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Prevention and Early Detection of Radiation Induced Heart Complications in Lymphoma Patients Treated with Modern Radiotherapy

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Chapter 1 – Introduction and outline of the project

The association between chest radiation therapy (RT) and cardiac complications is nowadays well known for patients cured from mediastinal lymphomas, breast cancer and lung cancers. Cardiac complications from thoracic irradiation were, anyway, considered rare and insignificant [**1**] for a long time, although the first report on the aftereffect of X-rays on the heart was described in 1897 [**2**]. First detailed and reliable descriptions of radiation induced heart disease (RIHD) date back to occasional case reports published 40-50 years ago [**3-4**]. Hancock et al. from Stanford University subsequently established that the risk is related to doses to the mediastinum [**5-6**] in Hodgkin lymphoma (HL) patients. Since then, several studies have become available, focusing mostly on childhood, HL and breast cancer survivors, connecting cardiac RT dose with the risk of cardiac morbidity and mortality [**7-10**]. Acute complications (within 6 months by the end of the treatment) often manifest as pericarditis, which is usually transient and easily curable with anti-inflammatory therapy. Late deficits, conversely, are composed by a miscellaneous series of events and, by affecting all the heart structures, manifest with chronic heart failure (CHF), unstable angina (UA), myocardial infarction (AMI), valve impairment and arrhythmia. The late effects may rise up several years after the end of the treatment, usually appearing in the second to the third decade post-therapy [**11**]. Radiation induced heart disease has become an important argument of research nowadays, leading to intensive debate on the risk-benefit ratio of RT in lymphoma patients. Indeed, many prospective randomized studies [**12-14**] have tried to omit altogether RT from first line, with the aim of reducing life threatening long term complications (mainly cardiac events and second cancer), admitting in change a slight reduction of disease control in patients receiving chemotherapy alone. However, the recent prominent improvement of RT techniques has significantly reduced the inadvertent irradiation of organs at risk, with a particular attention in the recent years for the heart. Techniques as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) and respiratory gating have the clear goal to decrease fields and doses of RT to all the organs at risk, including the heart, without

compromising long-term disease related outcomes. For that reason, RIHD is expected to reduce dramatically in the future even though, given the long latency of these events, the magnitude of the residual risk is still uncertain.

Purpose of my PhD. research is to evaluate the potential contribution of modern RT techniques in reducing RIHD in patients affected with mediastinal lymphomas and to investigate the efficacy of new diagnostic tools in detecting radiation induced heart damage in the early preclinical phase.

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Chapter 2: Evolving role of radiotherapy in the treatment of lymphomas

2.1 INTRODUCTION

A century has passed from the initial demonstration of X-ray effectiveness in Hodgkin Lymphoma (HL) [1], while the very first clinical results on disease control and survival have been published in 1935 and 1950 [2,3]. We are still using this powerful single agent against HL, albeit in a very different way. For decades, Extended Fields Radiotherapy (EFRT) has been considered the standard treatment for HL, on the basis of the ground-breaking work published by Henry Kaplan in 1968 [4]. It later become evident that EFRT was associated with a high risk of treatment-related complications, mainly represented by heart diseases, secondary cancers and endocrine dysfunctions [5,6,7,8,9]. Concomitantly, chemotherapy has been shown to improve results when combined with radiation, particularly for early stages [10]. A number of subsequent randomized controlled trials lead to re-think the role of RT, modifying its indications and use and/or questioning its role because of serious concerns on late toxicity. Through the years, the technological "revolution" occurred in Radiation Oncology made also possible a different technical approach to HL, applying the new concepts of high-precision image-guided and intensity-modulated RT, even when delivering doses in the range of 20-30 Gy. Aims of this chapter are ***a)*** to summarize and discuss the main changes and the current role of RT in the treatment for HL in light of recent findings, and ***b)*** to delineate the present and future research paths in RT, focused on maintaining efficacy while minimizing late effects on long-term survivors.

2.2 OVERVIEW OF CLINICAL TRIALS FOR EARLY STAGE.

The initial use of RT for early stage HL was based upon extensive treatment volumes covering both involved and uninvolved lymphatic sites. For the most common presentations in early stages, for example neck and mediastinum, this approach consisted of sub-total nodal irradiation (STNI), to the

dose of 40-44 Gy. The results obtained in the time lapse 1962-1984 by the Stanford group in early stages with STNI show complete remission rates of 100% and recurrence-free survival (RFS) rates of 80% in stages IA, IIA and IIB without large mediastinal tumors [11]. During the eighties, the German Hodgkin Study Group (GHSG) designed the HD4 trial, among the first studies addressing a specific RT-related question. The major aim of HD4 was to show whether the radiation dose to the non-involved lymphatic regions could be reduced while maintaining an effective tumor control. Patients with early stage HL without risk factors (large mediastinal mass, extra-nodal extension, massive spleen involvement, > 3 lymph node areas, high Erythrocyte Sedimentation Rate) were randomized between 40 Gy EFRT (arm A) and 30 Gy EFRT plus additional 10 Gy to the Involved Field region (arm B, IFRT). Results showed no statistically significant differences in RFS and overall survival (OS) between the two treatment arms, but the overall recurrence rate approached 20%. As relapsing patients underwent effective salvage therapy, RFS at 7 years came up to 80%, with an overall survival rate of 93% [12]. Due to the importance of an adequate quality for RT, GHSG promoted the creation of a task force for quality assurance (QA). For all patients enrolled in the study, a treatment plan was given by the radiotherapy reference Centre based on the documentation of the disease extension on case report forms. After completion of RT, an expert panel analyzed simulation and verification films of every individual patient, as well as treatment data. This retrospective quality control study showed that deviations of radiation treatment portals and radiation doses from prospective treatment prescriptions were unfavorable prognostic factors [13]. A second generation of trials compared, both in favorable and unfavorable presentations, EFRT vs. IFRT in combination with chemotherapy. Very valuable data came from these studies, showing that the combination of systemic agents and RT was superior to EFRT alone, both in terms of disease control and inferior toxicity. Moreover, these trials demonstrated that, when combined with chemotherapy, RT could be safely reduced in volume from EFRT to IFRT [14,15,16]. This evolution also led to an initial reduction of late toxicity, as described by the 2005 Cochrane review focused on the therapy of early stage HL and second cancer risks [17]. At the end of the nineties, a decisive step towards a further

reduction of the therapeutic burden was made by GHSG in 2 key studies, the HD10 ad HD11 (1998–2002). In these trials, irradiation was performed as IFRT only in all treatment arms, with reduced total doses in combination with different chemotherapy schedules. The whole treatment strategy was based upon a proper selection of patients by known prognostic factors. In HD10, stage I-II patients without risk factors (no bulky disease, less than 3 involved sites, low ESR values) were randomized in a four-arm study between IFRT 30 Gy vs. 20 Gy and 2 vs. 4 cycles of ABVD. To ensure that IFRT was performed exactly according to the RT prescriptions of the protocol, an extensive quality assurance program was performed. Results of HD10 were published in 2010 [18]: the two chemotherapy regimens did not differ significantly with respect to freedom from treatment failure (FFTF) (p=0.39) or OS (P=0.61). At 5 years, the rates of FFTF were 93.0% (95% confidence interval [CI], 90.5 to 94.8) with the four-cycle ABVD regimen and 91.1% (95% CI, 88.3 to 93.2) with the two-cycle regimen. When the effects of 20 Gy and 30 Gy doses of radiation therapy were compared, there were also no significant differences in FFTF or OS (p=0.61). HD10 demonstrated that treatment with 2 cycles of ABVD followed by IFRT 20 Gy is as effective as, and less toxic (acute toxicity), than treatment with 4 cycles of ABVD followed by IFRT 30 Gy. The GHSG HD11 trial [19], in patients with unfavorable early stage disease presentation (bulky disease, multiple involved sites, high ESR values), showed that, after 4 cycles of BEACOPP, IFRT 20 Gy was not inferior to 30 Gy, whereas inferiority of 20 Gy cannot be excluded after 4 cycles of ABVD.

Meanwhile, other research groups tested a chemotherapy alone strategy in early stage HL, based on similar criteria for patients' selection (low risk of treatment failure). Some of these studies were conducted on children and/or young adults. The CCG 5942 trial showed inferior 10-year event-free survival for the no RT versus the RT arm (82.9% vs. 91.2%, p=0.004). After stratification for risk factors, a significant difference was evident for low risk patients (89.1% vs. 100%, P=0.001), but not for the intermediate and high-risk groups (78.0% vs. 84% and 79.9% vs. 88.5%, respectively) [20]. Conversely, the GPOH-HD95 trial showed that the omission of RT was safe only for low-risk patients with complete response after chemotherapy (PFS of 96.8% versus 93.6%, p=0.42), whereas this

strategy was not proven to be safe for the intermediate and the high risk groups (PFS 69.1% vs. 92.4%, p<0.001 and 82.3% vs. 90.7%, p=0.08, respectively) [21]. In adults, the largest study to directly compare chemotherapy alone with combined modality therapy was the intergroup HD.6 study (NCIC), designed with the aim of comparing chemotherapy alone (4-6 ABVD cycles) to RT only or with 2 ABVD cycles (according to risk groups), with STNI 35 Gy. [22]. An obvious critical point is that STNI is no more part of current treatments protocols, and a direct comparison on late toxicity versus chemotherapy alone is unbalanced. In 2010, Herbst et al published a systematic review with meta-analysis of randomized controlled trials comparing chemotherapy alone with CMT in patients with early stage Hodgkin's lymphoma with respect to response rate, tumor control and overall survival. Five randomized controlled trials involving 1,245 patients were included. The hazard ratio was 0.41 for tumor control and 0.40 for OS for patients receiving CMT compared to chemotherapy alone [23]. The results of these studies raised an important debate in the scientific community, still ongoing at present. An individual patient meta-analysis was recently undertaken to compare HD10 and HD11 results with HD.6 study. On 406 patients who fulfilled the eligibility criteria, combined modality therapy was shown to give better time to progression (HR=0.44); progression-free survival (PFS) was superior but without reaching statistical significance, and OS was superimposable. Remarkably, the difference between the two treatments was particularly evident among patients in partial remission after chemotherapy [24]. Conversely, a recent retrospective observational cohort study derived from the National Cancer Database on a population of 29752 early stage HL cases [25] has shown a significant improved OS for patients receiving consolidation RT (94.5% vs 88.9% at 5 years, $p < 0.01$).

The following logical step was to try to better select patients at lower/higher risk of relapse and thus adapt the use of consolidation RT. PET-CT emerged as a powerful tool to predict early chemo-sensitivity in advanced stages [26], and was consequently introduced in early stages to stratify patients with different response to chemotherapy. Functional imaging was used to modulate therapy, comparing chemotherapy alone to combined modality treatment in patients achieving complete

remission. Three major trials were designed over the last years according to this principle, the H10 trial (EORTC/GELA/FIL), the GHSG HD16 trial and the UK NCRI RAPID trial. In all studies, a panel of expert Nuclear Medicine physicians reviewed all PET-CT scans.

H10 compared ABVD + RT vs. an experimental arm where the treatment was driven by interim (after 2 ABVD cycles) PET-CT results. Notably, H10 represented a very innovative step for RT, introducing the new concept of "Involved Node Radiotherapy" (INRT), a further reduction of radiation volumes on the basis of pre- and post-chemotherapy imaging [27]. Patients with favorable presentations according to EORTC criteria were randomized to ABVD x 3 + INRT 30 Gy vs. ABVD x 2 and, if PET negative, 2 more ABVD cycles (chemotherapy alone). This trial is now closed and the final results will be available within next 2 years. The independent data monitoring committee advised to stop the chemotherapy alone arm due to an excess number of relapses (in both favorable and unfavorable arms) [28]. This decision was deeply discussed, as probably a difference in failure-free survival between the two arms (the primary endpoint for non-inferiority), was to be accounted in the statistical design at the beginning, even in patients in metabolic complete response. Overall Survival is expected to be the same for both arms after adequate salvage therapy. The ongoing GHSG HD16 trial has a more "contemporary" design with regards to RT doses and compares, in favorable patients (according to GHSG criteria), a standard arm consisting of 2 ABVD cycles followed by IFRT 20 Gy to a PET-guided experimental arm consisting of 2 ABVD and observation (if negative) or IFRT 20 Gy (if positive). The purely RT-related issue on the potential equivalence of IFRT and INRT is being investigated in a parallel trial, the GHSG HD17 [29].

In the UK NCRI RAPID trial [30], low-risk patients (defined as stage I-IIA non bulky presentations) with a PET negative finding after 3 ABVD cycles were randomized either to 30 Gy IFRT or to observation only. Patients with a positive PET were treated with one more ABVD cycle plus 30 Gy IFRT. Results suggested, as expected, slightly inferior PFS rates for chemotherapy alone in comparison with chemo-radiotherapy in PET negative patients, representing 74.6% of patients using a prudential cut-off for positivity at Deauville's score 3 (3-year PFS: 90.8% vs. 94.6%, per protocol).

PET positive patients had 86.2% PFS rate. OS was equivalent, with most relapsing patients receiving efficient salvage therapies. Table I summarizes the results of major clinical trials with radiotherapy-related endpoints in early stage HL.

Table 2.1 – Summary of clinical trials investigating for RT-related endpoints in early stage Hodgkin's lymphoma.

Study	N	Median follow-up, mo	Treatment	OS, %	*P*	FFTF, EFS, FFP, PFS, %	*P*
GHSG (HD4)[12]	376	86	EFRT 40 Gy EFRT 30 Gy	91 at 7 yr 96 at 7 yr	NS	78 at 7 yr 83 at 7 yr	NS
Istituto Nazionale Tumori[14]	136	116	ABVD x 4 + STNI ABVD x 4 + IFRT	96 at 12 yr 94 at 12 yr	NS	93 at 12 yr 94 at 12 yr	NS
GHSG (HD8)[15]	1064	54	COPP/ABVD x 2 + EFRT COPP/ABVD x 2 + IFRT	90.8 at 5 yr 92.4 at 5 yr	NS	85.8 at 5 yr 84.2 at 5 yr	NS
EORTC (H8)[16]							
Favorable	542	92	STNI MOPP-ABV x 3 + IFRT	92 at 10 yr 97 at 10 yr	.001	74 at 5 yr 98 at 5 yr	< .001
Unfavorable	996		MOPP-ABV x 6 + IFRT MOPP-ABV x 4 + IFRT MOPP-ABV x 4 + STNI	88 at 10 yr 85 at 10 yr 84 at 10 yr	NS	84 at 5 yr 88 at 5 yr 87 at 5 yr	NS
GHSG (HD10)[18]	1370	90	ABVD x 2 + IFRT 20 Gy ABVD x 2 + IFRT 30 Gy ABVD x 4 + IFRT 20 Gy ABVD x 4 + IFRT 30 Gy	95 at 8 yr 94 at 8 yr 95 at 8 yr 94 at 8 yr	NS	86 at 8 yr 86 at 8 yr 90 at 8 yr 87 at 8 yr	NS
GHSG (HD11)[19]	1395	91	ABVD x 4 + IFRT 20 Gy ABVD x 4 + IFRT 30 Gy BEACOPPbase x 4 + IFRT 20 Gy BEACOPPbase x 4 + IFRT 30 Gy	94 at 5 yr 94 at 5 yr 95 at 5 yr 95 at 5 yr	NS	81 at 5 yr 85 at 5 yr 87 at 5 yr 87 at 5 yr	.02
CCG (5942)[18]	826	91	COPP/ABVD x 4 or COPP/ABV x 6 or 6 intensified cycles + IFRT COPP/ABVD x 4 or COPP/ABV x 6 or 6 intensified cycles + NFT	97.1 at 10 yr 95.9 at 10 yr	.05	91.2 at 10 yr 82.9 at 10 yr	.004
GPOH (HD95)[21]	925	120	OPPA/OEPA x 2 OPPA/OEPA x 2 + RT if PR OPPA/OEPA x 2 + COPP x 2 OPPA/OEPA x 2 + COPP x 2 + RT if PR OPPA/OEPA x 2 + COPP x 4 OPPA/OEPA x 2 + COPP x 4 + RT if PR	98.5 at 10 yr 98.7 at 10 yr 97.7 at 10 yr 98.1 at 10 yr 100 at 10 yr 95.3 at 10 yr	NS NS NS 	97.0 at 10 yr 92.2 at 10 yr 68.5 at 10 yr 91.4 at 10 yr 82.6 at 10 yr 88.7 at 10 yr	NS <.001 NS
NCIC/ECOG (HD.6)[22]	399	50	ABVD x 4-6 ABVD x 2 + STNI	96 at 5 yr 94 at 5 yr	NS	87 at 5 yr 93 at 5 yr	.006
EORTC/LYSA/FIL (H10 interim analysis)[24]							
Favorable	444	13	ABVD x 3 + INRT ABVD x 4 ABVD x 2 + BEACOPPesc x 2 + INRT	/ /		100 at 1 yr 94.3 at 1 yr	.017
Unfavorable	693		ABVD x 4 + INRT ABVD x 6 ABVD x 2 + BEACOPP x 2 + INRT	/ /		97.28 at 1 yr 94.7 at 1 yr	.026
UK NCRI (RAPID interim analysis)[30]	420 PET neg	48	ABVD x 3 + NFT (ITT) ABVD x 3 + IFRT (ITT) ABVD x 3 + NFT (PP) ABVD x 3 + IFRT (PP)	99.0 at 3 yr 97.1 at 3 yr / /	NS	90.8 at 3 yr 94.6 at 3 yr 90.8 at 3 yr 97.1 at 3 yr	NS 0.02

Abbreviations: yr, years; mo, months; OS, overall survival; FFTF, freedom from treatment failure; EFS, event-free survival; FFP, freedom from progression; PFS, progression free survival; RT, radiotherapy; EFRT, extended field radiotherapy; STNI, subtotal nodal irradiation; IFRT, involved field radiotherapy; NFT, no further treatment; INRT, involved nodal radiotherapy; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; COPP/ABVD, cyclophosphamide, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, vinblastine, and dacarbazine; MOPP/ABV, mechlorethamine, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, and vinblastine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; COPP/ABV, cyclophosphamide, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, and vinblastine; OPPA/OEPA, vincristine, procarbazine, prednisone, and doxorubicin/vincristine, etoposide, prednisone, and doxorubicin; PR, partial response; PETneg, positron emission tomography negative; ITT, Intention to treat; PP, per protocol.

