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Advanced Radiotherapy Techniques for Mediastinal Lymphomas: Results from an Italian Survey

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Abstract: Background: Multiple methods have been implemented to limit the impact of radiotherapy on patients affected by mediastinal lymphoma, including breathing control techniques, image-guided radiotherapy (IGRT) and intensity-modulated radiotherapy (IMRT), although the actual diffusion of such techniques is unclear. No surveys have been published to date evaluating the techniques adopted at different centers. Methods: A survey with a dedicated questionnaire was submitted to 195 Italian radiotherapy centers, assessing items regarding the characteristics of the center and clinical practice in the treatment of mediastinal lymphomas. Results: A total of 43 centers (22%) responded, the majority of which were university hospitals (37.2%) or cancer care centers (27.9%). In 95.4% of the centers, IMRT was used in the clinical practice, and the most frequently employed techniques were VMAT (48.8% of centers) and non-rotational IMRT (31.7%). Comparison of multiple plans was performed by 66.7% of the responding centers. Dose constraints for organs at risk were consistently prescribed. IGRT techniques were adopted by 93% of the centers, while breathing control or gating techniques were routinely used by only 25.6% of the centers. A necessity to standardize OAR constraints and define guidelines was perceived by almost all participants. Conclusions: Modern radiotherapy techniques are widely used in the Italian centers, although with heterogeneous characteristics.

Keywords: radiotherapy; lymphoma; survey; IMRT; mediastinal; IGRT

1. Introduction

Radiation therapy still has a primary role in combination with chemotherapy for treating early-stage lymphomas based on a risk and response-adapted strategy [1,2]. Considering the optimal prognosis, the common inclusion of the mediastinum in the clinical target volume (CTV) and the young age of most of the patients, long-term side effects are the main determinants of survival. Among the late sequelae of radiotherapy, principal concerns are radiation-induced malignancies (RIMs) and cardiovascular diseases (CVDs) [3–6].

The systematic adoption of PET-CT for the staging and evaluation of disease response and prognosis [7,8] allowed the reduction in prescription doses and treatment fields from extended field (EFRT) to the current standard of involved site RT (ISRT) or involved node RT (INRT) [9–13].

In parallel, the implementation of modern planning techniques led to the development of different intensity-modulated radiation therapy (IMRT) solutions, improving dose conformality. Conformal treatments generally reduce the volume of the OARs receiving high doses, with modeling studies predicting lower toxicity for IMRT, especially when combined with contemporary smaller fields and reduced doses [14,15].

In addition, other means to reduce the doses to OARs such as the use of image-guided RT (IGRT) to reduce CTV-PTV margins [16] and the adoption of respiratory motion compensation based on 4D-CT or breathing control techniques such as deep inspiration breath hold (DIBH) gating [17,18] have been introduced.

Nonetheless, given the complexity of the disease paradigm, although conformal techniques are advised, especially when the target is in proximity to critical structures, there is still no clear consensus regarding the optimal use of IMRT and other advanced technique elements [14,15].

The extreme variability of disease presentation and the necessity to tailor the treatment to each patient's individual pathological and anatomic features, in addition to the large variability of the availability of treatment technology, further contribute to a potentially heterogeneous situation in the current clinical practice.

Notwithstanding these uncertainties and the wide range of available options for the treatment of mediastinal lymphoma, no surveys have been published that provide an overview of techniques adopted at different radiotherapy centers. This survey therefore reports the use of modern radiotherapy techniques for the treatment of mediastinal lymphoma in Italian radiation oncology institutions.

2. Methods

The survey was sent to 195 Italian radiotherapy centers using the mailing list of AIRO (Associazione Italiana di Radioterapia e Oncologia Clinica—Italian Society of Radiotherapy and Clinical Oncology) as the reference database. It included items regarding patient numbers, characteristics of the centers and current clinical practice in the treatment of mediastinal lymphomas.

A dedicated questionnaire was sent to all participants, investigating the following points:

1. Characteristics of the center;
2. Total number of patients treated with external beam radiotherapy (EBRT) and number of patients with mediastinal lymphoma treated in 2017;
3. Adoption of IMRT in clinical practice for the treatment of mediastinal lymphomas, image fusion with diagnostic imaging, frequency of the use of the IMRT technique and comparison of 'rival' plans during treatment planning procedures (personalized approach to OAR sparing);
4. Use of specific dose constraints for the OARs; presence of differences with constraints used for solid tumors; contouring of cardiac sub-structures;
5. Adoption of breathing control and/or gating techniques;
6. Use and frequency of IGRT;
7. Perceived necessity of standardization of techniques and dose constraints.

