung dose staying within the QUANTEC threshold. Additionally, IMPT showed better homogeneity but worse conformity when compared to IMRT.

Conclusion: IMPT reduced the radiation doses to organs at risk while achieving adequate target coverage, which might translate to lower acute and late toxicities.

Key words: Dosimetric study, Non-Hodgkin's lymphoma, Proton therapy, IMPT

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Introduction

Lymphoma is a solid tumor of the immune system, divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). NHL, which accounts for 90% of lymphoma, is the fifth most frequently diagnosed cancer in the UK and the ninth in Thailand[1,2]. With the current treatment consisting of chemotherapy and radiotherapy, patients with primary mediastinal B-cell lymphoma (PMBCL) have much improvement in overall survival (OS) and progression free survival (PFS). Especially in younger patients, which after standard treatment, have 10-year OS rate up to 93% in HL and 77% in NHL[3,4]. However, survivors of thoracic lymphoma who underwent radiation therapy are at risk of developing late effects, such as myocardial infarction, pericardial effusion, congestive heart failure and radiation pneumonitis[4,5].

Radiation dose reduction is an effective method to reduce late toxicities. HL and NHL with complete response (CR) after chemotherapy

are irradiated with radiation dose 30-36 Gy. However, NHL with partial response (PR) after chemotherapy is irradiated with radiation dose 40-50 Gy. Radiotherapy can be omitted in PMBCL with negative PET-CT scan after rituximab combined with dose adjusted-EPOCH chemotherapy (R-DA-EPOCH)[6]. PET-CT scan and R-DA-EPOCH chemotherapy are generally not available in Thailand; therefore, high radiation dose is still prescribed.

Other methods to reduce late toxicities are radiation volume reduction and new radiotherapy techniques such as the adoption of involved-field radiotherapy and involved-nodal radiotherapy. When compared to mantle-field radiotherapy, involved-field radiotherapy reduced radiation dose to the total heart by 29%[7]. Proton therapy is a new emerging technique involving accelerating the proton, a positively charged particle, to treat cancer instead of using conventional ionization radiation, such as x-ray. Proton has a characteristic physical property called "Bragg peak" that, with the appropriate energy level, will cause the proton to deposit most of its energy at the tumor without transmitting energy further, which minimized the energy released to the surrounding tissue[8]. Nine published studies evaluating the benefit of proton therapy compared to photon therapy, seven of the studies showed improvement in heart's radiation dose and lowered the expected risk of long-term cardiotoxicity[9].

This study compares the dosimetry of intensity modulated proton therapy (IMPT) with the intensity modulated radiation therapy (IMRT), which uses high energy photons to decrease the radiation energy affecting the surrounding tissue.

Materials and methods

Under institutional review board approval (IRB 044/64), patients with early-stage PMBCL undergoing standard chemotherapy followed by radiotherapy treated between June 2015 - May 2021, who had evidence of residual disease by CT scan after chemotherapy, were included and the data from the CT simulator database server was retrieved. All patients who underwent CT simulation with 3-5 mm slice thickness were in supine position and immobilized with thermoplastic long mask to maintain position reproducibility and accuracy. All patients breath normally during CT simulation procedure, no motion restrictions were applied.

The clinical target volume (CTV) and organs at risk (OARs), including heart, lungs, and esophagus, were contoured based on International Lymphoma Radiation Oncology Group (ILROG)[10] and reviewed by radiation oncologist who specializes in lymphoma irradiation and optimization. The planning target volume (PTV) was CTV plus 1 cm margin to account for patient breathing motion.