The impact of the last "generation" of PET-adapted studies on the current role of RT outside clinical trials is challenging. Data suggest that the omission of RT, even in selected patients, lead to inferior PFS rates; on the other side, the entity of the difference is small and OS rates are similar. The use of early PET findings to guide therapy outside clinical trials is generally considered not appropriate, for two main reasons: an unclear role as prognostic marker in early stage in comparison with advanced stages, with controversial retrospective findings [31,32,33], and the need to have a strict quality control on images interpretation in daily clinical routine (in all trials, PET images were centrally reviewed by a panel of nuclear medicine experts). A balanced multi-disciplinary evaluation of individual patients should be encouraged for the proper selection of the best strategy according to age, disease extension, secondary cancer and heart diseases risk profile.

2.3 OVERVIEW OF CLINICAL TRIALS FOR ADVANCED STAGE HODGKIN'S LYMPHOMA

Advanced-stage HL usually includes stages III-IV, but many groups also include patients with stage IIB. Historically, less than 5% of these patients survived when left untreated or received single-agent chemotherapy. Table II summarizes the results of major clinical trials with radiotherapy-related endpoints in advanced stage HL. Combined modality treatment with multi-agent chemotherapy such as MOPP or ABVD + EFRT drastically changed the prognosis, reaching high cure rates. An Italian trial then demonstrated that ABVD plus EFRT was better than MOPP plus EFRT in terms of freedom from progression (80.8% vs 62.8%; $p < 0.002$) and overall survival (77.4% vs 76.9%; $p = 0.03$) [35]. These findings were later confirmed in different trials with longer follow-up. Subsequently, ABVD has been compared to multi-drugs hybrid regimens in order to find the best multi-agent chemotherapy schedule for advanced stage HL.

Table 2.2 – Summary of clinical trials investigating for RT-related endpoints in advanced stage Hodgkin's lymphoma.

Study	N	Median follow-up, mo	Treatment	OS, %	*P*	FFTF, EFS, FFP, PFS, %	*P*
Istituto Nazionale Tumori[35]	232	84	ABVD + EFRT 30-35 Gy MOPP + EFRT 30-35 Gy	77.4 at 7 yr 67.9 at 7 yr	0.03	80.8 at 7 yr 62.8 at 7 yr	<0.002
STANDORD V[37]	142	65	STANFORD V + radiotherapy 36 Gy in case of bulky disease (≥ 5 cm) or macroscopic splenic nodules	96 at 5 yr		89 at 5 yr	
EORTC 20884 (Aleman et al)[40]	421	79	MOPP-ABV + IFRT MOPP-ABV	85 at 5 yr 91 at 5 yr	NS	79 at 5 yr 84 at 5 yr	NS
HD9[42]	1201	54	A: COPP-ABVD + RT on original bulky disease or residual tumor B: BEACOPP baseline + RT on original bulky disease or residual tumor C: BEACOPP escalated + RT on original bulky disease or residual tumor	83 at 5 yr 88 at 5 yr 91 at 5 yr	A vs C 0.002	69 at 5 yr 76 at 5 yr 87 at 5 yr	A vs B 0.04 A vs C <0.001 B vs C <0.001
Intergruppo Italiano Linfomi[38]	355	61	A: ABVD + IFRT on original bulky or incomplete remission disease B: Stanford V + IFRT on original bulky or incomplete remission disease C: MOPPEBVCAD + IFRT on original bulky or incomplete remission disease	90 at 5 yr 82 at 5 yr 89 at 5 yr	A vs B 0.04	78 at 5 yr 54 at 5 yr 81 at 5 yr	B vs others: <0.01
HD12[43]	1670	78	A: BEACOPPbase x 4 + BEACOPPescalated +/- IFRT to bulky or residual disease B: BEACOPPescalated x 8 +/- IFRT to bulky or residual disease Subgroup analysis: - IFRT group - NO-IFRT group	90.3 at 5 yr 92 at 5 yr NA NA	NS	85 at 5 yr 87.5 at 5 yr 90.4 at 5 yr 87 at 5 yr	NS 0.07
GITIL/FIL HD0607[45]	773	34	A: ABVD x2 + BEACOPPbase x 4 +BEACOPPescalated (if PET2 positive) B: ABVD x6 (if PET2 negative) Randomization for RT (only for patients completing ABVD x 6): - IFRT to initial bulky disease - NO IFRT to initial bulky disease	86 at 4 yr 95 at 4 yr not yet available		62 at 4 yr 85 at 4 yr not yet available	
FIL HD0801[46]	519	27	A: ABVDx2 + HDCT/ASCT (if PET2 positive) B: ABVD x6 (if PET2 negative) Randomization for RT (only for patients completing ABVD x 6): - IFRT to initial bulky disease - NO IFRT to initial bulky disease	NA NA not yet available		76% at 2 yr 81% at 2 yr not yet available	NA

Abbreviations: yr, years; mo, months; OS, overall survival; FFTF, freedom from treatment failure; EFS, event-free survival; FFP, freedom from progression; PFS, progression free survival; RT, radiotherapy; EFRT, extended field radiotherapy; IFRT, involved field radiotherapy; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; STANFORD V, vinblastine, doxorubicin, vincristine, bleomycin, mechlorethamine, etoposide, prednisone; MOPPEBVCAD, mechlorethamine, vincristine, procarbazine, prednisone, vinblastine, epidoxirubicin, bleomycin, lomustin, doxorubicin, vidensine; COPP/ABVD, cyclophosphamide, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, vinblastine, and dacarbazine; MOPP/ABV, mechlorethamine, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, and vinblastine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; PET2, positron emission tomography after 2 cycles of chemotherapy.

The multicenter UK LY09 trial [36] showed no benefit for two different alternating hybrid regimens (ChlVPP/PABIOE and ChlVPP/EVA) compared to ABVD, which remained the standard for the

treatment of advanced HL. In this study patients were considered for consolidation RT (30 to 35 Gy) to residual masses or sites of original bulky disease. Patients who received RT had worse prognostic factors (bulky disease, residual masses after chemotherapy), but better outcomes, consistently across all prognostic groups (PFS 86% vs 71%, p = 0.001), thus suggesting that RT could contribute significantly to the cure rate for advanced HL.

Later on, an alternative US regimen, Stanford V, gave challenging results. Horning et al [37] reported interesting 5-years results (FFP = 89% and OS = 96%) on a population of 142 patients. Most patients (91%) received consolidation IFRT (median dose 36 Gy) to initial bulky sites >5 cm. An Italian prospectively randomized multicenter trial compared ABVD with Stanford V and MOPP-EBV-CAD demonstrating that Stanford V was associated with poorer failure free survival (FFS) (67% vs 83% or 85%) when compared with ABVD or MOPP-EBV-CAD [38].

Same results were obtained by a larger UK trial, that compared Stanford V with ABVD [39] obtaining complete remission rates rather similar across the cohorts (73% for ABVD and 69% for Stanford V) and no significant difference in FFS at 5years (74% for ABVD and 71% for Stanford V). Toxicities were more frequent in patients treated with Stanford V, partly due to the higher rates of patients receiving mediastinal RT in the Stanford V arm (73% vs 53%). More recently an Intergroup study (ECOG, NCIC and SWOG) failed to find a clinical benefit for patients treated with Stanford V compared to ABVD (FFS at 6.4 years 74% vs 71%, p = 0.32).

The European Organization for Research and Treatment of Cancer (EORTC) also performed a randomized trial to test the role of RT in the treatment of advanced stage HL patients [40]. Patients were randomly assigned to receive IFRT 24 Gy to the initially involved areas (30 Gy in cases of partial remission evaluated with CT scan) after completing chemotherapy according with MOPP/ABV schedule. IFRT did not improve outcomes in patients in complete remission (5-year EFS = 79% vs 84%, p = 0.35). However, patients in partial remission (higher rate of bulky disease) probably benefited from RT since the EFS and OS rates (76% and 84%, respectively) at 8 years resulted to be comparable to patients in complete remission who did not receive RT (77% and 85%,

respectively) [41]. Furthermore, the incidence of second malignancies in patients treated with IFRT was similar to non-irradiated patients. These results supported the use of RT for patients with partial response after chemotherapy.

More recently, the GHSG developed the BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone). The randomized phase III trial HD9 demonstrated a clear superiority of $BEACOPP_{escalated}$ over COPP/ABVD [42]. In this trial, RT was given to sites of initial bulky disease (at least 5 cm in diameter) to a dose of 30 Gy, followed by a 10 Gy boost to any residual site. Later on, the GHSG HD12 trial [43] has shown no benefit for patients receiving RT to sites of initial bulky disease in complete response after 8 cycles of BEACOPP (difference, -1.1%; 95% CI: -6.2% to 4%). Conversely, 5-year FFTF was inferior without RT in patients who had residual disease after BEACOPP chemotherapy.

The GHSG HD15 trial then tested 6 cycles of BEACOPP esc vs 8, showing better PFS (90.3% vs 85.6%) and OS (95.3% vs 91.9%) for the shorter schedule [44]. In addition, the treatment-related mortality was only 0.8% with 6 cycles as compared with 2.1% with 8 cycles. Patients with a persistent mass measuring more than 2.5 cm and PET positive scan also received IFRT 30 Gy. PFS at 4 years was 86.2% for PET positive patients vs. 92.6% for PET negative patients, respectively (p= 0.022). Hence, a positive PET was associated with a worse outcome, despite the use of RT. As the use of PET-guided RT was not assessed in a randomized fashion, the effects of chemotherapy and radiotherapy cannot be distinguished in PET positive patients. The ongoing HD18 trial maintains IFRT to the sites of persistent PET positivity.

In the Italian HD0607 trial, a specific aim was to assess the role of consolidative RT in bulky patients in complete remission (PET negative) after 2 ABVD cycles and continuing up to 6 cycles (for PET positive patients, intensification with BEACOPP was scheduled). Preliminary results of this trial, presented at the IMCL 2015 conference, [45] showed a 4-year failure-free survival of 62% for PET+ patients and 86% for PET- patients. Results regarding the role of consolidation RT after ABVD on initial bulky disease are not yet available and longer follow-up is needed to address this question. In

the FIL trial HD0801, patients with interim PET negativity were also randomized to receive consolidative RT to initial bulky lesion after completing 6 ABVD cycles. Early intensification with ASCT was shown to be efficient for patients with interim PET positivity (primary endpoint of the trial) [46], but results concerning the role of consolidation RT in PET negative patients are not yet available.

2.4 ROLE OF RADIOTHERAPY AT RELAPSE/SALVAGE THERAPY

Few retrospective studies investigated the role of RT in the context of salvage therapies for relapsed/refractory HL. Investigators from Memorial Sloan Kettering Cancer Center (MSKCC) published several reports in patients undergoing high-dose chemotherapy (HDCT) followed by autologous stem cells transplantation (ASCT). [47,48,49]. They incorporated RT into salvage programs by administering total lymphoid irradiation (TLI) before ASCT. The rationale was to harness the debulking effect of RT before ASCT. This strategy was shown to be feasible when given in accelerated mode, assuring that ASCT was not delayed. The radiation schedule consisted of IFRT to residual disease or previously bulky sites (18 Gy/10 fractions) followed by TLI in previously unirradiated patients (18 Gy/10 fractions). RT was administered twice daily over 2 weeks. The updated results of this schedule reported a 5-year EFS and OS of 63% and 71%, respectively, on a population of 153 patients [50]. However, this intensive RT approach has not been widely replicated in other Centres, due to the high rates of acute complications. A warning was reported by Tsang et al [51], who noticed 8 treatment related deaths out of 24 patients (33%) receiving TLI before ASCT. All deaths were related to fatal pulmonary complications. In order to further explore the role of peri-trasplant RT, other authors tested a less intensive approach, by omitting the TLI part of treatment. A report from Stanford University [52] evaluated the role of IFRT in a population of 100 relapsed/refractory HL patients. Twenty-four patients received RT to bulky lesion (>5 cm) at diagnosis or to sites of persistent disease after salvage chemotherapy and/or ASCT. No benefit was

shown for IFRT at 3 years in terms of both freedom-from-relapse (FFR, 75% vs 64%, p = 0.19) and OS (70% vs 61% p = 0.41). However, IFRT provided high rates of local control, with only 2 patients (8%) relapsed in radiated sites. A subgroup analysis on patients with limited disease at relapse (Stage I-III) and no prior history of RT showed that IFRT improved 3-year OS (90% vs 50%, p = 0.04) and PFS (100% vs 51%, p = 0.03).

Conversely, Wendland et al [53] from the University of Utah found no significant benefit for HL patients who received peri-transplant IFRT (n = 21) in a cohort of 65 patients. Five-year OS was 73.3% for IFRT group and 55.6% for no-IFRT group (p = 0.16), respectively. However, the incidence of bulky disease was higher for IFRT group (47.6% vs 31.8%, p = 0.05) and this intrinsic selection bias might have had an effect. A case-control study from Emory University [54], on a population of 92 relapsed/refractory HL patients (46 received IFRT), again showed no benefit for IFRT in terms of disease free survival (DFS) (p = 0.206). Bulky presentations were more common among the IFRT subgroup (63% vs 13%, p = 0.001), and stratification was required to compensate this bias. In patients with bulky disease, IFRT correlated with a significant improvement in DFS (p = 0.032). Moreover, at Cox analysis, only IFRT and non-bulky disease were favorable prognostic factors for DFS, with HR of 0.357 and 0.383, respectively. Biswas et al [55] also showed a marginal 3-year benefit in OS and disease specific survival (DSS) (p = 0.05 and p = 0.08, respectively) for HL patients receiving IFRT within 6 months from ASCT. This advantage was lost with longer follow up (p = 0.18 for OS and p = 0.38 for DSS), probably due to the small number of patients enrolled in this study (n = 62) and the limited follow up time (median: 2.41 years). Furthermore, at multivariate analysis only the presence of B-symptoms was prognostic for OS (HR 2.904, p = 0.02), while IFRT had a marginal role (HR 0.429, p = 0.06). Patients receiving IFRT had, however, improved local control in areas of previously recurrent disease (p = 0.03).

More recently, Eroglu et al. [56] published their experience on a cohort of 45 relapsed/refractory HL patients treated with ASCT. Of these, 20 patients received peri-transplant IFRT. They found that addition of IFRT provides a survival benefit only in patients with early stage disease (Stage I-II) at

relapse (81% vs 66% at 5 years, p = 0.045). We recently reported [57] on a population of 73 patients treated with ASCT for relapsed/refractory HL. Twenty-one patients received peritransplant IFRT. Overall, no difference appeared in 3-years OS and PFS (p =0.42 and p =0.39, respectively) between patients receiving RT (87.4% and 61.8%) and patients treated with CT alone (79.5% and 59.6%). At multivariate analysis, advanced stage at relapse and persistent disease prior to ASCT (PET+) were related to worse PFS and OS. Omission of IFRT, after adjustment for potential confounding factors due to an unbalanced distribution of prognostic variables between the treatment subgroups, had a marginal prognostic role both in term of PFS (HR =2.783, p =0.056) and of OS (HR =3.181, p =0.067). When stratified by stage at relapse and PET+, patients receiving peri-transplant IFRT showed higher 3-year OS rates (91.7% vs 62.3% respectively) and PFS rates (67.5% vs 50%) compared to patients treated with CT alone, even if the difference was not significant (p =0.13 and p =0.22, respectively).

Given the lack of prospective studies, the role of IFRT prior or after HDCT-ASCT is uncertain; its use could possibly compensate for the presence of negative prognosticators: particularly, IFRT seems to be an effective tool in decreasing the risk of relapse bulky/PET positive sites prior to ASCT.

2.5 INNOVATIONS IN RADIOTHERAPY AND STRATEGIES TO MINIMIZE RADIATION-INDUCED LATE TOXICITY.

The transition from EFRT to IFRT was relatively easy since IF were “sub-volumes” of EF, and the fields delineation was based on the anatomical boundaries typical of 2D RT, as exemplified by J. Yahalom and P. Mauch in their 2002 classic article [58].