Data were collected using the Survey Monkey online platform, and statistical analysis was performed using Statistical Package for Social Science (SPSS) software version 25.

3. Results

The questionnaire was completed by 43 centers (22%). Results are reported grouped by categories of questions.

3.1. Characteristics and Treatment Volumes of Participating Centers

Forty-three centers participated in the survey and compiled the questionnaire. The majority were university hospitals (37.2%) or cancer care centers/scientific institutes for research (IRCCS) (27.9%), while another 27.9% were represented by non-university hospitals, and two were private institutions. The mean and median total numbers of patients treated with external beam RT at each center in 2017 were 1027 and 808 (range 511–3500), with 41.9% of the responding centers treating more than 1000 patients. The mean and median estimated numbers of patients treated for mediastinal lymphoma in 2017 at each center were, respectively, 16.1 and 10.

3.2. Use of IMRT for the Treatment of Mediastinal Lymphoma

Results are summarized in Figure 1. In almost all centers (41/43, 95.4%), IMRT was used in clinical practice; eight centers reported that IMRT was not consistently used but adopted only in selected cases, and the main reasons to refrain from its adoption (multiple options available) were concerns of toxicity due to 'low dose bath' (75%) and a perceived absence of evidence of a clinical benefit (25%), while in only 12.5% of cases, the reason was a lack of experience with the technique and/or absence of equipment. Among the 41 centers using IMRT, co-registration of diagnostic imaging with simulation CT scans was performed in all cases. The main employed technique was VMAT in 48.8% of cases, non-rotational IMRT in 31.7% and tomotherapy in 9.8%. A comparison of different rival plans to define the optimal IMRT technique for each patient was performed by two thirds of the responding centers.

3.3. Dose Constraints to the OARs for the Treatment of Mediastinal Lymphoma

All 43 participating centers used dose constraints for organs at risk. In 62.7% of the cases, the constraints were different from those used for solid thoracic malignancies. The dose limits were mainly derived from the published literature (81.4%), while a minority used data based on local experience of the center (16.3%) or personal experience (2.3%). While all the participating centers defined dose constraints for the heart, only in 20.9% of the participating centers were cardiac sub-structures defined as OARs.

3.4. Adoption of Breathing Control and/or Gating Techniques

Breathing control techniques were not routinely performed in 74.4% of the centers, likely due to the limited availability of devices and/or the implementation of dedicated protocols for lymphoma patients. Moreover, as there is currently no consensus regarding the best technique to use, a wide range of different options (illustrated in Figure 2) was adopted among different centers.