The IMPT with pencil beam scanning technique was created using 3 fields; anteroposterior field (0°) left anterior oblique (30-45°) and right

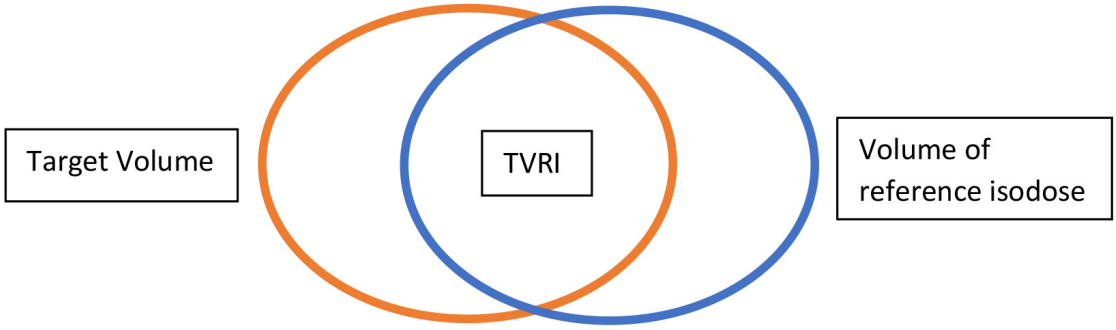
anterior oblique (30-45°). Robust optimization was performed on the CTV structure using 5 mm setup uncertainty and a 5% range uncertainty and normalized so that CTV received at least 98% of the prescription dose. The IMRT was created with 6 MV photon beams with 7 or 9 beam angles and optimized so that PTV received at least 95% of the prescription dose. All plans were optimized with the same radiation physicist and the prescription dose was set to 45 Gy in 25 fractions in both plans.

The radiation doses' data of the CTV (for IMPT), PTV (for IMRT) and OARs (mean dose, V5 to V40) had been investigated and compared. The heterogeneity index (HI) and conformity number (CN) were also investigated and compared. The HI according to ICRU 83[11] was defined as (D2% - D98%) / prescribed dose (4500 cGy) and CN, according to RTOG definition[12], was defined as (TVRI / TV) x (TVRI / VRI) as shown in **Figure 1**.

Paired T-test (for normally distributed data) and Wilcoxon match pair signed-rank test (for difference in dose volume histogram) were used to compare the result between IMPT and IMRT. All tests were 2-sided with p-value ≤ 0.05 for significant level.

Results

From June 2015 - May 2021, 21 patients with PMBCL were sent to Division of Radiation Oncology, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Thailand. Nine patients had complete response of bulky disease after standard chemotherapy, were irradiated with



TVRI = target volume covered by the reference isodose

TV = target volume

VRI = volume of the reference isodose

Figure 1 Conformity number according to RTOG definition

radiation doses of 30-36 Gy and excluded from this study. Twelve patients with residual disease by CT scan were included in this study and 24 plans were created. The median PTV size was 763.91 ml, at least 98% of CTV in IMPT plan and 95% of PTV in IMRT plan received the prescribed dose (45 Gy in 25 fractions). The dose to CTV, PTV, OARs, mean integral dose to whole body, HI and CN were shown in **Table 1**.

Table 1: The dose to CTV, PTV, OARs, HI and CN

Parameter	Toxicity end point	IMPT (Mean ± SD)	IMRT (Mean ± SD)	P-value
95% of PTV (Gy)		30.16 (± 9.55)	45.15 (± 0.16)	
98% of CTV (Gy)		45.11 (± 0.61)	46.51 (± 0.63)	
Heart (mean)	Myocardial infraction, Pericarditis, Congestive heart failure	4.43 (± 3.08)	10.77 (± 8.47)	0.013
Heart (V25)	Long term cardiac mortality	7.58% (± 5.55)	16.57% (±15.6)	0.022
Heart (V30)	Pericarditis	6.13% (± 4.60)	14.1% (± 13.9)	0.022
Lung (mean, Gy)	Symptomatic pneumonitis	7.12 (± 2.74)	14.05 (± 2.94)	0.011
Lung (V20)	Symptomatic pneumonitis	13.03% (± 5.9)	27.0% (± 10.0)	0.011
Esophagus (Mean,Gy)	Esophagitis	18.88 (± 9.00)	23.02 (± 8.84)	0.011
Mean integral dose to whole body (Gy)		282.66	647.12	0.011
HI (CTV for IMPT and PTV for IMRT)		0.10	0.14	0.038
CN (CTV for IMPT and PTV for IMRT)		0.53	0.78	< 0.001

Abbreviation: PTV=planning target volume, CTV= clinical target volume, Vx = volume of organ received x Gy, IMPT= intensity modulated proton therapy, IMRT= intensity modulated radiation therapy, HI= heterogeneity index, CN= conformity number

The mean heart doses were significantly decreased from 10.77 Gy in IMRT to 4.43 Gy in IMPT (absolute difference of 6.34 Gy, HR 0.411, p-value = 0.013) as shown in **Figure 2**. The heart's V5-V40Gy in IMPT were significantly lower than IMRT as shown in **Figure 3**. The V25Gy was within the QUANTEC threshold of 10% and may translate to long term cardiac mortality of less than 1%.