When CT simulation and 3D reconstruction software became available, radiation oncologists began to delineate smaller volumes, corresponding to a new way of considering IF-RT in comparison with the 2D era. At the same time, pre-chemotherapy imaging (CT and PET-CT) became the basis for volumes delineation, actually corresponding to involved sites at diagnosis. This concept has been

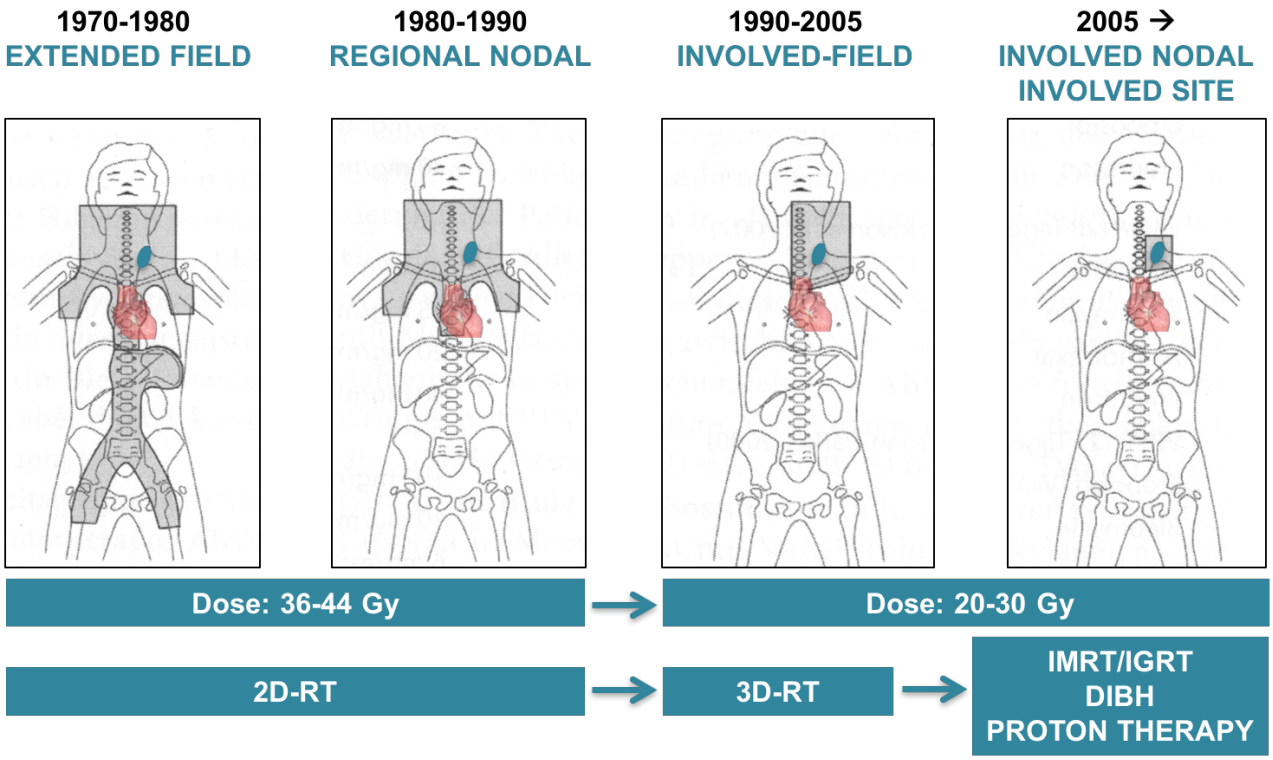
recently defined as “involved-site radiotherapy” (ISRT), according to the HL radiotherapy guidelines published by the International Lymphoma Radiation Oncology Group (ILROG) [59], and was developed on the basis of the INRT concept defined by EORTC in H10 trial [28].

In both INRT and ISRT, the pre-chemotherapy involvement determines the clinical target volume, and the resulting irradiated volume is significantly smaller than with IFRT. When pre-chemotherapy imaging is available, the contouring process could be divided into 4 steps:

1. delineation of the initially involved lymphoma volume on pre-chemotherapy CT (GTV-CT) as determined by morphology;
2. delineation of the initially involved lymphoma volume on pre-chemotherapy PET-CT (GTV-PET) as determined by FDG uptake;
3. pre-chemotherapy PET-CT images co-registration with post-chemotherapy planning CT scan (the GTV-CT and GTV-PET are imported from the pre-chemotherapy CT to the post-chemotherapy CT);
4. delineation of the post-chemotherapy volume using the information from both pre-chemotherapy PET and pre-chemotherapy CT, taking into account tumor shrinkage and other anatomic changes. In this way, a CTV is obtained encompassing all the initial lymphoma volume while sparing normal tissues that were never involved such as lungs, chest wall, muscles and mediastinal structures. INRT actually represents a special case of ISRT, in which pre-chemotherapy imaging is ideal for post-chemotherapy treatment planning.

Outside clinical trials specifically investigating new radiation volumes (i.e. H10 or HD17), radiation fields currently used in clinical routine (henceforth to be called ISRT) are significantly different from the traditional approach of IFRT. High-quality retrospective clinical data show that INRT is safe and effective in terms of disease control [60-62]. Figure 1 represents the mayor timeline changes for RT in HL.

Figure 2.1 – Radiotherapy evolution in the treatment of early stage Hodgkin's lymphoma



Beyond the ISRT/INRT concept, the technological break-troughs in radiation oncology also led to the introduction in clinical practice of highly conformal techniques such as Intensity Modulated Radiotherapy (IMRT). Standard radiation technique consisted in the past of simple parallel-opposed anterior-posterior fields (AP-PA); also in the era of 3D-conformal radiation therapy (3D-CRT), the AP-PA approach still represented the most classical solution. Reduced and better defined radiation volumes, together with the advances in treatment planning tools, now allow for the utilization of more conformal radiation therapy, based on more consistent imaging and advanced radiation delivery techniques. As underlined in the ILROG guidelines [59], although the advantages of IMRT include the tightly conformal doses and steep gradient next to normal tissues, target definition and treatment delivery verification need even more attention than with conventional RT to avoid the risk of geographic miss and subsequent decrease in tumor control. Image guidance may be required to ensure

full coverage during the whole treatment; preliminary retrospective clinical data on the combination of image guidance and IMRT with reduced volumes (ISRT) support the safety of this approach [63]. Comparative planning studies showed both that INRT may offer a substantial dosimetric benefit in comparison with IFRT and that IMRT may result in a better dose distribution around the target volumes, especially for unfavorable mediastinal presentations (bulky disease, involvement of the anterior mediastinum) [64-70]. IMRT can also reduce the mean dose received by critical thoracic structures such as heart and coronary arteries. Van Nimwegen et al [71] have recently demonstrated that the risk of coronary artery disease increases linearly with the mean heart dose (excess relative risk per Gy = 7.4%), thus dose reduction to the heart is expected to significantly lower cardiac complications.

With the optimized dose distributions achievable with advanced IMRT in lymphomas [72,73], it is currently possible to better spare the heart in comparison with 3D-CRT, and modelling studies showed that the risk of cardiac toxicity was reduced accordingly to the heart mean dose reduction (even if not abrogated). The IMRT dosimetric gain on heart is usually associated with a larger amount of other normal tissues such as breasts or lungs receiving very low doses (1-2 Gy out of 30 Gy), with a potential negative impact on radiation-induced secondary malignancies risk. Notably, the shrinkage of radiation fields from EFRT to IFRT has been shown to decrease the risk of second cancers, as reported by De Bruin et al [74]. This effect might be significant also when shifting from IFRT to ISRT/INRT, especially in specific disease presentations (according to the disease extent and the involved lymph nodes anatomical location). Few interesting modelling studies were conducted with the aim of evaluating both the impact of reduced volumes and low doses distribution of IMRT on secondary cancers risk in early stage HL [75-78]. Results showed that INRT, at least theoretically, may reduce the risk of secondary cancers in comparison with IFRT; the findings on IMRT vs. 3D-CRT were rather unclear, depending on both the IMRT technique and the radiobiological models used for risk estimation. The previously cited “butterfly” fields arrangement [72,73] offers a good technical solution to spare heart while maintaining, at least theoretically, a similar or even lower risk

of secondary malignancies. However, reliable data on the incidence of secondary tumors after combined modality therapy with INRT-IMRT will only become available over the next years. On the other hand, one study has even shown a survival benefit in select subgroups of patients receiving IMRT, when compared to 3D-CRT for all stages of HL [79].

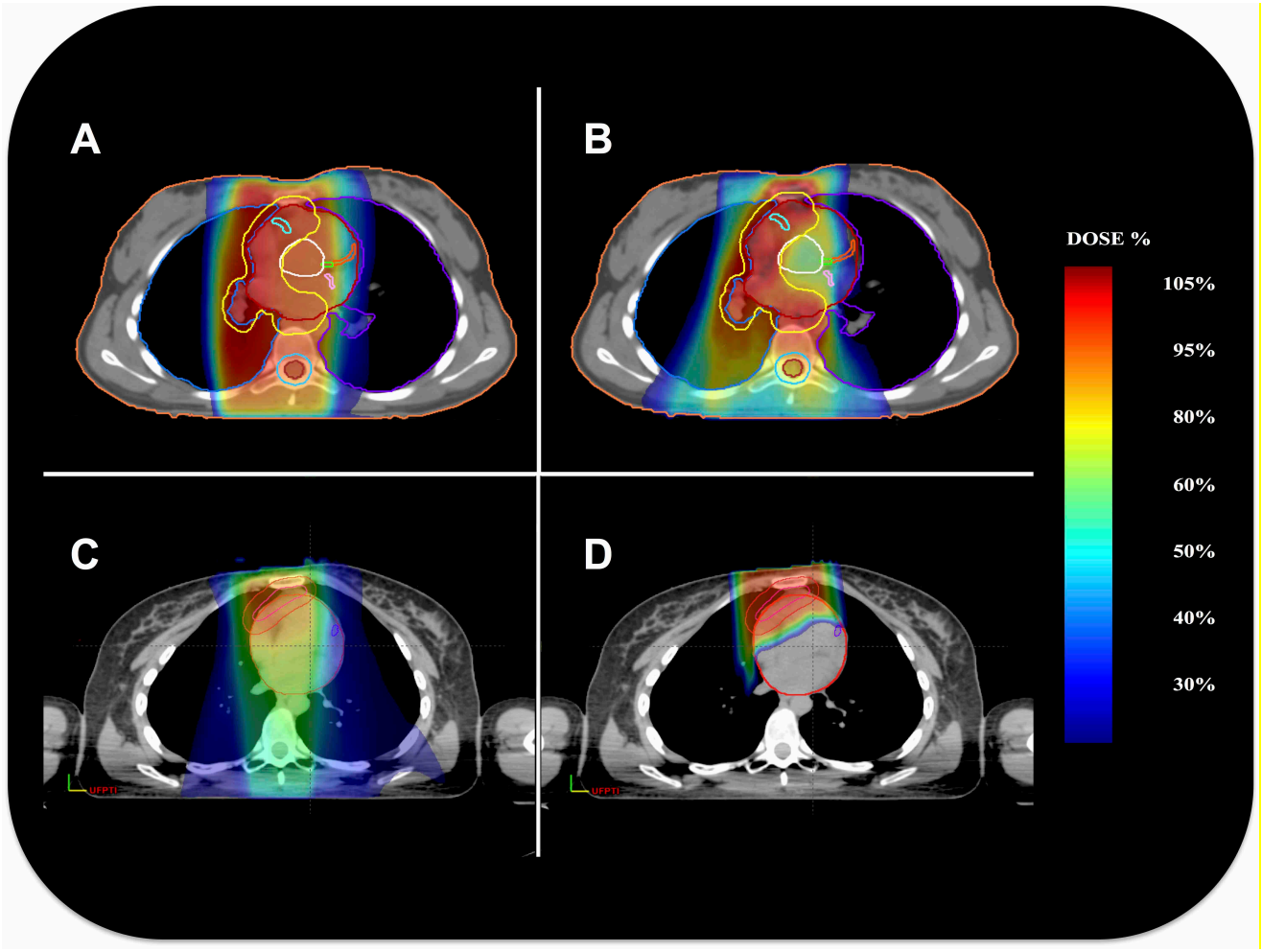
Further refinements in treatment delivery with either 3D-CRT or IMRT for mediastinal lymphomas include deep inspiration breath-hold (DIBH) technique. DIBH is an advanced strategy to compensate for breathing motion for patients with tumors of the lung, breast, and mediastinum. Studies have shown that DIBH can effectively reduce the estimated dose to the heart and lung, with equal doses of radiation to the breast tissue in female patients [80,81]. This treatment technique (when compared to free-breathing treatment) is yet another way to lower a patient's lifetime excess risks of cardiac and pulmonary toxicity without compromising target coverage. Combining IMRT with DIBH is still investigational in many centers and may have promising outcomes. With the optimized dose distributions achievable with advanced IMRT in lymphomas, modelling studies showed that the risk of cardiac toxicity was reduced accordingly to the heart mean dose reduction [72,78]; a larger amount of other normal tissues such as breasts or lungs may receive very low doses to larger volumes in comparison with 3D-CRT, however radio-biological estimates showed that the risk of secondary malignancies associated to this low-dose exposure is very limited [77-78].

Another innovation growing in use for HL is proton therapy (PT). Unlike x-rays (as used in IMRT), PT utilizes charged particles to deliver the radiation to a specific depth, eliminating the exit dose, and minimizing collateral damage to the organs at risk. Figure 2 depicts examples of static, dynamic IMRT and PT for typical mediastinal presentations of stage I-II HL.

PT can be delivered using passive scatter or scanning beam techniques. Compared with 3D conformal and IMRT photon techniques, PT was associated with lower dose to the heart [78,82,83,], lungs [82,84], esophagus [84], and total body [84]; in a study by Maraldo et al, PT was associated with the overall fewest life years lost due to 2nd cancers and cardiac complications when compared with 3D-CRT or VMAT [78]. In addition, although the long term benefit from PT will take decades to

recognize, Chung al [85] reported a 50% reduction in second cancers among a large cohort of patients of different disease types treated with PT at MGH were compared with patients treated with photon radiation in the SEER registry. Currently, pencil beam scanning (PBS) represents the one of the modern and complex approaches for delivering proton therapy with good early experience with robust treatment planning in HL [86].

Figure 2.2 – Comparison of color-wash dose distribution between different techniques in two patients. On the upper part, involved-site 3DCRT (A) vs. optimized VMAT(B) in a 21-year-old male patient presenting with stage IIA mediastinal-supraclavicular Hodgkin's lymphoma (Radiation Oncology Department, University of Torino, Italy). In the lower part, step and shoot IMRT (C) vs. proton therapy (D) in a 28-year-old female patient with stage IIA Hodgkin's lymphoma (Radiation Oncology Department, University of Florida, Jacksonville, USA)



Early clinical experience with PT in HL has demonstrated similar relapse rates as seen with 3D-CRT and IMRT without any grade 3 toxicity [87,88,89]. Consequently, National Collaborative Cancer

Network guidelines for Hodgkin's lymphoma now support the utilization of the treatment technique that may best spare the OARs including IMRT or PT, and advanced modalities should be considered on a case-by-case basis by the highly-skilled radiation oncologist [90].

2.6 CONCLUSIONS

HL patients should be possibly included in clinical trials investigating for treatment optimization. In clinical routine, combined modality therapy represents a standard for early stage, with some recent findings showing that CT alone could be an option in patients with low risk disease, at the price of a lower PFS; the role of RT is also still debated for advanced-stage, with a particular focus on the potential benefit of consolidative RT on bulky presentations at diagnosis. Waiting for the result of the ongoing trials, radiation oncologists should be aware of the opportunity to minimize the risks of late toxicity by using smaller fields and most recent technological improvements in radiation planning and delivery.

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Chapter 3 – Estimation of heart motion and definition of compensatory expansion margins for coronary arteries

3.1 BACKGROUND

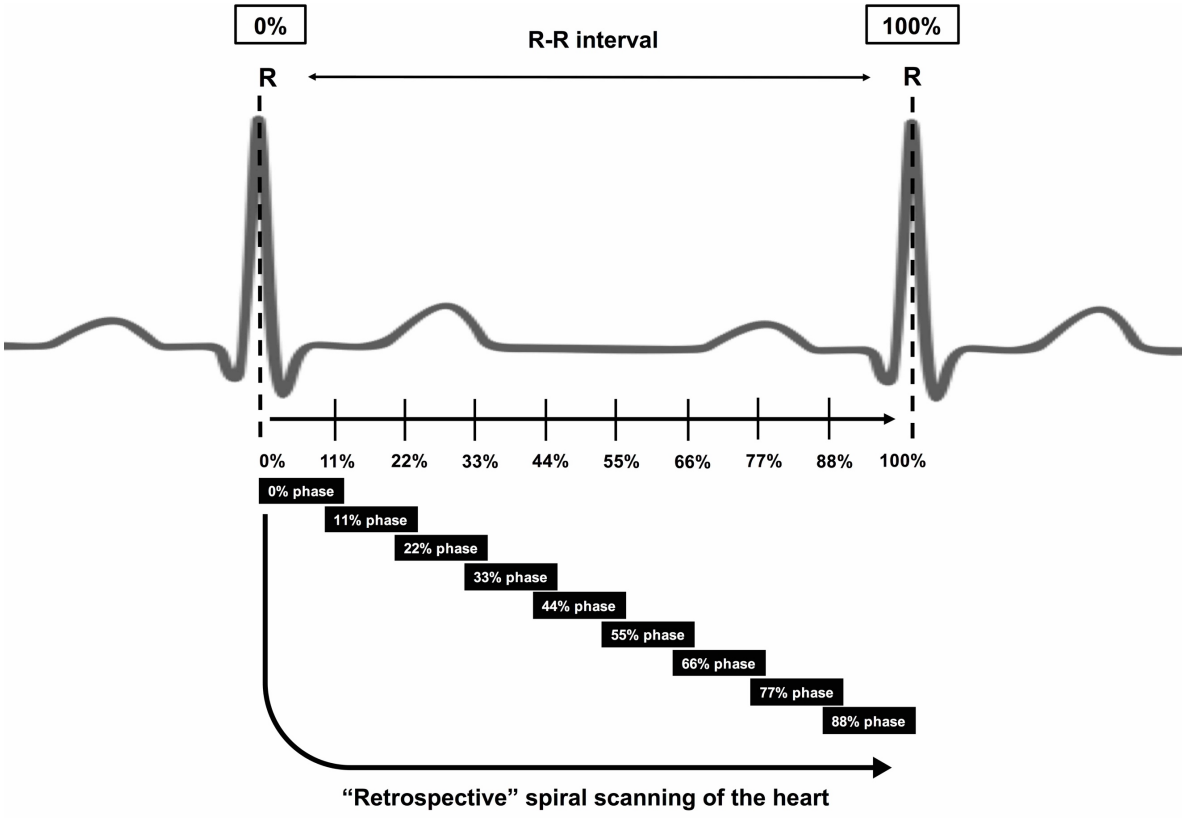
Radiation therapy (RT) for mediastinal lymphomas and other thoracic tumors frequently entails the involuntary exposure of the whole heart and its substructures. Several studies, conducted on large cohorts of Hodgkin lymphoma and breast cancer long-term survivors, have reported an increased risk of cardiovascular complications and death for those patients who received thoracic RT [**1-4**]. All these studies indicated a clear relationship between the dose received by the whole heart and the incidence of long-term cardiovascular complications, particularly ischemic events [**5-6**]. Mean and maximum heart dose have been largely used as dose-volumetric parameters for RT treatment optimization; however, these constraints do not account for the different dose received by important cardiac substructures such as coronary arteries (CA). This dose may be strictly dependent on the definition of the target and organs at risk volume, and modern contouring attitudes include the separate delineation of CA, with the aim of maximally sparing these structures [**7**]. To date, very few studies [**8-9**] have explored the correlation between the dose received by CA and long-term events such as coronary stenosis, and CA dose was essentially derived from retrospective studies based on "a posteriori" reconstruction of the treated thoracic volumes. A prospective contouring of CA has not been routinely incorporated into RT treatment flow, mostly due to: *a)* the absence of clear dose-constraints; *b)* the complexity and time-consuming contouring procedure; *c)* the blurring effect, even when adopting intravenous contrast; *d)* the difficulty in locating such thin vessels; *e)* the uncertainties in quantifying heart-beating related motion. Nevertheless, given that ischemic heart disease is the most relevant cardiac complication after thoracic RT, and that high dose-gradient techniques such as intensity modulated radiotherapy (IMRT) may allow for a better heart sparing, efforts should be done in better defining CA, also compensating for cardiac motion. In the present study, we aimed to

quantify CA motion in relation with cardiac activity, and to estimate an expansion margin that might be able to compensate for CA displacement.