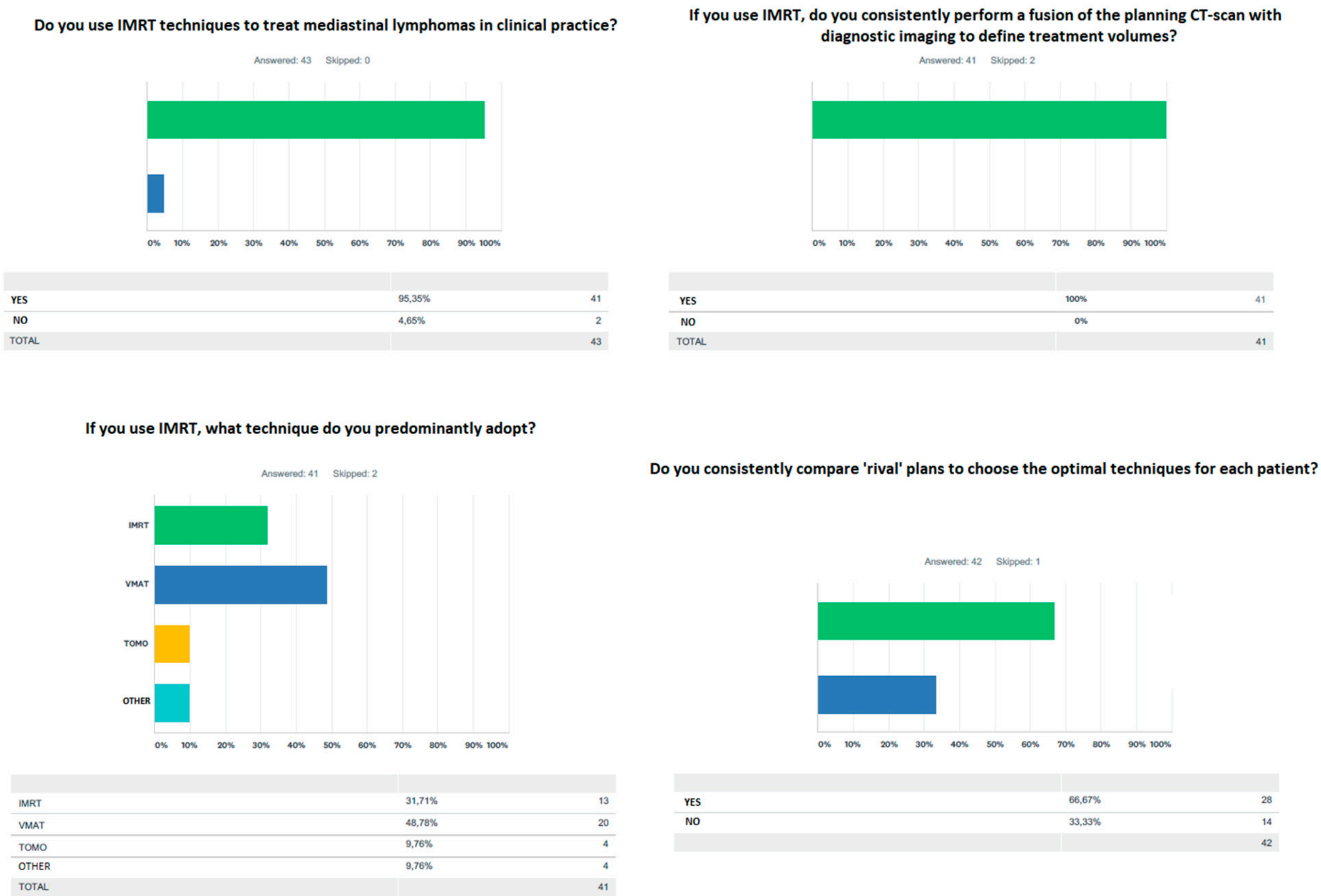

Figure 1. Adoption of intensity-modulated radiotherapy (IMRT), fusion with diagnostic imaging and preferential technique used (VMAT = volumetric modulated arc therapy; Tomo = tomotherapy) across different centers.

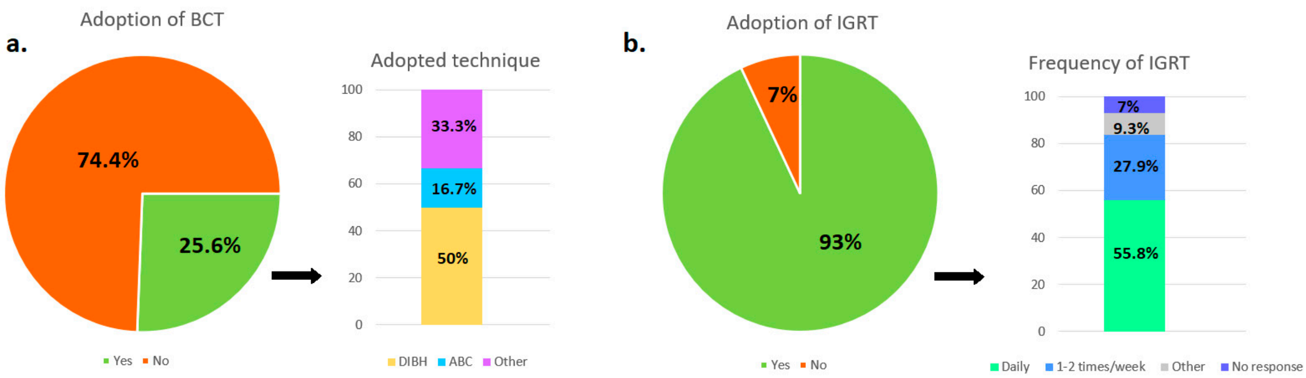

Figure 2. Adoption of breathing control techniques (BCTs) (**a**) and type of technique adopted (DIBH = deep inspiration breath hold; ABC = active breathing control), and adoption of image-guided radiotherapy (IGRT) (**b**) and frequency of its use across different centers.

3.5. Use and Frequency of IGRT Procedures

IGRT was adopted by 93% of the participating centers, although its frequency varied: most of the centers (55.8%) performed daily controls, while others used different schedules (such as bi-weekly imaging or personalized schedules for each patient, as reported in Figure 2).

3.6. Perceived Necessity of Standardization

The large majority or participating centers (90.7%) declared to consider standardization of techniques for the treatment of mediastinal HL desirable. Likewise, the implementation of guidelines or consensus papers defining dose constraints for OARs for the treatment of mediastinal HL was considered useful by 97.7% of participants.