The advantages of IMPT over IMRT were also observed in mean lung doses (7.12 Gy vs 14.05 Gy, HR 0.507 p-value 0.011) as shown in **Figure 4**. The mean lung dose in IMPT was within the QUANTEC threshold of 13 Gy, which might produce less than 10% of symptomatic pneumonitis. Moreover, the advantages of IMPT over IMRT were also observed in mean esophagus doses (18.88 Gy vs 23.02 Gy) as shown in **Figure 5**, both techniques were within the QUANTEC threshold (mean esophagus dose less than 34Gy)

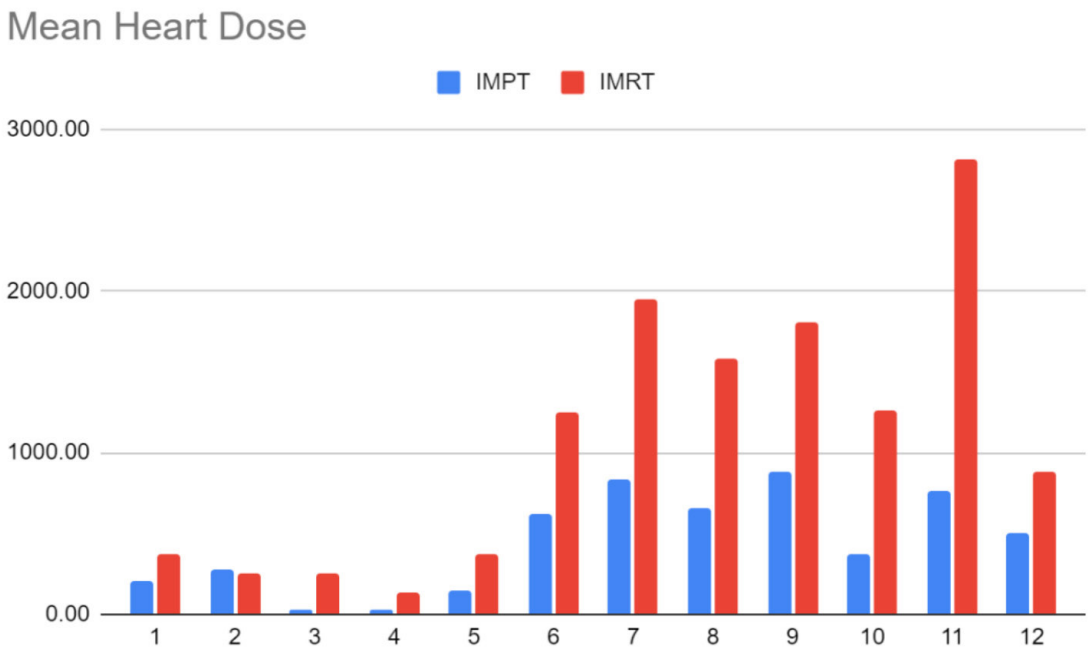


Figure 2 Comparison of mean heart dose (cGy) between IMPT and IMRT in each patient