3.2 MATERIAL AND METHODS

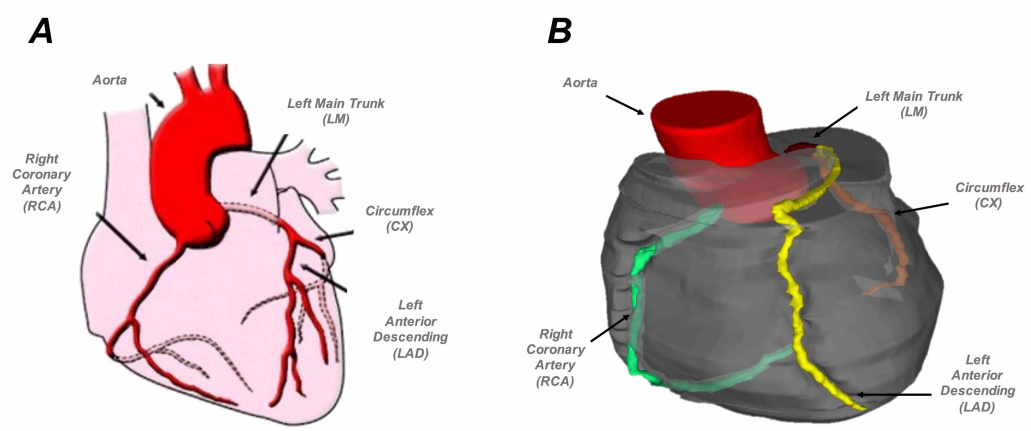
Eight subjects without any cancer history were included in this pilot study. All patients were referred to the Radiological Department of our Hospital between April and May 2016 for a diagnostic ECG-gated CT scan. Our Hospital authorized the retrospective use of the anonymized image set for the study purposes. All ECG-gated CT scans were performed on the same 64 slices CT scanner (Lightspeed VCT Scanner, General Electric Healthcare, Waukesha, WI, USA), with intravenous contrast (Ultravist 370 mg/ml), adopting a dedicated retrospective ECG-gated spiral algorithm [**10-12**]. A spiral CT scan with continuous table movement and data acquisition was performed; simultaneously, the patient's ECG was recorded and images acquired across different heartbeats, creating a heart phase-consistent sequence. The consequent delineation of CA across all different heart phases allowed for the quantification of coronary motion. All reconstructions were performed in 11% steps over the entire heart cycle, defined as the interval between the R waves (R–R interval) of the QRS complex, leading to the definition of 9 different datasets for each patient, as shown in Figure 1. All phases were determined as relative to the R peak for every cardiac cycle, and as a percentage of the R–R interval. The end-systole phase was defined as 10-20% and the end-diastole phase as 70-80%, respectively. For images acquisition, patients were asked to hold their breath after a mild hyperventilation. Images were reconstructed at 0.625 mm slice thickness with an increment of 0.4 mm. Those patients with a heart rate >75 beats per minute were medically treated before acquisition.

Figure 3.1 – Outline of the "retrospective algorithm" adopted. Scan data are continuously acquired during the table movements. Image datasets obtained from a complete R-R interval where then reconstructed in 9 cardiac phases.



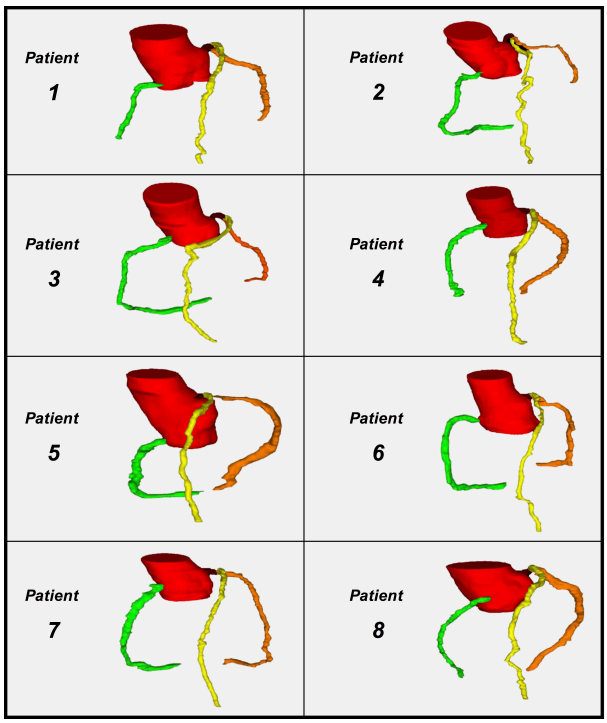
Contrast medium was injected with an 18-gauge catheter at 5 ml per second flow rate. The total contrast dose per patient was roughly 1.0 mg/kg body weight, followed by 50 ml of saline chase at the same flow rate. All 9 (per patient) reconstructed image sets were then exported to Velocity^{TM} (Varian Medical System, Palo Alto, CA, USA) contouring workstation. The following vessels were then contoured on the basis of a "slice by slice" delineation: left main trunk (LM), left anterior descending (LAD), left circumflex (CX) and right coronary artery (RCA), as shown in Figure 2. All contours were performed by two experienced radiation oncologists according to the atlas published by Feng M et al. [**13**]. For an optimal visualization, a level of 100 and window of 800 was employed.

Figure 3.2 – Coronary anatomy. A) outline of the coronary arteries. B) 3D reconstruction of the coronary tree on a mid-diastolic phase (44%) of one patient included in the study.



LM was contoured from its origin to the bifurcation in LAD and CX. The latter trunks were contoured from their origin till the caudal edge of endocardial surface. Septal, diagonal and marginal branches were not contoured. RCA was contoured from its origin to the caudal edge of endocardial surface. Figure 3 depicts the three-dimensional reconstruction of the coronary tree as contoured for each patient.

Figure 3.3: 3D view (44% phase) of the coronaries contoured for the eight patients enrolled in the study. Colors: Aorta = red; left main trunk = garnet; left descending artery = yellow; circumflex = orange; right coronary artery = green.



With the aim of confirming or not the good contouring quality by radiation oncologists, two cardiac radiologists and two cardiologists were asked to contour the whole coronary tree on one complete image series of 3 patients. They all delineated CA on a "blinded" basis, and contours were then compared for consistency. Two different "references" were adopted for comparison: the most experienced radiologist and the most experienced radiation oncologist. The two cardiologists and the less experienced radiation oncologist and radiologist were considered as comparators for inter-observer evaluation. Contours were assessed by adopting the DICE similarity coefficient, which is a spatial overlap index and a reproducibility validation metric. The DICE similarity coefficient value ranges from 0, indicating no spatial overlap between two volumes, to 1, indicating complete overlap [**14**]. Center of mass (COM) was estimated for every structure after 3D reconstruction. Displacement of each substructure was then assessed by calculating the difference in COM positioning in all 3 spatial coordinates between the 9 reconstructed images, for each patient. Afterwards, an expansion margin (PRV or *P*lanning organ at *R*isk *V*olume) was estimated, by applying the McKenzie and van Herk formula [**15**] for organs at risk ($m\text{PRV} = 1.3^{*}\Sigma + 0.5^{*}\sigma$), thus accounting both for systematic and random positioning errors. Systematic error is different for each patient and the standard deviation of the combined errors is called Σ; $1.3^{*}\Sigma$ ensures that in every single direction the mean position of the distal PRV edge will be encompassed in 90% of plans. Random errors are characterized by standard deviations, which are summed in quadrature to yield a combined value σ.

3.3 RESULTS

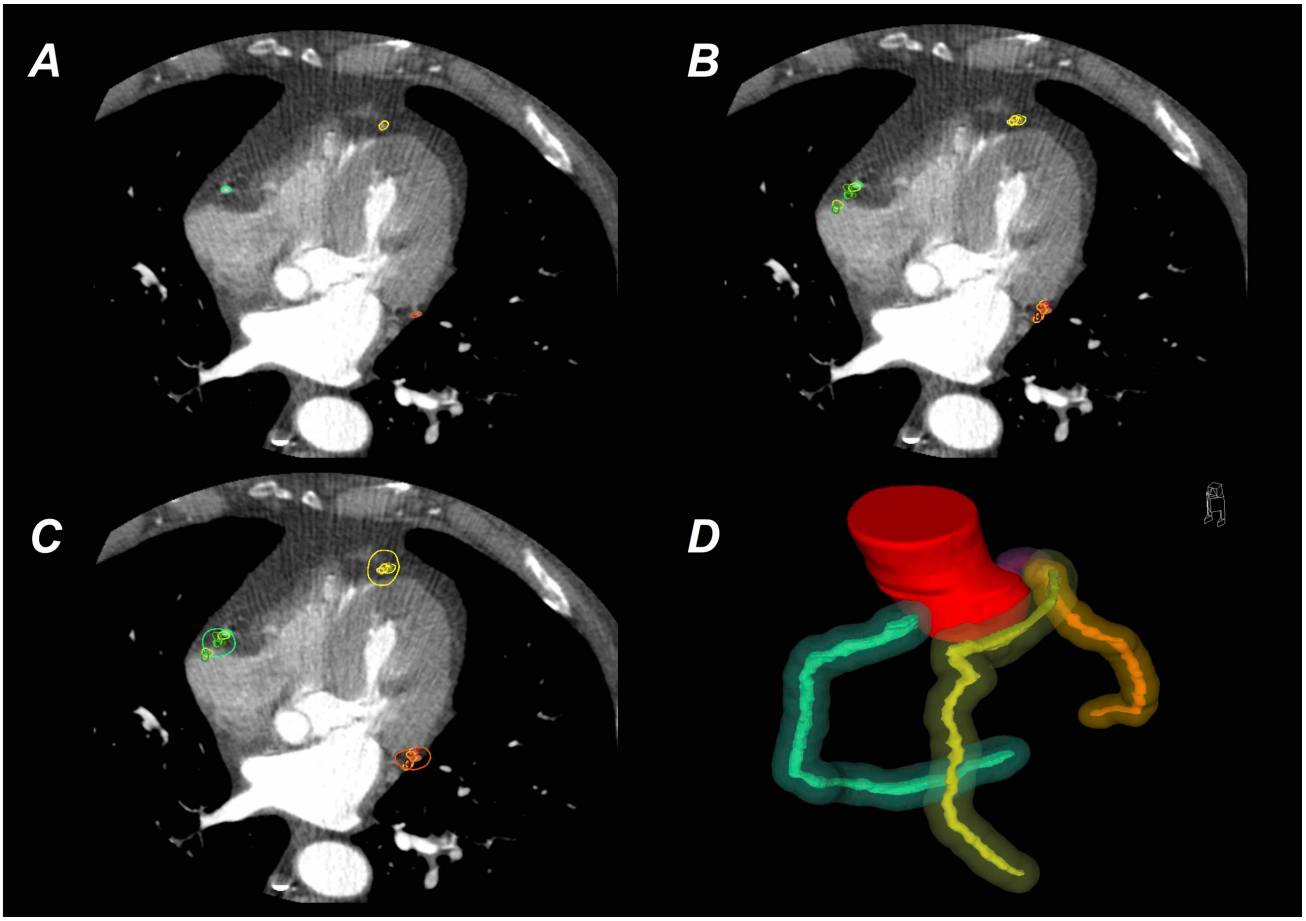
Mean age was 63 years old (range 45-75 years). All patients were in sinus rhythm, with an average heartbeat rate of 67 per minute (range 56-89). Mean displacements (mm) of the 4 CA, derived from the 9 samples per 8 patients (for a total of 72 image sets), were calculated according to the McKenzie and van Herk formula in latero-lateral (X), cranio-caudal (Y) and antero-posterior (Z) directions, and are reported in Table 1.

*Table 3.1 – Mean coronaries displacements (mm), evaluated with the McKenzie - van Herk formula [**15**] for organs at risk (mPRV = 1.3*Σ + 0.5*σ), for the overall population of 8 patients enrolled in this study.*

Coronary Artery	Displacement (mm)			Suggested PRV margin (mm)
	Left-Right (X) Σ and σ	Cranio-caudal (Y) Σ and σ	Antero-posterior (Z) Σ and σ	
Left Main Trunk (LM)	3.6 0.215 and 0.169	2.7 0.143 and 0.177	2.7 0.143 and 0.162	**3**
Left Anterior Descending (LAD)	2.6 0.143 and 0.154	5.0 0.228 and 0.395	6.8 0.413 and 0.291	**5**
Circumflex (CX)	3.5 0.196 and 0.179	4.5 0.239 and 0.283	3.7 0.183 and 0.256	**4**
Right (RCA)	3.6 0.169 and 0.276	4.6 0.232 and 0.324	6.9 0.355 and 0.446	**5**

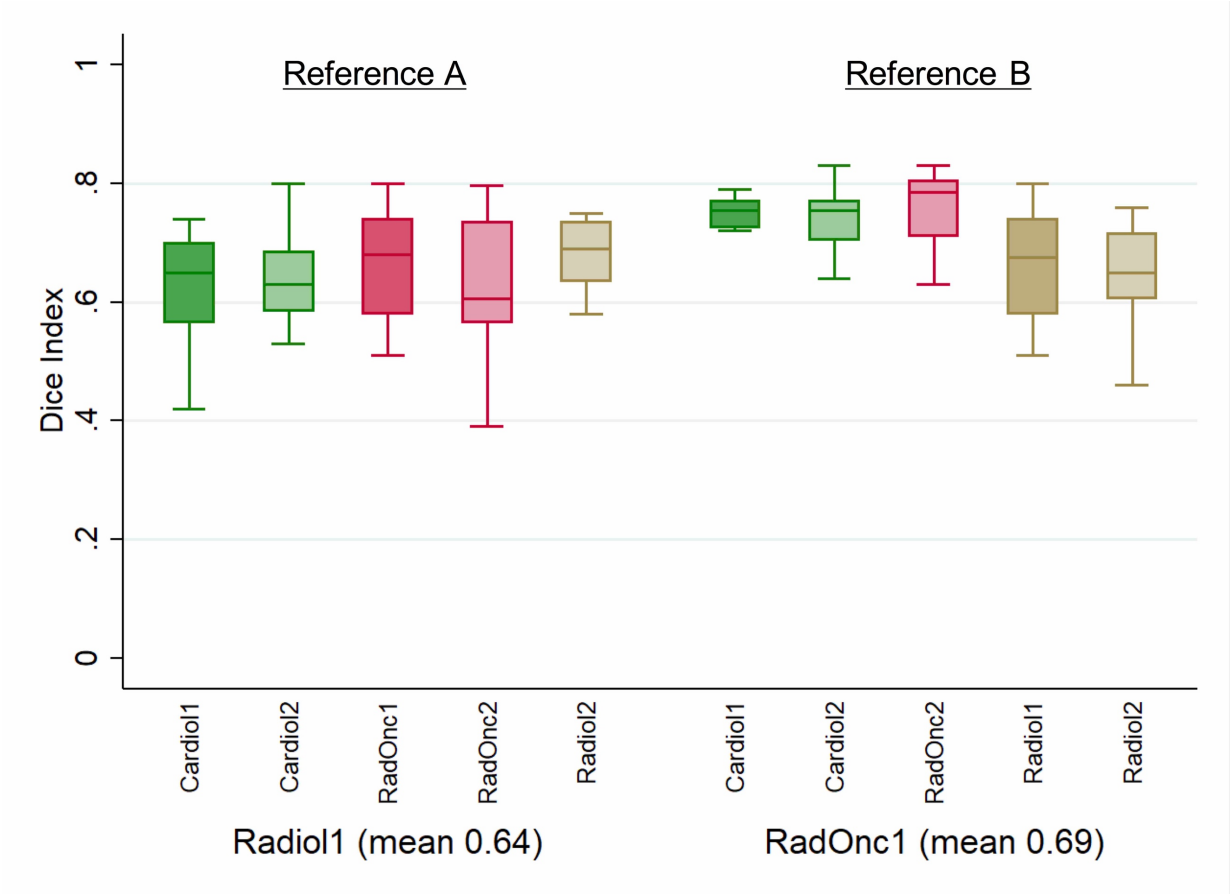
Maximum recorded displacement was between 3.6 (for the LM in latero-lateral direction) and 6.9 mm (for the RCA in antero-posterior direction), while mean 3D displacement was 3 mm for LM, 4.8 mm for LAD, 3.9 mm for CX and 5 mm for RCA, respectively. According to these values, we then proposed a specific PRV for CA (Figure 4), which is reported on Table 1 together with detailed displacements.

Figure 3.4: Model of the expansion margins for the coronary tree. A) Axial slice (44% phase) showing the contours of circumflex, right and left descending coronaries. B) Coronary contours, delineated in every cardiac phase, superimposed all together on a mid-dyastolic (44%) CT dataset. C) Axial slice with an example of the coronary expansion margin for circumflex, right and left descending coronaries. D) 3D reconstruction of the coronaries (solid lines) contoured on the 44% phase with the dedicated PRV (transparent lines). Colors: Aorta = red; left main trunk = garnet; left descending artery = yellow; circumflex = orange; right coronary artery = green.