4. Discussion

As the prognosis of lymphomas has gradually improved, reaching very high cure rates for HL, the reduction in treatment-related toxicity has become increasingly important.

Methods to reduce the dose to OARs have therefore been implemented to optimize treatment safety. The shift towards the ISRT paradigm and reduction in prescribed doses have already improved the radiation exposure of healthy tissues with a reduction in RIMs risk [19,20], but multiple other methods might further decrease the dose to OARs.

Highly conformal techniques such as IMRT, VMAT and tomotherapy allow a reduction in the volumes of OARs exposed to high doses in comparison with 'conventional' treatments, with the drawback of a larger volume that receives low doses.

Although it was widely believed that the increased volumes exposed to ionizing radiations using IMRT could lead to a higher risk of developing RIMs, this was based on models that assume a nonlinear dose–risk relationship, consequently favoring 3D techniques over IMRT [21,22]. When applying modern risk models, no increased risk of secondary malignancies is estimated for IMRT over 3D-CRT [23]. Clinical epidemiological data and meta-analyses regarding HL patients [24–26] demonstrated a linear dose–response for radiation-induced tumors. Using linear models, IMRT mostly resulted in similar [23,27,28] or even lower [29,30] risk estimates for RIMs compared with 'traditional' treatments as low-dose spread is counterbalanced by a reduction in volumes receiving high doses.

Our analysis highlights the widespread use of IMRT across Italian radiation oncology centers, as 95.4% of participating centers confirmed its adoption in clinical practice for the treatment of mediastinal lymphoma. The fear of 'low dose bath' thus does not seem to halt its use, although a minority of participants reported that IMRT is used in selected cases only, mainly due to this concern, especially in young patients. Only in a few cases was IMRT not utilized due to a lack of perceived evidence of a clinical benefit in the literature (4.7%) or insufficient experience/equipment (2.3%). In line with ISRT guidelines [12,13], deformable registration between diagnostic imaging and planning CT scans was universally performed to define target volumes. On the other hand, the 'preferred' IMRT techniques varied across centers, with VMAT (48.8%) and non-rotational IMRT (31.7%) emerging as the most frequently used paradigms. This likely also reflects different equipment availability and experience among centers.

Since, as discussed above, it is impossible to identify the universal superiority of one modulation technique over another, and as the difference between simple (e.g., AP-PA) 3D geometries and modulated treatments has been well described, comparisons of multiple plans to select a particular treatment option are no longer essential. The definition of the optimal plan is an iterative process, with the priority to define the best trade-off between the volume coverage and dose received by different OARs. Individual risk factors (such as age, gender and comorbidities) must be considered in the definition of a personalized approach to planning.

Another available option to limit the dose to OARs is the adoption of breathing control techniques or respiratory gating [17]. Although the adoption of breathing control techniques is suggested by the current guidelines, with the aim to limit doses to OARs and/or to reduce the risk of missing targets [12,13], its use is not yet considered mandatory, as reliable data regarding a quantifiable clinical benefit are still lacking. While no differences were observed in PTV coverage between radiotherapy planned in free breathing or with breathing control techniques (mostly DIBH), doses to the organs at risk were consistently reduced in the previously published experiences [17,31–35]. Due to the extreme heterogeneity of disease presentation, it is difficult to quantify the dose reduction achieved with breathing control techniques. As for irradiation of the heart, a reduction in the mean dose from about 10% to 55% has been reported, while the mean dose to the lungs was reduced from about 15% to 40.6%. On the other hand, a slight and generally non-significant increase in the dose was reported for the breasts. Dosimetric benefits were reported regardless of the delivery technique and resulted in a reduction in risk estimates of cardiovascular diseases and secondary cancers [32], comparable with that achieved with proton therapy [34].

Moreover, for many centers, the use of breathing control techniques is limited by the availability of specific devices and the implementation of dedicated protocols. This could, at least partially, explain why 79.1% of the participating centers reported not to use any breathing control techniques. Although a wider diffusion of these techniques is desirable, it should be noted that, currently, there is no consensus regarding the best technique to use, also due to the lack of direct comparisons. As a consequence, a wide range of different techniques were used among different centers, likely reflecting differences of experience and available equipment.

IGRT was adopted by the vast majority of centers, as its potential to reduce treatment margins and thus toxicity is intuitive. A clear pattern regarding imaging frequency has not emerged from this survey, though most centers (58.5%) performed daily controls.