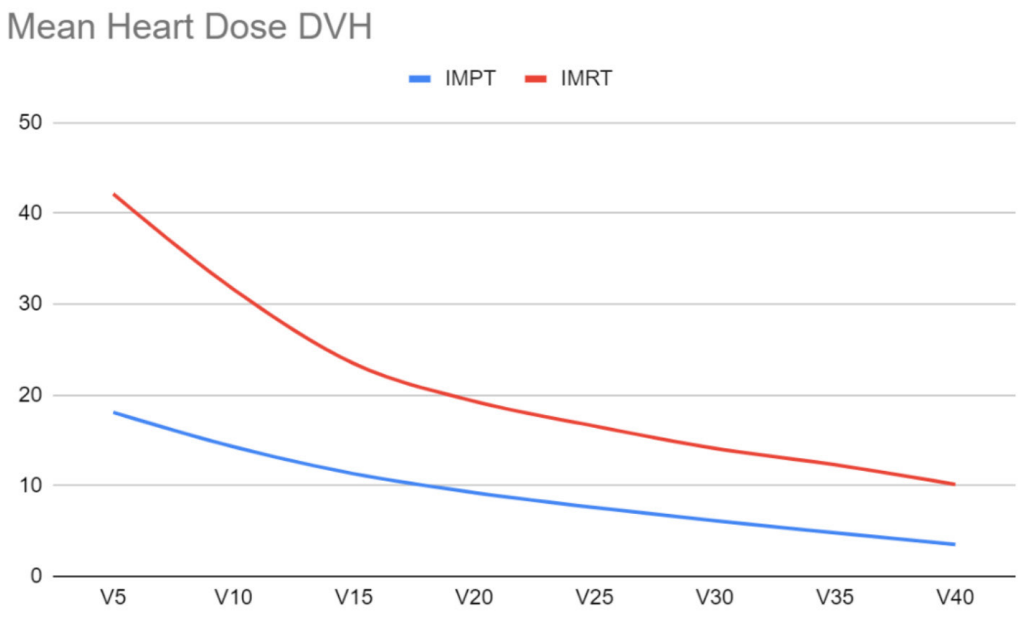


Figure 3 Mean dose volume histogram of heart dose (Gy) between IMPT and IMRT

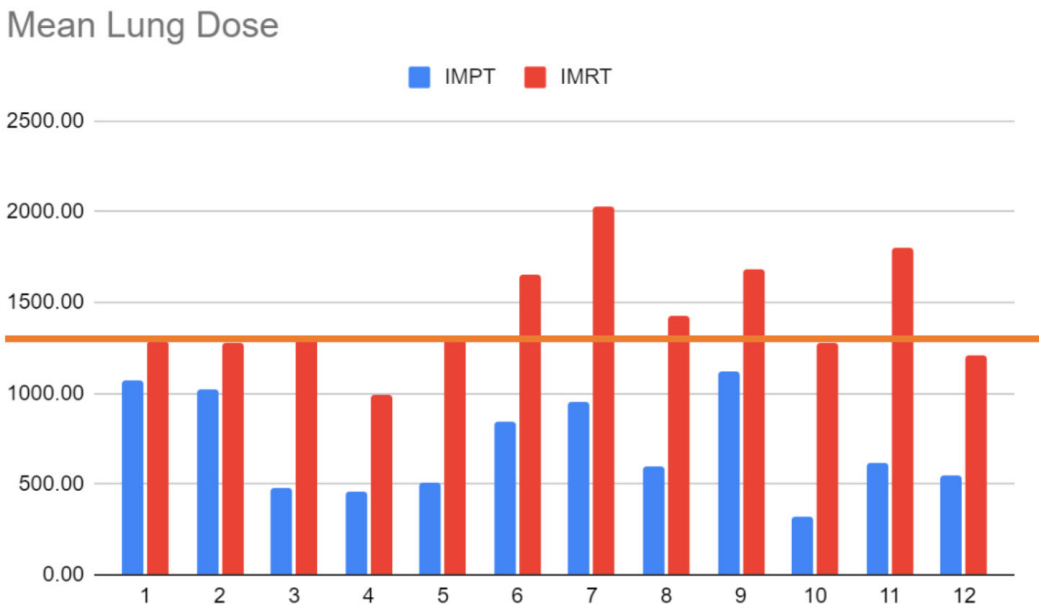


Figure 4 Comparison of lung dose (cGy) between IMPT and IMRT in each patient, and QUANTEC threshold of 13 Gy