The inter-observer comparison, estimated on the overall surface of all coronary arteries, showed a good concordance between all clinicians, regardless of the "reference" adopted, with a mean DICE similarity coefficient of 0.64 for experienced radiologist and 0.69 for radiation oncologist (Figure 5).

Figure 3.5 – DICE similarity coefficient between the references and the comparators. Reference A is the most experienced Radiologist, while Reference B is the most experienced Radiation Oncologist. The mean concordance value was 0.64 for Reference A and 0.69 for Reference B.



3.4 CONSIDERATIONS

Thoracic RT may be associated with an increased risk of long-term CA disease, through a multifactorial mechanism involving multiple pathways and converging to inflammatory, cellular, molecular and genetic changes that result in atherosclerotic deposits, thrombosis, endothelial fibrosis and coronary spasms [**16-17**]. These long-lasting processes, responsible of radiation induced ischemic disease, often require 15-20 years to manifest, but the clinical evolution may be rapid. Particularly, ostial lesions are frequent in patients receiving RT for mediastinal lymphomas [**18**], because proximal CA segments are frequently the most exposed, being close to the target volumes [**9**]. This characteristic location of stenotic plaques may be a potentially life-threatening complication, through

the abrupt appearance of acute coronary syndrome or sudden death as initial manifestations [**19**]. The complex cardiac anatomy, made up of muscle, thin arteries and valves, get as result that mean heart dose may not be the better predictor for all types of radiation-related heart diseases. That is particularly true when using high dose-gradient techniques such as IMRT [**20-21-22**], when a lower mean heart dose may be achieved, while maintaining an acceptable "low dose bath" on breasts and lungs, but hotspots in critical and small sub-structures such as CA are frequent. Given the well documented correlation between stenosis probability and high-dose hotspots for both breast cancer [**8**] and Hodgkin lymphoma [**9**] patients, CA should be regarded as a complex organ at risk that deserves a special attention. A potential strategy is to include CA in the planning optimization process, but several factors hampers this possibility in practice, particularly the difficulties in CA contouring on CT scans and the lack of appropriate constraints to be used for dose optimization. Modern atlases for a correct heart delineation, including CA, have been recently published [**13,23**], facilitating the contouring process and the incorporation of CA in dosimetric studies. Heart motion represents a serious obstacle for a correct delineation, potentially leading to consistent discrepancies between provisional and truly delivered dose.

In the present study, we focused on CA contouring method, including inter-observer variability, and on the creation of a margin able to compensate for longitudinal, radial and circumferential movements across the whole heart cycle using cardiac gating. Previous studies applied empirical CA margins ranging from 5 mm to 1 cm [**24**], and inter-observer variability was shown to possibly lead to substantial variation in CA dose estimation (as far as 30%) [**25**], particularly when these vessels are not contoured by experienced physicians nor in accordance with published guidelines. On the other hand, a recent publication from Wennstig et al [**26**] suggested that CA delineation could be reliably reproduced by different radiation oncologists, if well trained, with acceptable inter-observer spatial variation and dose estimation discrepancies.

In our study, we found a good consensus between all observers and the two references, with a DICE index approaching 0.7 for both of them (0.64 for radiologist and 0.69 for radiation oncologist,

respectively). With the aim of quantifying the impact of cardiac activity on CA motion and creating an adequate expansion margin, we applied the McKenzie-van Herk formula to CA after an accurate contouring on every phase of the ECG-gated CT scan. In our sample, CA showed different ranges of displacements: first, LAD and RCA had higher ranges of motion than LM and CX; second, we observed that cardiac activity was responsible for heterogeneous movements, with a maximum shift in antero-posterior direction for LAD and RCA, in cranio-caudal direction for CX and latero-lateral direction for LM, respectively. The dissimilar displacements of each CA are justified by asymmetric cardiac motion over the heart cycle and correspond to reported observations [**27-28**]. Our results are especially consistent with a recent publication from Kataria et al [**29**], showing mean systo-diastolic coronary shifts ranging from 4 to 7 mm in breath-hold among a cohort of 20 patients. However, respiratory-induced heart motion was responsible for the larger displacements, particularly in cranio-caudal direction, with a mean range of 7-13 mm in free-breathing. In their study, the Authors extrapolated only 4 reconstructed image sets from the ECG-gated CT scan: end-inspiratory systole, end-inspiratory diastole, end-expiratory systole and end-expiratory diastole. Afterwards, they derived the mean shifts by contouring the CA only on these end-systolic and end-diastolic phases, which probably led to an overestimation of the overall cardiac displacements. We adopted a different strategy, choosing to contour every single phase that has been segregated by the ECG-gated CT scan. The margins for CA were then estimated by applying a robust methodology, derived by the McKenzie-van Herk formula. Thus, we are confident that in 90% of cases the dose-volume histogram of the PRV would not underestimate the contribution of the high-dose components [**15**]. The mean displacements along the 3 axes were then combined to obtain a clinically applicable PRV; by this method, we were able to estimate an expansion margin accounting for the different movements (PRV of 3 mm for LM, 4 mm for CX, 5 mm for LAD and RCA, respectively), allowing for a more accurate dose estimation. The major limit of our report is that we did not account for respiratory-related coronary motion, as CT scans were all acquired in breath-holding. Although greater displacements could be expected in free-breathing, we would like to emphasize that the adoption of respiratory

gating is increasingly used in clinical practice, and that the integration of deep inspiration breath holding (DIBH) techniques, together with IMRT, might be of great additional value for heart sparing. Respiratory gating is currently recommended for patients affected with mediastinal lymphomas [**30**] and breast cancer [**31**], in reason of the meaningful dosimetric benefit. The expansion margins around CA that we defined, obtained in breath-holding, could be safely adopted to patients receiving thoracic RT, particularly when DIBH is applied. Although this is a preliminary analysis on a limited series, and further investigations would add more precise data on coronary motion, we suggest that our findings might be useful for CA contouring when a radiation course is planned for a heterogeneous group of thoracic malignancies, including left-sided breast cancer.

In conclusion, in the present study CA were shown to be relevantly displaced over the heart cycle when contoured on ECG-gated CT scans, and we suggest to create a PRV by applying an isotropic margin of 3 mm for LM, 4 mm for CX and 5 mm for LAD and RCA, respectively.

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Chapter 4 - Reduction of radiation induced ischemic complication with modern techniques.

4.1 BACKGROUND

The combination of brief chemotherapy followed by radiation therapy (RT) represents the therapeutic golden standard for early stage Hodgkin lymphoma (HL) [**1**]; nonetheless, the role of radiation is still debated with some concerns for late toxicity (second malignancies, cardiac disease). Current radiation therapy protocols may combine limited radiation volumes with advanced planning and delivery techniques, such as intensity modulated RT (IMRT), tomotherapy and proton therapy. This innovative approach should be associated with less radiation-related morbidity through an improved sparing of normal tissues. Various IMRT solutions have been implemented over the years, generally showing superior target coverage and sparing of organs at risk (OAR; mainly heart and coronary arteries) [**2-4**], compared to 3D conformal (3D-CRT) approaches. However, the heart sparing effect of IMRT at high-intermediate dose is usually achieved at the price of a larger amount of thoracic tissues receiving low or very low doses (breasts, lungs). Given this particular dose distribution, the appropriateness of IMRT in young HL patients was questioned, giving the potential increase in radiation-induced malignancies by low-dose exposure of larger volumes [**5**]. Second cancers are indeed a leading cause of death in HL long-term survivors [**6**], and studies based on radiobiological risk estimations have been conducted in recent years based on individual patient dose-volume histograms (DVH). Comparative studies have detected that the heart sparing is counterbalanced by a slightly increased dose to the breasts with IMRT, regardless of the solution adopted, compared to the traditional 3D-CRT approach. Nevertheless, in most studies that dosimetric flaw did not translated in an increased risk of secondary cancer or in a reduction of life expectancy [**7-11**]. On the other hand, all these studies concluded that the variable anatomic presentation of disease may greatly affect the second cancer and cardiac risk of HL survival and new treatment techniques should not be

implemented indiscriminately for all patients based on dose planning studies with a small number of patients. Therefore, no single best radiotherapy solution is recommended and the decision should be made at the individual level, considering also the expertise and the techniques available at each radiation oncology department. We previously developed at our institution the "butterfly-VMAT" class solution [**12**], a multiarc beam arrangements and optimization parameters primarily on breasts and lungs and secondly on whole heart for patients with supra-diaphragmatic HL. More recently, considerations of cardiac toxicity became crucial when developing RT plans, given the robust documentation of late toxicity and its correlation with the heart dose after mediastinal irradiation in HL patients [**13-16**]. Some studies have investigated the relationship between doses and subsequent damages to particular substructures [**17-18**], intimating that whole heart dose is not, anymore, the best predictor of all types of radiation-related heart disease. Therefore, an accurate contouring of all cardiac substructures (valves, coronary arteries, chambers) is recommended to optimize RT plans for HL patients. With the aim of assessing the dosimetric profile and the associated risk of developing coronary artery disease (CAD) and second cancers, we tested two different volumetric arc therapy (VMAT) solutions, specifically optimized to heart structures, breasts and lungs, among a cohort of patients treated with involved-site radiotherapy (ISRT) for different presentations of mediastinal HL.

4.2 MATERIAL AND METHODS

4.2.1 Patients

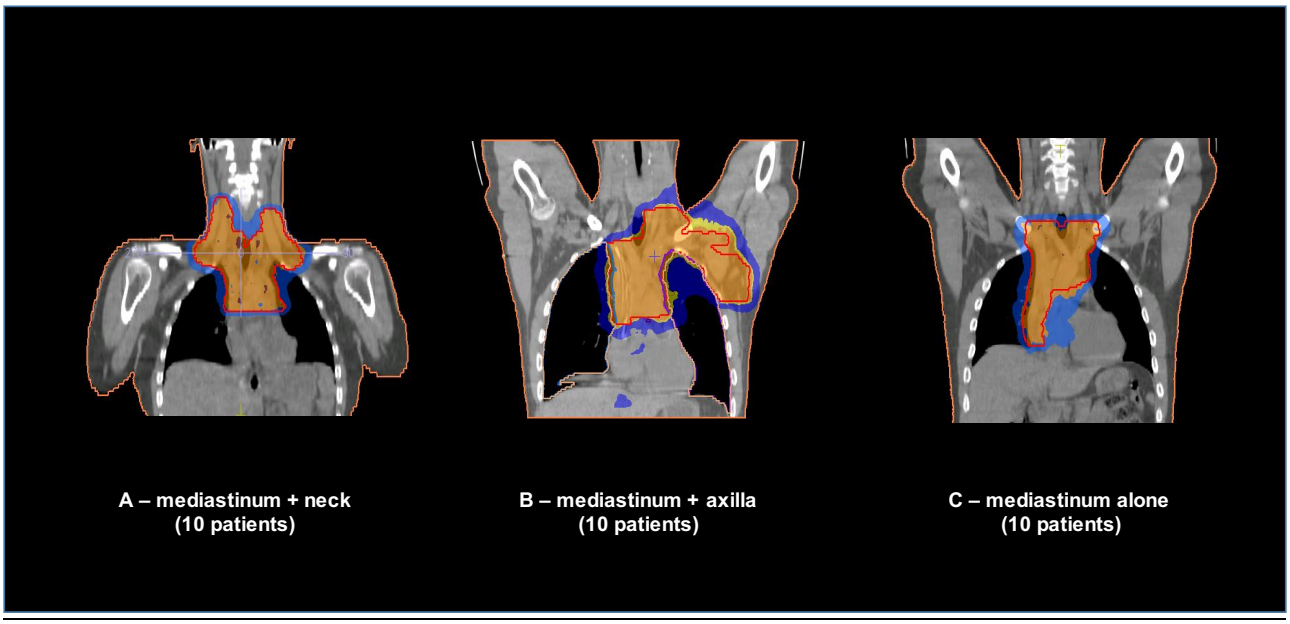
We included in the study 30 consecutive patients (15 males and 15 females) affected with mediastinal HL treated with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy followed by ISRT. Twenty-one patients (70%) had a stage I-II, while the remaining 9 (30%) had a stage III-IV disease. Fifteen patients (50%) had a bulky disease at diagnosis (>10 cm). Detailed patient characteristics are presented in Table 1.

Table 4.1 – Patients characteristics

Characteristic	Number	%
Patients	30	100
Age (years)		
Range	15-48	
Median	25,5	
Sex		
Male	15	50%
Female	15	50%
Ann Arbor Stage		
I	2	6.7%
II	19	63.3%
III	4	13.3%
IV	5	16.7%
Bulky disease	15	50%
Involved Sites		
Mediastinum alone	10	33,30%
Mediastinum + axilla	10	33,30%
Mediastinum + neck	10	33,30%

We divided our population in three homogeneous groups according to disease presentation at diagnosis (Figure 1): mediastinum alone (n=10, 33.3%); mediastinum plus neck involvement (n=10, 33.3%); mediastinum plus axillary involvement (n=10, 33.3%). Male and female patients were equally distributed in the three subgroups.

Figure 4.1: Disease presentations

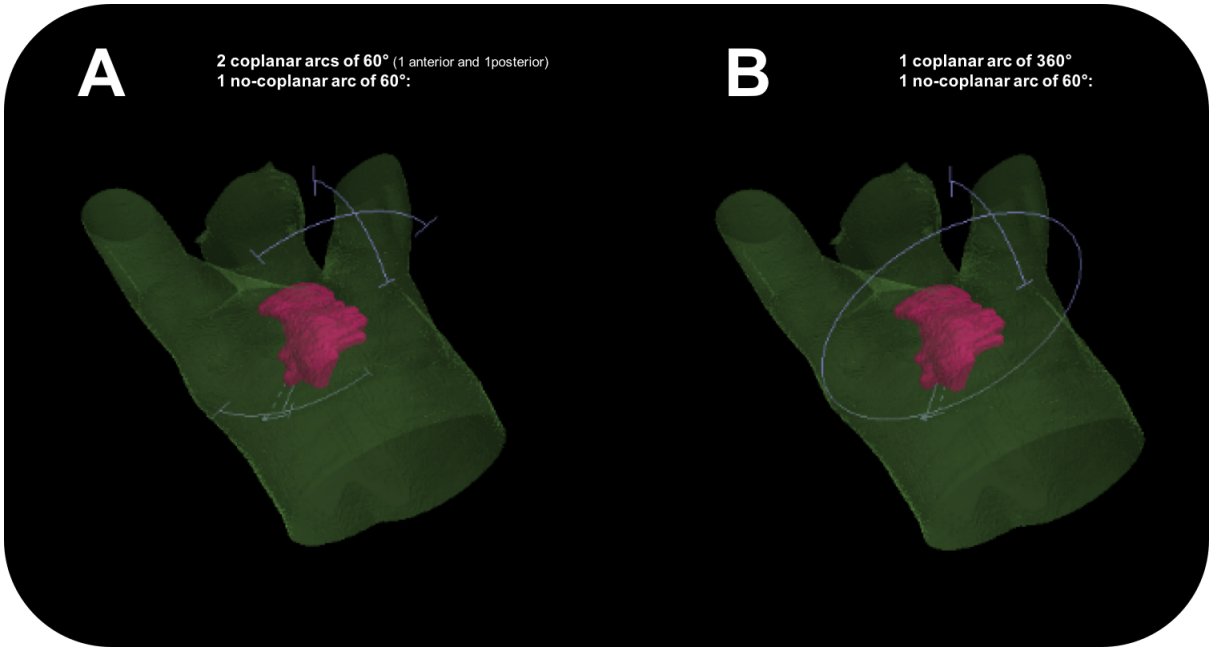


4.2.2 Radiation therapy technique

The same two radiation oncologists performed the delineation of clinical target volumes (CTV) and OAR for all patients. CTV were delineated as involved sites. A 5-mm isotropic margin was added to the CTV to generate planning target volumes (PTV), considering the use of daily cone-beam computed tomography (CT) image guidance. Lungs, thyroid, breasts, and cardiovascular structures (whole heart; left main, left anterior descending, circumflex and right coronaries; left and right ventricles, left and right aria; aortic, pulmonic, mitral and tricuspid valves;) were defined as OARs and delineated on axial planning CT scans. Cardiac structures were contoured according with the atlas published by Feng et al [**19**]. Prescription dose was 30 Gy in 2-Gy daily fractions for all patients. Dose constraints for breasts and lungs were derived from previous reports [**7-20**]. The dose to the heart structures was kept as low as reasonably achievable, in respect to the ALARA principles, due to the lack of precise constraints from the literature. The plan optimization for the heart was first directed to the coronary arteries, left ventricle and aortic valve, because these structures were considered more relevant from a clinical point of view. Two multiarc VMAT plans, both optimized for mediastinal HL, were generated for each patient. Briefly, the "comparator" plan was the so-called

"Butterfly" VMAT (B-VMAT) [**12**], consisting of 2 coplanar arcs of 60° (gantry starting angles of 150° and 330°) and 1 noncoplanar arc of 60° (gantry starting angle of 330° and couch angle of 90°). Beam arrangements were individually customized to provide tumor coverage while minimizing exposure to nearby critical organs. The basic principle in the beam choice was to avoid lateral or nearlateral beams [**3**] to keep the bath dose as low as possible to breasts and lung, even at price of suboptimal beam conformation and PTV homogeneity. The "investigational" plan consisted of a complete coplanar arc of 360°, with the addition of the same noncoplanar arc of 60° (gantry starting angle of 330° and couch angle of 90°) of the B-VMAT. For that reason, this innovative VMAT approach was called "Full-arc Butterly-VMAT" (FaB-VMAT). Figure 2 illustrates the two different class solutions.