The increasing focus on late effects highlights the necessity of defining specific dose constraints for OARs. Such constraints were suggested by recent Italian guidelines, and specific constraints were adopted by all the participating centers, mostly based on the published literature (81.4%). While dose constraints were always defined for the heart, its sub-structures were contoured by only 20.9% of the participants. In light of the recent studies, the mean heart dose alone might be a sub-optimal parameter to prognosticate heart toxicity [36,37]., and contouring different cardiac structures could improve dose optimization as knowledge about differential sensitivity of cardiac sub-structures improves, with guidelines (the most recent ones published after this survey [13,14]) being constantly updated. The performance of auto-contouring algorithms is steadily improving and may limit the necessary resources dedicated to complex contouring to a minimum. On the other hand, constraints for most of the heart sub-structures are yet to be defined, and also published data are quite heterogeneous among different experiences [36,37].

A large majority of participating centers considered the standardization of radiotherapy techniques for the clinical practice of mediastinal lymphoma treatment and the creation of guidelines or position papers establishing specific dose constraints for the treatment of lymphoma desirable. As discussed above, several new guidelines and recommendations were published after this survey was completed [13,14], as summarized in Table 1, partially responding to this request. Nonetheless, currently suggested constraints are mostly provided as relatively ample ranges, adjustable to the specific clinical situation of each patient. While adopting an ALARA (as low as reasonably achievable) approach is ideal whenever possible, the identification of the ideal trade-off corridor between exposure levels of multiple involved OARs will further be refined by improving our knowledge about dose–effect relationships based on patients' individual DVHs.

Although this analysis is limited by the relatively low number of responding centers (43/195, 22%), it should be considered that, generally, patients affected by mediastinal lymphoma are 'centralized' in large centers for systemic therapy and radiotherapy, due to the complexity of the disease and potential side effects of the treatment. Therefore, many centers may not have responded as they usually do not treat such patients. This is reflected by the large proportion of university hospitals (37.2%) or cancer care centers/scientific institutes for research (27.9%) among the responding centers.

Multi-institution cooperative networks could allow gathering data from large patient cohorts in order to better define dose–response relations. An increased participation in multi-institution cooperative networks (such as FIL—Federazione Italiana Linfomi) of centers treating relevant numbers of lymphoma patients might significantly contribute to further improving the knowledge in all areas of lymphoma treatment, constantly confirm the solidity of treatment recommendations and facilitate their application.

Table 1. Dose constraints to the organs at risk proposed by FIL (left) and ILROG (right) current guidelines for the treatment of Hodgkin lymphoma.

	FIL Guidelines			ILROG Guidelines			
	Optimal	**Required**	**Avoid**	**Optimal**	**Acceptable**	**If Necessary**	**Avoid**
Heart	Mean < 5 Gy	Mean, 5–15 Gy	Coronary vessels	Mean < 5 Gy	Mean 5–10 Gy	Mean 10–18 Gy	Coronary artery and left ventricle
Left ventricle	Mean < 2 Gy	Mean, 5–10 Gy	Coronary vessels	/	/	/	
Breasts (whole breasts)	Mean dose < 4 Gy	V4 < 50%	Glandular tissue	Mean dose < 4 GyV4 < 10%	Mean dose 4–15 Gy; V4 10–20%; V10 < 10%	Mean dose > 15 Gy; V4 > 20%; V10 > 10%	Glandular tissue
Lungs (minus PTV)	V5 < 55%	V5 55–60%		V5 < 35% V20 < 20% Mean dose < 8 Gy	V5 35–45% V20 20–28% Man dose 8–12 Gy	V5 45–55% V20 28–35% Man dose 12–15 Gy	
	V20 < 30%	V20 < 35%					
	Mean dose < 10 Gy	Mean < 13.5 Gy					
Thyroid	V5 < 93% V20 < 82% V25 < 63% V30 < 62% 2.2 mL < 25 Gy	V25 < 70%	Whole thyroid	V25 < 62.5%			Whole thyroid

5. Conclusions

This survey highlights a widespread use of IMRT across Italian radiation oncology centers. The most frequently used techniques varied between centers, likely reflecting different equipment availability and experience. Respiratory gating or breathing control techniques were used infrequently. IGRT, on the other hand, was implemented, although with a variable imaging frequency, by almost all centers. Despite recent recommendations, only a minority of centers defined cardiac sub-structures as primary interest OARs. Efforts for standardization of radiotherapy techniques and clinical dose constraints for mediastinal lymphoma treatment were considered useful by almost all participating centers, and recent guidelines may be helpful. Patient-individual dosimetry data linked to clinical outcomes will constantly refine our knowledge about treatment toxicity and help to further reduce long-term treatment sequelae. Multi-institution cooperative networks such as FIL might significantly accelerate reaching this goal.

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