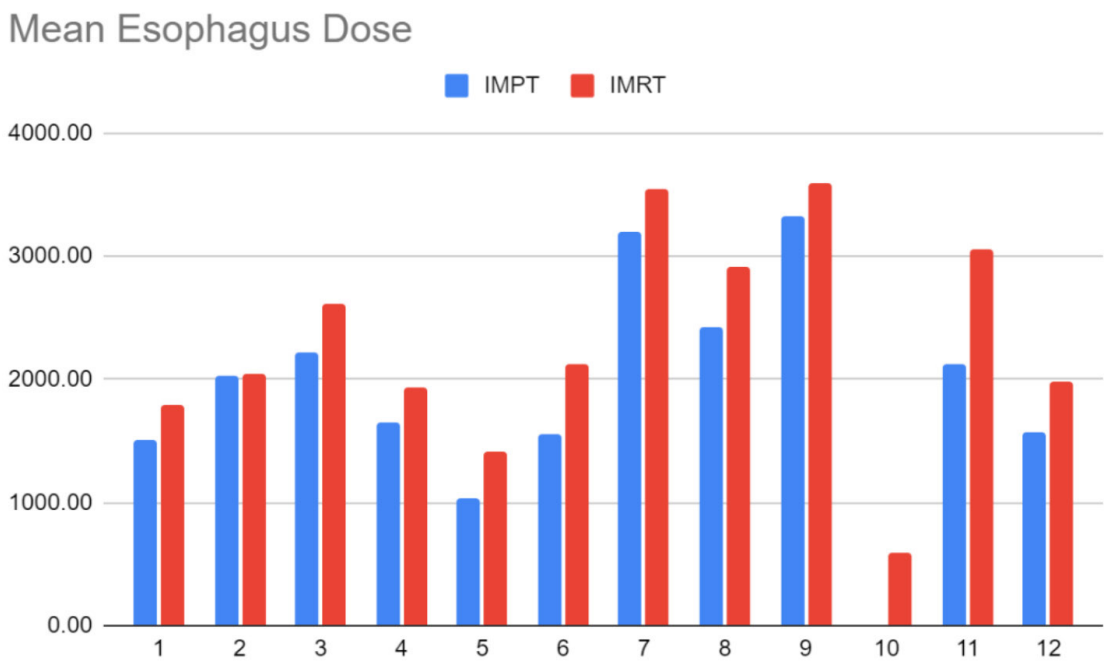


Figure 5 Comparison of esophagus dose (cGy) between IMPT and IMRT in each patient

Discussion

Radiotherapy is an essential part in the treatment of bulky disease or partial response NHL after chemotherapy. Due to excellent outcome with the current treatment, minimizing chemotherapy and reduction of radiation dose to the OARs are necessary to diminish the late toxicities. Decreasing radiation dose in PMBCL's patients is challenging due to proximity of critical OARs (heart, lung, and esophagus).

IMPT is one of the novel techniques used to mitigate radiation dose to other organs due to less entrance dose and minimal exit dose, while providing equivalent or better coverage to the target volume[13]. From this study we observed the reduction in mean heart, lung and esophagus dose which contributed by the reduction of low to intermediate dose volume.

Cardiovascular disease, including myocardial infraction, coronary artery disease, vascular disease and pericarditis is one of the main mortalities in long term lymphoma survival[14]. Several studies comparing proton therapy with 3D-CRT, IMRT and VMAT in patients with HL demonstrated reduction in mean heart dose [15-18]. Nimwegen et al.[19] conducted a case-control studies and report a linear radiation dose-response relationship between mean

heart dose and risk of coronary heart disease, which increased by 7.4% for 1 Gy (46.9% when applied with the data from our study)

Radiation pneumonitis is also another potentially fatal toxicity, which affects quality of life in patients receiving mediastinal radiotherapy. According to QUANTEC threshold, if mean lung dose is less than 13 Gy, rate of symptomatic pneumonitis would be expected to be less than 10%. This threshold was also in line with previous studies, Lewis et al.[20] demonstrated that radiation pneumonitis was seen only in patients with mean lung dose over 12.4 Gy and purposed mean lung dose of 13.5 Gy to be predictive threshold of radiation pneumonitis. Koh et al.[21] also found that mean lung dose of over 14.2 Gy was related to symptomatic radiation pneumonitis.

IMPT also achieved better homogeneity but showed worse conformity when compared to IMRT. However due to difference in volume of interest used for calculating homogeneity index and conformity number (CTV for proton and PTV for photon) comparing IMPT and IMRT in this aspect may have some limitation.