Figure 4.2 – illustration of the two different VMAT solutions: A) Butterfly VMAT; B) Full-arc Butterfly VMAT



4.2.3 Risk estimation and statistical analysis

For the second cancer risk estimation, we adopted the organ equivalent dose (OED) model [**21**], as previously described in details [**8**]. OED can be calculated from the dose volume histograms for each organ and represents the equivalent uniformly distributed dose (Gy), which causes the same radiation-

induced cancer incidence. An organ specific dose-response relationship may be used, on the basis of a combination between the low-dose component derived by atom-bomb survivor data and an intermediate/high dose component derived from epidemiological studies of second cancer incidence after RT. From OED we estimated the excess absolute risk (EAR) for a western population for each organ and EAR was then translated to lifetime attributable risk (LAR), which is determined by the combination of age at exposure and life expectancy for each patient. Individual LAR values were calculated according to the equations previously published by Schneider et al [**22**] and by Kellerer et al [**23**]. For studies including subjects with limited follow-up time, Schneider et al [**22**] suggested using a follow-up time interval instead of the life expectancy (estimated from the general population of the same age), and we used a 30-year time interval from radiation treatment. For risk estimation of coronary artery disease (CAD) we adopted the model published by van Nimwegen et al. [**16**] for HL survivors, and derived by the first observation of Darby et al. [**24**] on breast cancer patients. This risk model demonstrates a linear dose-response relationship between mean heart dose (MHD) and CAD risk, with an excessive relative risk (ERR) for coronary events of 7.4% per Gy. We then adapted the model to the mean dose of the "overall coronary volume", defined as the sum of all the coronary tree, with the rational of relating the risk for ischemic disease to the endothelial tissue instead of a surrogate volume as the whole heart. Dosimetric parameters and mean values of OED, LAR, and AER to the OAR with B-VMAT and FaB-VMAT were compared using Student paired t test, with a two-tailed significance level of .05. All statistical analyses were performed using STATA vesion 13.1 statistical software.

4.3 RESULTS

Doses received by target volume and OARs (lungs, breasts and whole heart) are reported in Table 2, while table 3 presents dosimetric data of all the cardiac substructures. Maximum dose (D_{max}), mean dose (D_{mean}) and most significant volumetric parameters are reported for each structure.

Table 4.2 – dose to Target volume and organs at risk for all 30 patients with B-VMAT and FaB-VMAT.

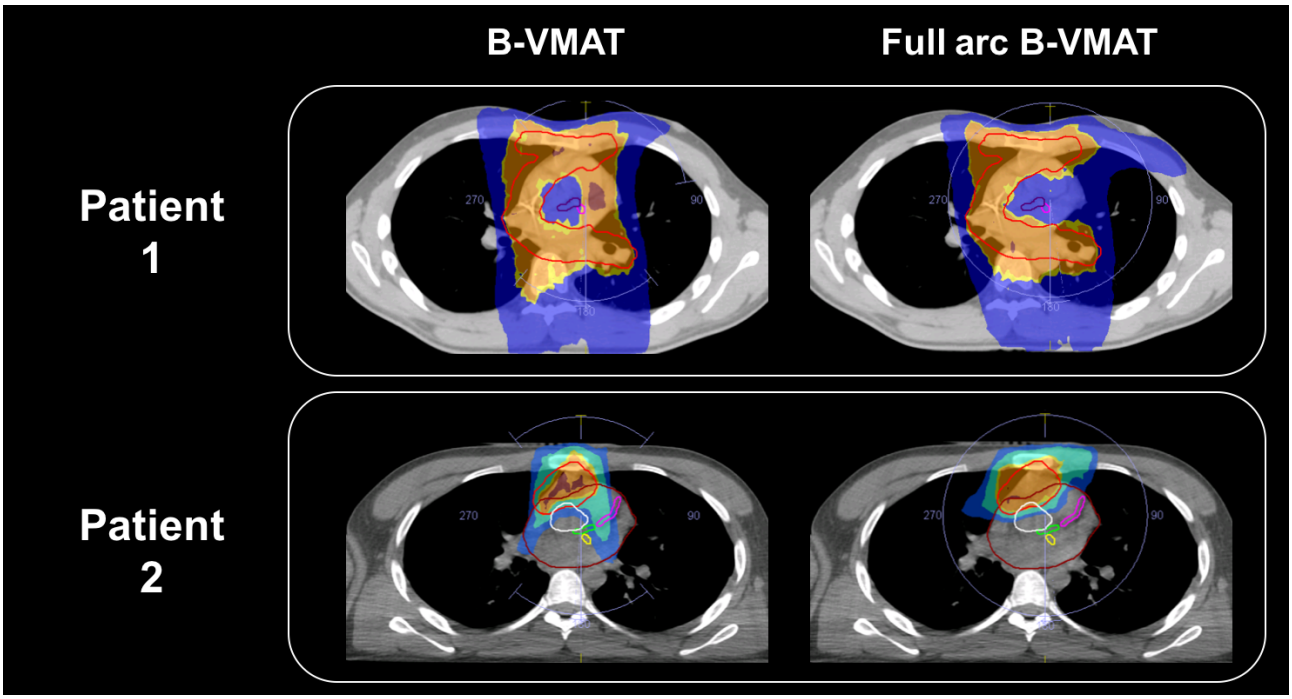
Structure	Parameters	B-VMAT (VMAT1)	FA (VMAT2)	p-value
PTV	DMEAN (Gy)	30,4 ± 1,9	30,4 ± 1,8	0,694
	DMAX (Gy)	34,7 ± 2,1	34,6 ± 1,8	0,545
	V95 (%)	5,7 ± 5,2	5,4 ± 2,9	0,8
	V107(%)	2,0 ± 1,0	2,0 ± 1,5	0,875
Lung	D MEAN (Gy)	7,5 ± 1,9	7,5 ± 1,7	0,954
	DMAX (Gy)	33,4 ± 2,2	33,7 ± 1,9	0,407
	V5 (%)	39,8 ± 9,5	41,1 ± 7,4	0,157
	V10 (%)	27,9 ± 7,3	27,5 ± 7,1	0,393
	V20 (%)	15,4 ± 5,9	14,4 ± 5,4	**0,008**
Breast	D MEAN (Gy)	2,8 ± 3,0	3,5 ± 2,7	**0,033**
	DMAX (Gy)	27,2 ± 9,5	27,7 ± 9,4	0,53
	V4 (%)	16,6 ± 16,1	22,2 ± 15,5	**0,041**
Heart	D MEAN (Gy)	7,6 ± 5,1	6,9 ± 4,8	**0,0028**
	DMAX (Gy)	32,8 ± 3,6	42,5 ± 55	0,34

Table 4.3 – dose to cardiac structures for all 30 patients with B-VMAT and FaB-VMAT.

Structure	Parameters	B-VMAT (VMAT1)	FA (VMAT2)	p-value
Coronary Arteries				
1) Left Main Coronary	DMEAN (Gy)	19,5 ± 7,7	15,9 ± 7,5	**0,0001**
	DMAX (Gy)	25,8 ± 5,9	21,6 ± 7,4	**0,0001**
2) Left Anterior Descending	DMEAN (Gy)	15,6 ± 9,0	13,2 ± 8,9	**0,0001**
	DMAX (Gy)	26,2 ± 8,5	21,9 ± 10,6	**0,0001**
3) Left Circumflex	DMEAN (Gy)	14,0 ± 8,6	10,7 ± 7,8	**0,0001**
	DMAX (Gy)	22,7 ± 7,9	17,9 ± 9,0	**0,0001**
4) Right Coronary	DMEAN (Gy)	17,0 ± 11,4	15,8 ± 11,6	**0,005**
	DMAX (Gy)	23,1 ± 11,5	20,9 ± 12,6	**0,006**
5) Coronary Sum (Overall)	DMEAN (Gy)	16.1 ± 9,3	13.5 ± 8,9	**0,0001**
Chambers				
1) Left Atrium	DMEAN (Gy)	13,10 ± 6,73	11,11 ± 6,56	0,364
	DMAX (Gy)	29,25 ± 6,04	28,40 ± 7,13	0,775
2) Left Ventricle	DMEAN (Gy)	4,2 ± 4,7	3,4 ± 3,7	**0,007**
	DMAX (Gy)	25,6 ± 9,8	21,9 ± 11,1	**0,0001**
3) Right Atrium	DMEAN (Gy)	12,58 ± 7,29	11,9 ± 7,69	0,095
	DMAX (Gy)	30,76 ± 5,46	30,74 ± 5,34	0,899
4) Right Ventricle	DMEAN (Gy)	7,3 ± 6,2	7,0 ± 6,1	0,17
	DMAX (Gy)	31,1 ± 5,7	30,2 ± 6,9	0,08
Valves				
1) Aortic Valve	DMEAN (Gy)	15,7 ± 9,0	13,2 ± 8,7	**0,0004**
	DMAX (Gy)	23,3 ± 9,1	22,8 ± 10,0	0,42
2) Pulmonic Valve	DMEAN (Gy)	19,91 ± 7,75	18,69 ± 7,92	0,153
	DMAX (Gy)	28,35 ± 6,42	26,77 ± 7,06	0,135
3) Mitral Valve	DMEAN (Gy)	8,97 ± 4,93	8,76 ± 7,48	0,939
	DMAX (Gy)	19,94 ± 6,02	14,95 ± 10,37	0,232
4) Tricuspid Valve	DMEAN (Gy)	9,74 ± 8,5	9,40 ± 9,70	0,809
	DMAX (Gy)	16,86 ± 10,82	15,02 ± 11,7	0,068

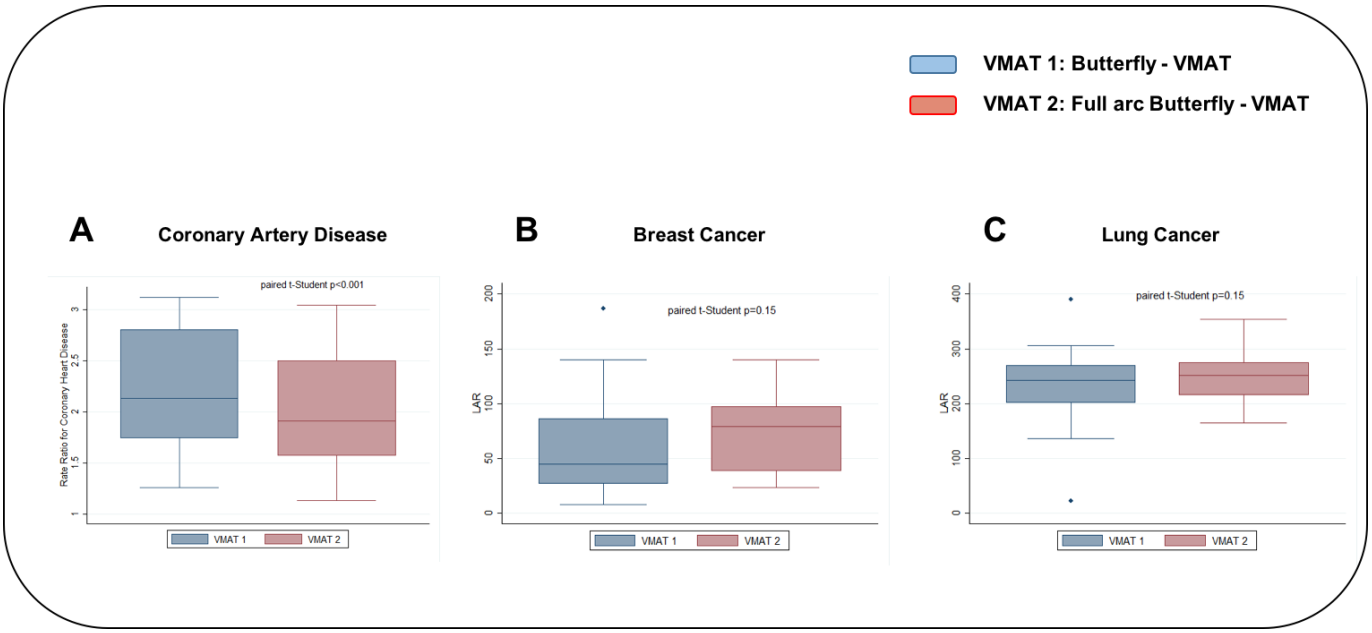
A significant dosimetric difference between B-VMAT and FaB-VMAT was evident in favor of the latter one for lung V20 ($p = 0.008$) and mean heart dose ($p = 0.0028$), while mean breast dose ($p = 0.033$) and breast V4 ($p = 0.041$) were slightly inferior with B-VMAT approach. Doses received by all the coronary arteries, left ventricle and aortic valve were significantly lower with FaB-VMAT, compared to B-VMAT. Figure 3 shows the different dose distribution achievable with the two different VMAT approaches in 2 sample patients.

Figure 4.3 – Examples of dose distributions achieved with B-VMAT and FaB-VMAT in 2 sample patients.



The dosimetric gain to the coronary arteries translated in a lower relative risk (RR) for coronary disease with FaB-VMAT ($p < 0.001$), compared to B-VMAT. On the other hand, OED, EAR and LAR for breast and lung cancer did not differ between the two VMAT solutions. Figure 4 shows the most significant risk parameters for lung and breast cancer and for CAD.

Figure 4.4 – Relative risk for CAD (A) and LAR for breast cancer (B) and lung cancer (C) between B-VMAT (blue plots) and FaB-VMAT (red plots)



After a stratification for gender, female patients had a significant reduction of D_{max} ($p = 0.03$) to circumflex coronary and a marginal reduction of lung Dmean ($p = 0.06$), V10 ($p = 0.06$) and OED ($p = 0.06$) with FaB-VMAT, compared to male patients.

In patients with solitary mediastinal involvement, D_{mean} to Circumflex coronary was significantly reduced ($p = 0.04$) while D_{mean} to the overall coronary volume ($p = 0.06$) and relative risk of coronary events ($p = 0.06$) were marginally inferior with FaB-VMAT, compared to patients with other disease presentations. On the other hand, with FaB-VMAT OED, EAR and LAR for breast cancer were significantly higher ($p = 0.03$ for each value) and breast V4 marginally higher (17.6% vs 27.2%, $p = 0.08$) in the subgroup of patients with bulky involvement at baseline. With FaB-VMAT we observed a marginal increase of breast OED, EAR and LAR also for patients with disease presentation in the mediastinum aone ($p = 0.07$ for each value).

In patients with axillary involvement, conversely, B-VMAT was responsible of higher D_{max} to the right coronary ($p = 0.014$) and D_{mean} to the left ventricle ($p = 0.03$). Moreover, when comparing OED,

EAR and LAR for breast cancer in female patients with or without axillary disease presentation, we found a marginally higher risk ($p = 0.071$ for all parameters) with FaB-VMAT in the second group.

4.4 CONSIDERATIONS

The aim of this study was to assess the risk of developing second cancer and cardiovascular disease associated with a new optimized VMAT planning solution (FaB VMAT) in patients with mediastinal HL versus B-VMAT, while considering the potential impact of different anatomical presentations. The strength of the present study is the enrollment of patients with the most frequent anatomical presentation of disease, including bulky and axillary involvement, which are probably the most challenging both for cardiovascular and second lung/breast cancer risk. We applied the ISRT concept, including only lymphatic sites originally involved by macroscopic disease at presentation into the treatment volume. In previous reports [**3,8**], the B-VMAT approach resulted to avoid excess exposure to heart, breasts, lungs, and spinal cord to doses of 30 or 20 Gy, with a mild increase in V5 to breasts, in comparison with standard 3D-CRT. In this report, we compared the popular B-VMAT with an investigational full-arc (360°) VMAT approach, integrated with the addition of the B-VMAT "trademark" of the no-coplanar arc, named "Full-arc Batterfly-VMAT".

B-VMAT has gained interest in these years for its peculiar ability, compared to other IMRT and VMAT approaches, to reduce the low dose bath, at the expense of a slight decrease in conformity. Reduction of the low dose bath may be extremely relevant because low doses to the lung, such as the volume receiving 5 Gy or more (V_5), is predictive of radiation induced pneumonitis. Moreover, the particular arcs arrangement, avoiding beam entrance from the lateral sides, eases the preservation of female breasts from higher doses. On the other hand, the decrease in conformity may generate hotspots in OARs closed to the PTV, with a potentially critical clinical impact, given the proximity of coronary arteries to the target of treatment in most HL patients with mediastinal involvement.

Conversely, the innovative FaB-VMAT provides a higher beam conformation in reason of the 360° arc, thus reducing the risk of hotspots to adjacent OARs, but presumably at the price of higher dose-bath to the lungs and to the breast, compared to B-VMAT.

Our findings indicated that FaB-VMAT decreases significantly the maximum and mean dose received by all the coronary arteries compared to B-VMAT, and this dosimetric gain translates in a reduced risk of coronary artery disease in the long-term survivors. In the meantime, the risk of secondary breast and lung cancer is not statistically different between the two VMAT solutions ($p = 0.15$ in both cases). Interestingly, even after a stratification for gender and different extension of disease, the relative risk for CAD remained lower with FaB-VMAT, stating the definite superiority of this new treatment solution in sparing the coronary arteries compared to B-VMAT. The novelty of our study was the adaptation of the van Nimwegen model [**16**] to the mean dose of the "overall coronary volume" in replacement of the mean heart dose. In fact, most published data have shown a clear relationship between mean heart dose and "all-cause" cardiac toxicity [**13,16,24,25**], and there are currently not sufficient data indicating the potential contribution of coronary arteries dose-volume variables to provide a meaningful improvement in risk prediction compared to mean heart dose. Anyway, our results are in accordance with a recent publication from Princess Margaret Cancer Centre [**26**], which showed for the first time that a risk model including coronary artery variables is superior to a model based on the mean heart dose, when the clinical outcome is CAD. On the other hand, they noticed that mean heart dose is a sufficient dose parameter and fit better than coronary arteries dose to the prediction of "all-cause" cardiac events in long term HL survivors who received mediastinal RT. Unfortunately, van Nimwegen et al [**16**] did not evaluate coronary dose in their large cohort of long term HL survivors, but our model "adaptation" to the coronary tree is in respect with the evidence of some previous reports. A French [1**7**] and a Swedish [**27**] groups showed that the highest of the coronary dose distributions was on damaged coronary segments, suggesting the need for the integration of coronary dose parameters in the plan modeling. Likely, different cardiac substructures have different dose-risk relationships, therefore an optimization of the RT plan and the

adoption of dedicated dose constraints for each heart structure may be the best strategy to reduce cardiac toxicity in the future. Despite the accurate contouring of all cardiac structures and the attempt to create dedicated risk-modeling, the estimation of cardiac events is extremely complex in this cohort of long term survivors, and suffers even for the overlap of many "non-RT-related" factors as combined chemotherapy and concomitant cardiovascular risk-factors (hypertension, diabetes, dyslipidemia and obesity) hardly assessable within such a dynamic and complex risk-modeling.

