



Evolution of radiotherapy techniques for mediastinal Hodgkin lymphoma: a single-center experience

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Hodgkin lymphoma (HL) is a rare hematological malignancy associated with a high curability rate, ranging between 80% and 90% (1). Limitation of treatment-related toxicities is consequently of prime importance. Consolidation radiation therapy following first-line chemotherapy improves progression-free survival (PFS) for favorable and unfavorable early-stage HL (2); however, first-generation bidimensional (2D) techniques, which used extended fields, largely exposed thoracic organs-at-risk (OAR), leading to an increased risk of late radiation-induced adverse events, such as cardiac failure, pulmonary toxicity and second cancers (3). More recently, target volumes were limited to the initially involved sites and technical progresses were made in order to spare OAR, substantially reducing the delivered integral dose. Such technical developments included intensity-modulated radiation therapy (IMRT) and intensity-modulated proton therapy (IMPT) (4). The aim of this study was to analyze the evolution of the RT techniques for mediastinal HL irradiation in our Department of Radiation Oncology on a period of 17 years between January 2005 and January 2022. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Institut Curie (date: 2112021) and individual consent for this retrospective analysis was waived.

Since 2005, an institutional database records all lymphoma patients referred to the radiation oncologists of our department for radiotherapy planning; the aim of this retrospective study was to describe the technical

evolution of consolidative radiotherapy for mediastinal HL irradiation from 2005 to 2022. During this period, 68 new mediastinal HL patients were addressed to our department: of them, 16 were treated with tridimensional conformal radiotherapy (3D-CRT) on a period between 2005 and 2018, 37 were treated with IMRT (either with volumetric modulated arc therapy or helical tomotherapy) which was introduced in this indication in 2010, and 15 were treated with IMPT, which was introduced in this indication in 2018. IMPT was systematically delivered on a gantry with spirometer-controlled deep-inspiration breath hold, based on the involved-site radiation therapy standard, and normofractionated. The proportion of IMPT treatments was 0% before 2018, 33.3% in 2018 (1 patient/3), 28.6% in 2019 (2 patients/7), 28.6% in 2020 (2 patients/7), and 58.8% in 2021 (10 patients/17). The evolution of 3D-CRT, IMRT and IMPT distribution for mediastinal HL irradiation is shown in *Table 1* and *Figure 1*.

The main indications for mediastinal HL proton therapy were young patients (less than 30 years old), considering that the cumulative incidence of secondary cancer increased when the age at first treatment decreased with a long-lasting risk (5), or patients with a significant cardiovascular risk either due to baseline cardiovascular risk factors or to the localization of the initially involved sites in the vicinity of critical cardiac substructures. Among the 15 institutional patients treated with IMPT, 13 were women and the median age was 26 years (range, 18–37 years); there were 12 stage II unfavorable HL, 2 stage II favorable HL, and 1 “grey zone” lymphoma. Median prescription dose was

Table 1 Evolution of the indications for IMRT and IMPT

Radiotherapy techniques	2005–2009	2010–2014	2015–2018	2019–2022
All HL patients treated with RT	15	9	13	31
Patients treated with 3D-CRT	15 [100]	–	1 [8]	–
Patients treated with IMRT	–	9 [100]	11 [85]	17 [55]
Patients treated with IMPT	–	–	1 [8]	14 [45]

Data are presented as n or n [%]. IMRT, intensity-modulated radiation therapy; IMPT, intensity-modulated proton therapy; HL, Hodgkin lymphoma; RT, radiation therapy; 3D-CRT, tridimensional conformal radiotherapy.

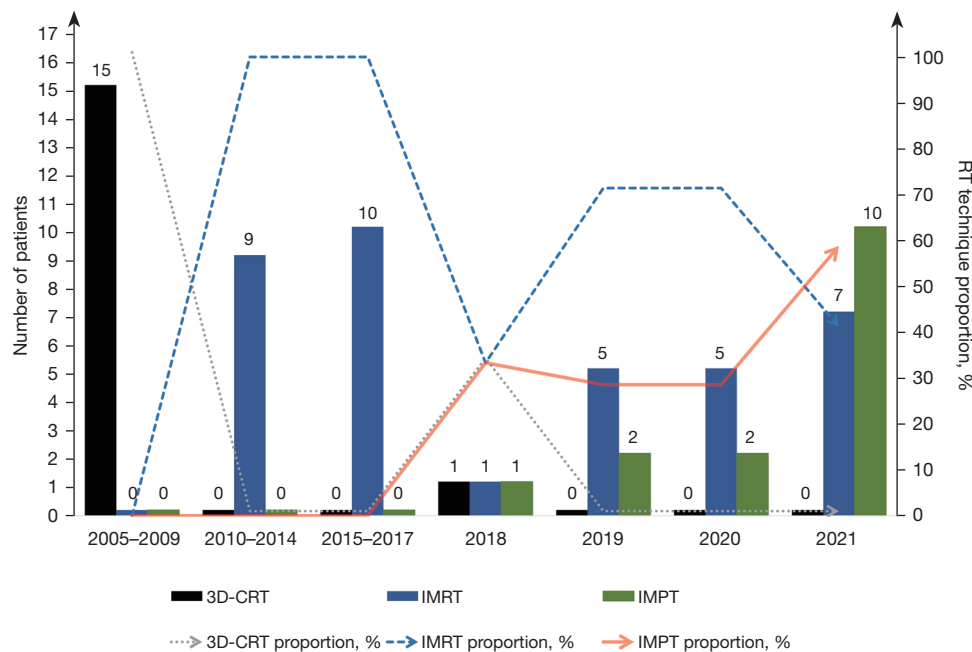


Figure 1 Technical evolution for mediastinal HL radiotherapy at Institut Curie (January 2005–December 2021). 3D-CRT, tridimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; IMPT, intensity-modulated proton therapy; HL, Hodgkin lymphoma.

30 Gy (range, 30–36 Gy). IMPT is expected to significantly reduce radiation exposure to OAR and to improve target coverage compared with IMRT. Based on a dosimetric comparison between IMRT and IMPT, we found that IMPT significantly reduced mean doses to the heart (2.36 *vs.* 0.99 Gy, $P < 0.01$), to the left ventricle (0.67 *vs.* 0.03 Gy, $P < 0.01$) and to the valves (1.29 *vs.* 0.06 Gy, $P < 0.01$) (6). While IMPT treatments are still minority in our department and are systematically subject to a dosimetric selection process based on a comparison between optimal IMRT and IMPT plans (7,8), proton therapy has become the main technique for mediastinal HL lymphoma. IMPT is currently facing multiple challenges, such as limited access to proton therapy facilities, reimbursement issues,

development of new effective regimens for HL management (such as targeted therapies or immunotherapies) and optimal selection process which is still subject to debate (7). In any case, the National Comprehensive Cancer Network (NCCN) guidelines still consider IMRT/volumetric-modulated arc therapy (VMAT) as a standard technique (9) and the ILROG guidelines on the utilization of IMPT suggest a careful adoption of this latter, taking into account all the physical limitations of IMPT in a delicate and anatomically complex district, as it is the thorax (10).

While a longer follow-up for IMPT is needed to evaluate its efficacy and late toxicity profile, this single-center experience evidences how proton therapy, once only used for highly selected patients, could become a reference

technique in the treatment of mediastinal HL patients, despite multiple challenges including limited availability and financial cost.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board of the Institut Curie (date: 2112021). Individual consent for this retrospective analysis was waived.

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