This study exhibits several limitations. Firstly, due to its dosimetric nature, there is a need for a clinical study to validate its clinical significance. Secondly, the study included only 12 patients with PMBCL, which is a relatively small sample size; including a larger number of patients may yield more reliable data. Finally, considering the existence of similar studies, the degree of innovation in this study is somewhat constrained.

Conclusion

IMPT maintains the dose coverage to the target volume while minimizing the mean dose received by the OARs, which potentially results in lower acute and late toxicity compared to those treated with the photon therapy.

Appendices

1. Terminology[22]

Gross Tumor Volume (GTV): GTV represents the observable extent and location of the tumor. In cases treated with radiation therapy (RT) alone, it includes radiologically evident lesions (typically PET-positive) present at the time of diagnosis. In combined modality therapy, "prechemo" GTV signifies visible lesions before systemic treatment, while "postchemo" GTV signifies radiologically evident or biopsy-proven disease sites after systemic therapy.

Clinical Tumor Volume (CTV): CTV encompasses GTV and/or a volume containing subclinical malignant disease that has a certain probability of occurrence and is relevant for therapy. In cases of RT alone, this volume includes GTV and adjacent lymph nodes. In combined-modality therapy, it includes any "postchemo" GTV, as well as the tissue volume that initially contained involved lymph nodes and sites of infiltrative disease (i.e., the "prechemo" GTV), which may have become PET-negative or normalized on structural imaging after systemic therapy. Depending on specific clinical contexts, CTV may also include sites considered at particular risk based on the

understanding of natural disease progression and spread patterns. The inclusion of equivocal nodes in GTV or CTV depends on the clinical context.

Equivocal Nodes: Equivocal nodes are lymph nodes near definite disease sites that are either enlarged (>1 cm) but PET-negative, normal in size with equivocal FDG uptake, or present in an increased number or with an asymmetrical distribution. The decision to include equivocal nodes in GTV or CTV depends on the clinical context.

The Internal Target Volume (ITV) and Planning Target Volume (PTV) should be determined following institutional practice.

2. Involved-Site RT[10]

Involved-Site Radiation Therapy (ISRT) is based on the concept that the prechemotherapy GTV determines the CTV. This concept assumes that chemotherapy eradicates microscopic disease adjacent to or within regional lymph nodes, and ISRT targets the identifiable prechemotherapy disease. ISRT results in a smaller irradiated volume compared to involved-field RT because it intentionally spares adjacent lymph nodes that appear grossly uninvolved. However, ISRT is suitable for cases where optimal prechemotherapy imaging, particularly high-quality imaging in the treatment-planning position, is not available to the radiation oncologist. In ISRT, clinical judgment, combined with the best available imaging, is used to contour a CTV that accommodates uncertainties in defining the prechemotherapy GTV for each individual case. Therefore, ISRT typically encompasses a slightly larger irradiated volume than involved-node RT.

In situations where prechemotherapy imaging of all initially involved lymphoma sites is available but image fusion with post-chemotherapy planning CT is not feasible, the radiation oncologist must contour the target volume on the planning CT scan using prechemotherapy images. This should account for contouring uncertainties and differences in positioning by including a larger volume in the CTV, with the extent of enlargement determined by the level of uncertainty.

When no prechemotherapy imaging is available (e.g., patients presenting with neck disease but lacking neck imaging in the initial staging), the radiation oncologist faces a more challenging scenario. Gathering as much clinical information as possible regarding the pre- and post-chemotherapy location of pathological lymph nodes is crucial. The CTV should be contoured based on this information, with generous allowances made for the numerous uncertainties involved.

3. Clinical Target Volume[10]

The Clinical Target Volume (CTV) includes the original lymphoma volume adjusted to account for normal tissue boundaries and expanded to accommodate uncertainties in determining the prechemotherapy volume, as outlined above.

The Internal Target Volume (ITV) should only be added to the CTV when there is concern about internal organ movement. The CTV is then further expanded to create the Planning Target Volume (PTV). In situations where RT is the primary treatment, larger margins must be applied to encompass subclinical disease.

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