After a stratification for different disease presentations, we observed that FaB-VMAT increased significantly the risk of breast cancer in patients with bulky disease ($p = 0.03$) and marginally in patients with mediastinal involvement alone ($p = 0.07$). It should be noted that all patients with single mediastinal disease had a bulky lesion and the latter factor is predominant for the risk of secondary breast cancer. No significant differences in the risk of lung cancer appeared between FaB-VMAT and B-VMAT in our cohort, regardless of stratification for clinical (gender, bulky) parameters and disease presentations. However, the individual variations are substantial and experiments comparing average doses or average risk estimates (OED, LAR, AER) for different techniques may carry important limitations in describing what happen in individual patients. Second cancer induction risk could also be dependent on factors such as inter-observer variability in target volumes and OAR delineation, margins around CTV and/or dose calculation uncertainty. Moreover, a substantial difference in results can be seen when different radiobiological models are used. Anyway, a systematic review of all published studies for second solid tumors after conventionally fractionated RT showed an overall tendency for a linear dose-response relationship, with the only exception of a downturn for thyroid cancer after 15-20 Gy, thus supporting the currently used theoretical models [**28**].

Our results indicate that the novel FaB-VMAT approach is more effective, compared to B-VMAT, in reducing the risk of coronary events in an overall population of HL patients, regardless of the disease presentation. Anyway, in female patients with a huge tumor burden, particularly in case of single mediastinal involvement, the dosimetric benefit to the coronary tree is counterbalanced by higher doses to the breast and by an increased risk of secondary breast cancer in the long term. As

previously stated by other modeling studies, there is not a "gold-standard radiotherapy plan" when treating HL, and the conundrum on the best VMAT approach for a female patient with mediastinal bulky lesion will probably remain unsolved. However, the radiation oncologist may integrate all the clinical, dosimetric and predictive information in order to evaluate the risk profile of each patients and to tailor the treatment on the basis of an individualized approach.

In the end, it should be noted that the results from this study were derived from a risk-model simulation of a prospective plan comparison. Therefore, we cannot provide definitive conclusion, given the lacking of clinically described late effects, that would require 20-30 years of follow up. As already mentioned, our modeling study may provide a useful tool to guide the selection of the best treatment planning for each single patient, taking in to account the individual risk-profile for long term complications. A further logical step in this field would be the introduction of a decisions supporting tool considering all different late toxicity endpoints into the clinical routine, such as proposed by Brodin et al [**29**]. This tool might allow quantitative estimation and visualization of the risks associated with every plan, facilitating the clinical decision-making and the individualization of the treatment approach.

4.5 CONCLUSIONS

Among a heterogeneous cohort of mediastinal HL patients, reflecting the most frequent clinical presentations, an innovative FaB-VMAT planning solution, compared to b-VMAT – both optimized for multiple organs at risk according to specific lymphoma dose constraints – significantly decreased the RR for CAD with similar second breast and lung cancer risks. Results were anyway influenced by the different anatomical presentations – the major benefit was observed for patients with an exclusive involvement to the mediastinum – supporting the need for an individualized approach.

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Chapter 5 – Subclinical diagnosis of heart complications with advanced echocardiography in lymphoma patients: the CARDIOCARE project

5.1 BACKGROUND

Treatments-related cardiotoxicity is a critical issue in long term lymphoma survivors, particularly at young age [**1-4**], and its early identification is fundamental to prevent clinically relevant cardiac events. Amongst HL long-term survivors who received mediastinal RT, particularly, cardiovascular disease is the most common causes of death [**5**]. Studies have shown that these patients have an increased risk for coronary events, valvular heart disease, congestive heart failure and sudden death. The risk is particulrly high in patients treated before the age of 40 years [**6-7**]. In the absence of cardiovascular risk factors, the value of primary and secondary prevention in these patients is debatable. On the other hand, younger patients should be accurately screened, particularly in the presence of risk factors, because this population has a considerable life expectancy and, consequently, high chances to develop cardiac events [**5**]. Notably, some subclinical cardiac changes can occur over weeks and months after RT, and can be detected either based on functional dysfunction or anatomical modification mesaurements. Early detection of these subclinical alterations may effectively prevent clinically significant cardiac events, occurring many years later, by adopting adeguate monitoring and preventive treatment. Particularly, modern cardiac echography may count on the global longitudinal strain (GLS) test, which is a recent technique for detecting and quantifying subtle alterations of left ventricle (LV) systolic funtion. GLS evaluates alterations of the strain of myocardial fibers and seems to be an effective tool in detecting preclinical systolic changes to the cardiac funtion after thoracic radioterapy [**8-9**] even when the ejection fraction is preserved. Based on these clinical experiences, GLS is considered a valuable detector of early subclinical cardiotoxicity after chemo-radiotherapy and its utilization is strongly suggested also by recent position papers of the European and American Society of Cardiology for the evaluation of cardiovascular complications of cancer patients [**10-11**]. Our purpose is to investigate for early detection of subclinical chemo and radiation-

induced changes in left ventricular function using a complete echocardiographic assessment including 2-dimension global longitudinal strain (2D-GLS) in patients undergoing chemotherapy alone or combined chemo-radiation for different types of lymphoma.

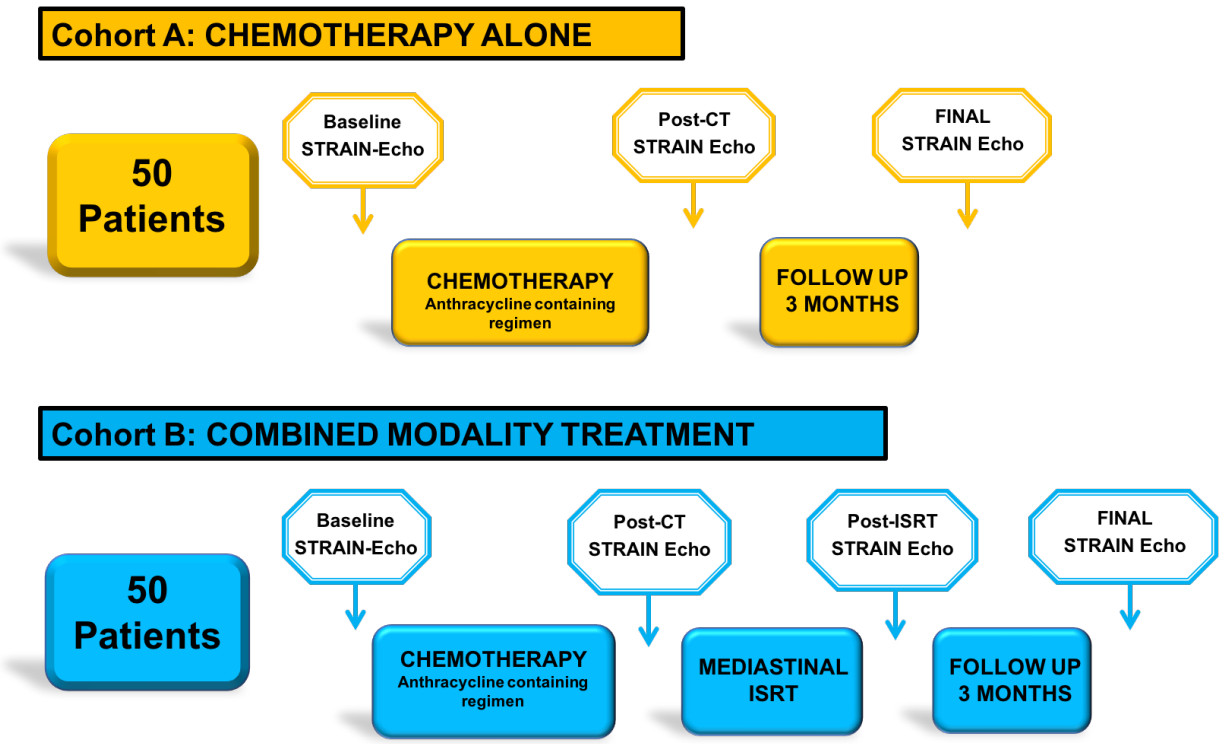
5.2 MATERIAL AND METHODS

This is an ongoing project consisting in a monocentric prospective observational study, approved by the ethic committee of the A.O.U. City of the Health and of the Science hospital of Torino (approval number: CS/370). The full title is: "*A Prospective, Observational Study Evaluating Early Subclinical Cardiotoxicity With Global Longitudinal Strain Imaging In Lymphoma Patients Treated With Chemotherapy +/- Mediastinal Radiotherapy: The CARDIOCARE Project.*" The study is also registered on *ClinicalTrial.gov* (identifier number: NCT03480087). The planned accrual will finally include 100 patients, of which 50 treated with chemotherapy alone (CT-alone) and 50 treated with chemotherapy + mediastinal radiotherapy (CMT). The study flow-chart is depicted in Figure 5.1.

Patients aged 18-70, affected with either Hodgkin (HL) or diffuse large B-cell (DLBCL)/primary mediastinal lymphomas (PMBCL) are eligible to enter the study provided that they should receive an anthracycline containing regimen. Exclusion criteria are previous mediastinal radiotherapy, severe kidney and liver failure, poor performance status (ECOG PS >2) and an echocardiographic acoustic window unsuitable to a proper evaluation of the strain imaging. Patients receive a complete echocardiographic assessment including 2D-GLS at baseline, after chemotherapy, after radiotherapy (if contemplated), and 3 months after end of treatment. Chemotherapy schedules were selected by the treating hematologist according with the lymphoma type and the clinical features. All HL patients received 2 to 6 cycles of ABVD chemotherapy, while PMBCL and DLBCL patients received 3 to 6 cycles of R-CHOP chemotherapy. Patients who received additional radiotherapy were treated according with the recent ILROG guidelines [**12-13**]. All contours were made by 3 radiation oncologists and based on the "involved-site" radiotherapy (ISRT) concept. The following heart

structures were contoured: whole heart, coronary arteries (left main trunk, left descending, circumflex and right coronary), valves (aortic, pulmonic, mitral and tricuspid) and chambers (left and right atria, left and right ventricles). Dosimetric parameters, incuding maximum dose (Dmax) and mean dose (Dmean) were evaluated for each substructure. Paired samples T test correlations are applied to evaluate GLS changes at each time-point. The cumulative dose of anthracycline and the adsorbed dose of whole heart and cardiac substructures (coronaries, chambers and valves) are assessed for each patient. All patients have to sign an informed consent before the enrollment.

Figure 5.1 – Flow-chart of the Cardiocare Project



The primary endpoint is:

- To test the efficacy of strain rate imaging in detecting early subclinical alterations of myocardial function in lymphoma patients undergoing anthracyclines-based chemotherapy +/- mediastinal irradiation

The secondary endpoints are:

- To establish and quantify the entity of GLS modification after treatment and eventual recovery 3 months after end of treatment
- To find any eventual correlation between chemo-radiotherapy dose and GLS alteration
- To evaluate the ability of early GLS modifications to predict cardiovascular complications during the follow up.

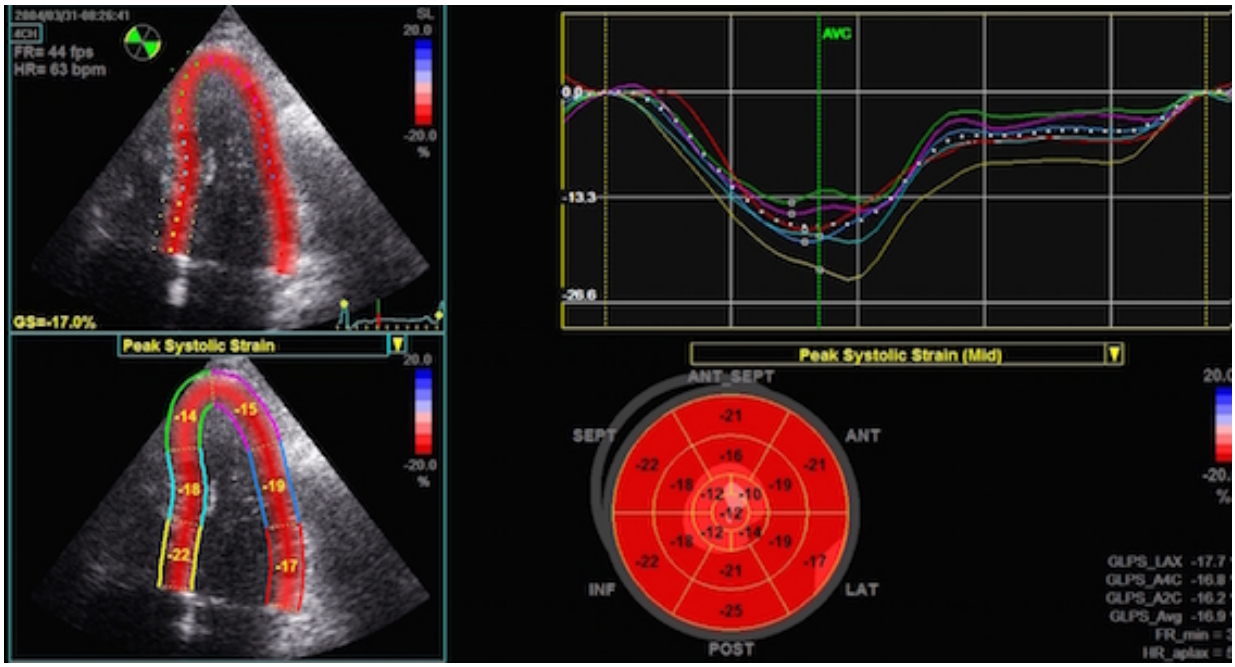
5.2.1 Echocardiographic evaluation

All patients receive an advanced echocardiographic evaluation, including 2D-GLS detection, at each time-point of the study. All exams are acquired and stored for subsequent analysis by two experienced cardiologists, adopting always the same echocardiographic scan (GE Healthcare Vivid 7 Dimension). Within the echocardiographic exam, we evaluated all the conventional systolic and diastolic parameters. Moreover, we added the evaluation of the advanced strain parameters (2D-GLS), which were acquired with the software EchoPac PC (GE Healtcare), adopting the AFI (automated function imaging) method, which generates the strain systolic longitudinal peak (2D-GLS).

Strain parameters evaluate the elastic deformations of the myocardial fibers, and has a high sensitivity in detecting early and subclinical myocardial dysfunction. 2D-GLS is evaluated with the *"speckle tracking"* analysis, which is a modern technique evaluating contraction of the myocardial fibers by following the different acoustic markers of the different areas of the left ventricle at the 2D evaluation. The random distribution of the speckles ensures that each region of the myocardium has a unique *"fingerprint"*. The speckles will then follow the motion of the myocardium, so when the myocardium moves from one frame to the next, the position of this fingerprint shifts slightly, remaining fairly constant in physiological conditions. With the acquisition of the strain parameters in different views and planes, it is possible to locate alterations of 2D-GLS in particular segments of the left ventricle. Figure 5.2 shows the typical graphical presentations of 2D-GLS, with the *"bull's eye"* diaphragm.

The reduction of 2D-GLS >15% after an oncologic treatment (both chemotherapy and radiotherapy) is considered predictive of early myocardial toxicity and is strongly correlated with a reduction of the ejection fraction, unless a proper preventive cardiac therapy is quickly started. Therefore, we looked also for the patients that experienced a lowering of the 2D-GLS values >15%, in order to find any correlation with any clinical and/or dosimetric parameter.

Figure 5.2 – Model of 2D-GLS speckle tracking. Left part: acquisition of the parameter on the 4 chambers view at the apical plane. Right part: linear and "bull's eye" diaphragms, showing the results of the evaluation.



5.3 RESULTS

5.3.1 Population

We have enrolled, to date, 52 patients with a median age of 29.5 years (range 19-69). Thirty-six patients (69.2%) were female, and HL was the most prevalent histology (69.2%). Bulky disease was present in 21 patients (40.4%). General characteristics are reassume in Table 5.1

Table 5.1 – General characteristics

Characteristics	Population N = 52 (%)
Gender	
Male	16 (30,8%)
Female	36 (69,2%)
Median age	29,5 (range 19-69)
PS ECOG	
0	47 (90,4%)
≥ 1	5 (9,6%)
Histology	
HL	36 (69,2%)
DLBCL	9 (17,3%)
PMBCL	7 (13,5%)
Stage	
I	9 (17,3%)
II	23 (44,2%)
III	10 (19,2%)
IV	10 (19,2%)
B symptoms	
Yes	14 (26,9%)
No	38 (73,1%)
Lymph nodal sites (n)	
0 (extranodal involvement)	4 (7,7%)
1	10 (19,2%)
2	14 (26,9%)
3	11 (21,2%)
4	4 (7,7%)
5	5 (9,7%)
6	2 (3,8%)
7	2 (3,8%)
Mediastinal Bulky lesion	
Yes	21 (40,4%)
No	31 (59,6%)
Extranodal Involvement	
Yes	13 (25%)
No	39 (75%)

5.3.2 Chemotherapy regimes

All patients enrolled in the CARDIOCARE project received an anthracycline-containing chemotherapy regimen. Chemotherapy regimens and doses are reassumed in Table 5.2.

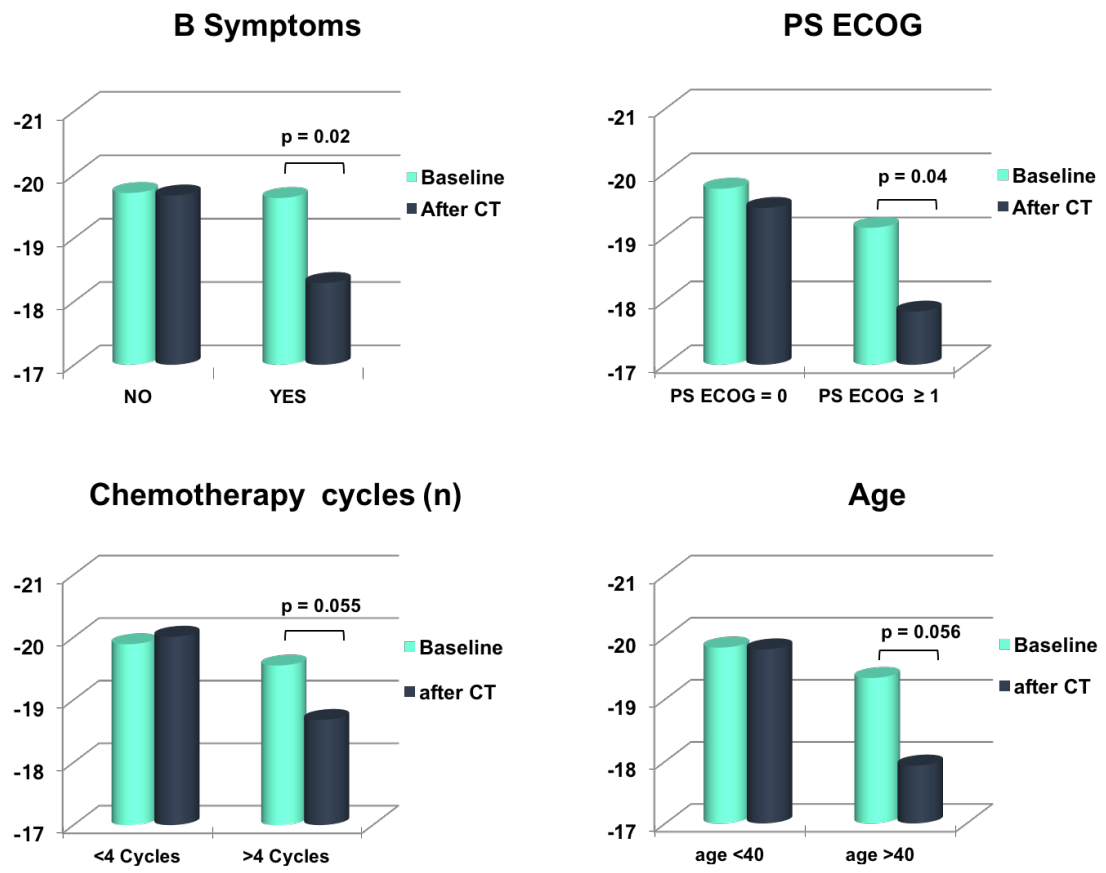
Thirty-six patients diagnosed with HL received 2 to 6 cycles of ABVD, according with disease stage, while all 16 patients with DLBCL or PMBCL but one received 6 cycles of R-CHOP14 or R-CHOP21. In general, 84.7% of patients received 4 or more cycles of chemotherapy, for a mean cumulative anthracyclines dose of 420 mg. Patients in CT-alone group received higher doses of chemotherapy compared to patients in CMT group, with a marginal statistical difference between the 2 cohorts for the median dose (493 mg vs 397 mg, respectively, p = 0.09)

Table 5.2 – General characteristics of chemotherapy treatment

Characteristics	population N° = 52 (%)
Regimen	
ABVD	36 (69,2%)
RCHOP	16 (30,8%)
Cycles (n)	
2	6 (11,5%)
3	2 (3,8%)
4	14 (26,9%)
6	30 (57,8%)
Anthracyclines cumulative dose (mg)	
mean	419,72 ±114,90
median	463,00
min	135,00
max	600,00

After chemotherapy, GLS parameters had no significant impairment in the overall population ($GLS_{baseline}$ -19.69 vs $GLS_{post\text{-}CT:}$ -19.29, p = 0.25). After stratification, we observed a significant impairment of GLS after chemotherapy for patient with B symptoms (-19.63 vs -18.29, p = 0.02) and PS ECOG >1 (-19.14 vs -17.82, p = 0.04). A marginal reduction of 2D-GLS was noticed after chemotherapy for patients in CT-alone arm ($GLS_{baseline}$: -19.24 vs $GLS_{after\text{-}CT:}$ -18.42, p =0.06), in those with age >40 (-19.34 vs -17.93, p =0.056), with stage III-IV disease (-19.14 vs -18.22, p = 0.06) and receiving >4 cycles (-19.55 vs -18.68, p =0.055). Figure 5.3 shows the most relevant GLS modifications after chemotherapy.

Figure 5.3 – Variables related with a significant or marginal reduction of GLS after chemotherapy



We then tested which variables, if any, was related to a "pre-clinically" relevant impairment, defined in accordance with the published guidelines as a reduction >15%. After a univariate analysis, only age >40 determined a significant decrease of GLS above the aforementioned limit (HR 7.20, 95% CI 1.15-45.17, p = 0.035).

5.3.3 Radiotherapy

Thirty-four patients received radiotherapy; of these, only 28 were radiated to the mediastinum, while the remaining 6 patients were treated to other sites (4 to the neck, 1 to the pelvis and 1 to the abdominal lymph-nodes). Median prescription dose was 30 Gy (range 20-40 Gy), wth only 4 patients (11.8%) having a prescribed dose to PTV <30 Gy. We estimated the dose received by whole heart and all cardiac structures, whose dosimetric results are reassumed in Table 5.3. Particularly, heart Dmean

was 5.77 Gy, and left ventricle Dmean was 3.26 Gy. Similarly, left interventricular septum and lateral wall of the left ventricle received low Dmean (3.02 Gy and 2.56 Gy, respectively).

Table 5.3 – Dosimetric parameters for the whole heart and all the cardiac substructures

Heart structure	pts n°	Mean dose (Gy)	Median dose (Gy)	SD	Min value (Gy)	Max value (Gy)
Heart						
D_{mean}	28	5,77	4,84	3,9	0,54	15,01
V_{15}		15,94	11,38	15,53	0,00	65,84
$V_{7.7}$		26,1	21,51	18,17	0,03	62,41
Left Ventricle						
D_{max}	28	21,28	24,55	12,23	1,23	40,98
D_{mean}		3,25	2,25	3,06	0,28	13,44
Septum						
D_{max}	25	13,93	12,70	11,81	0,69	38,26
D_{mean}	23	3,02	1,80	2,87	0,29	10,77
Lateral wall						
D_{max}	25	12,23	8,60	11,94	0,62	40,80
D_{mean}	23	2,56	1,74	2,90	0,21	11,17
Right Ventricle						
D_{max}	28	26,82	30,76	9,75	1,22	45,77
D_{mean}		5,95	4,35	4,77	0,40	18,58
Left Atrium						
D_{max}	28	23,07	24,34	9,79	2,29	34,18
D_{mean}		8,50	6,6	6,31	1,01	22,61
Right Atrium						
D_{max}	28	25,83	29,08	10,08	1,77	40,86
D_{mean}		8,20	6,30	6,29	0,63	23,79
Aortic Valve						
D_{max}	28	21,02	24,85	10,17	1,83	34,49
D_{mean}		12,68	12,21	7,80	1,04	27,53
Pulmonic Valve						
D_{max}	24	25,70	31,44	11,05	1,54	38,86
D_{mean}		19,54	23,04	10,25	1,09	34,04
Mitral Valve						
D_{max}	17	8,78	4,70	10,09	0,33	30,14
D_{mean}		5,47	2,32	7,10	0,27	23,03
Tricuspid Valve						
D_{max}	16	9,36	3,30	11,93	0,34	39,26
D_{mean}		6,20	1,94	8,93	0,27	30,32
Left main trunk						
D_{max}	28	20,58	21,88	8,15	2,79	33,12
D_{mean}	27	15,70	15,78	7,85	1,84	29,33
Left descending						
D_{max}	27	20,68	24,66	10,57	3,60	38,97
D_{mean}		11,40	11,85	7,99	1,59	35,48
Circumflex						
D_{max}	28	15,51	13,45	9,89	1,87	31,40
D_{mean}	27	9,80	6,60	7,96	1,02	26,79
Right coronary						
D_{max}	28	18,14	19,44	11.40	1.23	39.31
D_{mean}	27	11,42	6,53	9.38	0.84	27.81

We noticed that, overall, after radiotherapy GLS parameters had no significant impairment in the 28 patients treated to the mediastinum ($GLS_{after\text{-}CT}$ -20.24 vs $GLS_{after\text{-}RT:}$ -19.59, p = 0.13). Nevertheless, after stratification, we observed a significant impairment of GLS in patients that received higher doses doses of radiation, as shown in Table 5.4.

Table 5.4 – List of the dosimetric parameters related with a significant impairment of GLS

Variables	GLS after-CT	GLS after-RT	p value	CI 95%
D_{max}				
D_{max} heart				
<30	-19,75	-19,58	0,82	(-1,81 - +1,47)
>30	-20,61	-19,60	0,055	(-2,05 - +0,02)
D_{max} left ventricle				
<11	-19,99	-20,67	0,42	(-1,24 - +2,61)
>11	**-20,37**	**-19,01**	**0,002**	**(-2,14 - -0,58)**
D_{max} septum				
<10	-20,89	-20,56	0,57	(-1,58 - +0,93)
>10	**-20,10**	**-18,67**	**0,006**	**(-2,34 - -0,51)**
D_{max} lateral wall				
<8	-20,67	-20,70	0,95	(-0.97 - +1,03)
>8	**-20,31**	**-18,53**	**0,002**	**(-2,73 - -0,83)**
D_{max} right ventricle				
<30	-19,37	-19,23	0,83	(-1,53 - +1,24)
>30	**-21,18**	**-19,98**	**0,04**	**(-2,32 - -0,07)**
D_{mean}				
D_{mean} heart				
<4.5	-20,35	-20,51	0,77	(-1,01 - +1,34)
>4.5	**-20,09**	**-18,39**	**0,007**	**(-2,81 - -0,59)**
D_{mean} left ventricle				
<2	-20,81	-20,65	0,74	(-1,24 - +0,92)
≥2	**-20,17**	**-18,58**	**0,006**	**(-2,61 - +0,57)**
D_{mean} septum				
<2	-20,87	-20,66	0,67	(-1,28 - +0,86)
≥2	**-20,21**	**-18,45**	**0,01**	**(-2,98 - -0,53)**
D_{mean} lateral wall				
<2	-20,55	-20,22	0,49	(-1,32 - +0,67)
≥2	**-20,61**	**-18,84**	**0,02**	**(-3,20 - -0,35)**
D_{mean} right ventricle				
<4	-20,35	-20,51	0,77	(-1.01 - +1,34)
>4	**-20,09**	**-18,39**	**0,007**	**(-2,81 - -0,59)**

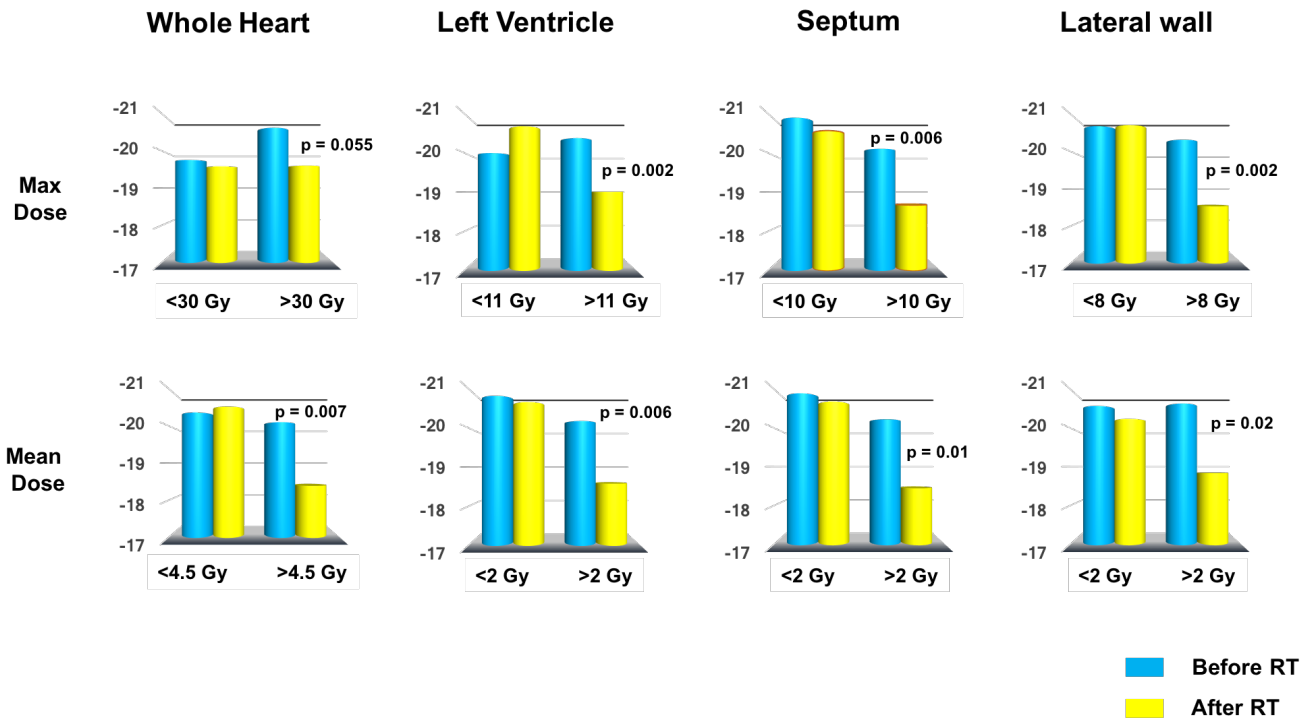
Thus, we were able to identify a significant GLS fall for patient that received the following doses:

A. Dmax >11 Gy to the left ventricle (p = 0.002, 95% CI -2.14 – -0.58), >10 Gy to the interventricular septum (p = 0.006, 95% CI -2.34 – -0.51) and >8 Gy to the lateral wall of the left ventricle (p = 0.002, 95% CI -2.73 – -0.83);
B. Dmean >4.5 Gy to the whole heart (p = 0.007, CI 95%: -2,81 – 0,59) and >2 Gy to the left ventricle (p = 0.006, CI 95%: -2,61 – -0,57), to the interventricular septum (p = 0.01, CI 95%: -2,98 – -0,53) and to the lateral wall of the left ventricle (p = 0.02, CI 95%: -3,20 – -0,35).

Figure 5.4 depicts the dosimetric variables related with a significant impairment of the GLS.

After RT, we were not able to find any correlation between the dosimetric parameter and a decrease of GLS >15%, because only 3 patients satisfied this inclusion criteria.

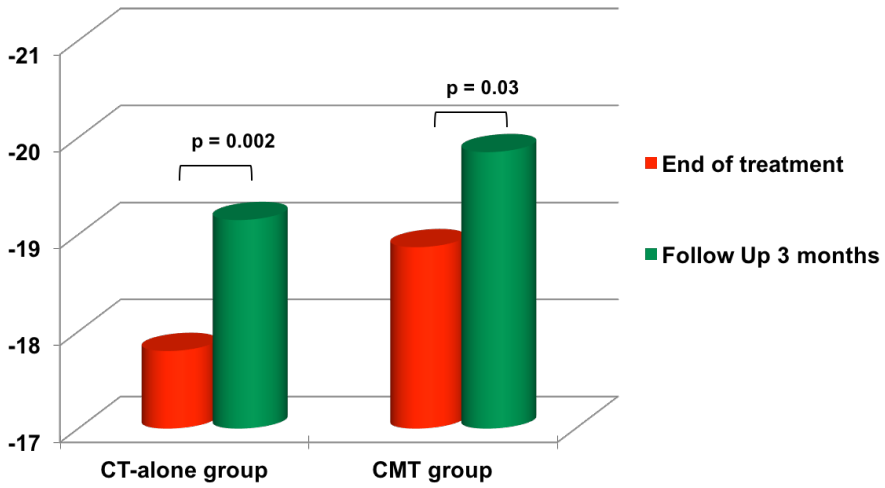
Figure 5.4 – Dose parameters related with a significant or marginal reduction of GLS after radiotherapy



5.3.4 Echocardiographic evaluation and GLS recovery 3 months after end-of-treatment

The echocardiographic analysis at 3 months after end of treatment showed a significant upturn of GLS parameters both in CT-alone ($GLS_{after\text{-}CT}$ -17.80 vs $GLS_{3\text{-}months:}$ -19.65, p = 0.002) and CMT groups ($GLS_{after\text{-}RT}$ -18.87 vs $GLS_{3\text{-}months:}$ -19.85, p = 0.03), as shown in figure 5.5.

Figure 5.5 – GLS recovery after 3 months by the end of treatment in both CT-alone and CMT groups



5.4 CONSIDERATIONS

The CARDIOCARE project is an innovative attempt to test, prospectively, the potential role of advanced echocardiography – integrated with the 2D-GLS testing – to early detect, in the preclinical phase, myocardial impairment after chemo and/or radiotherapy in lymphoma patients. Few studies have previously demonstrated the efficacy of 2D-GLS in detecting myocardial alterations in cancer patients. Erven et al. [**8**] noticed a significant reduction of GLS parameters in a prospective cohort of female patients treated with radiotherapy alone for a left-sided breast cancer. Interestingly, the major

impairment of GLS was reported on the heart apex, which is frequently exposed to higher doses of radiation during a breast cancer course.

GLS is even a valuable tool to detect a preclinical alteration of the myocardial function during the follow-up of cancer treatments, as observed by Armstrong et al [**14**] in a large cohort of long-term childhood cancer survivors. In this study, 31.8% of the patients reported a pathological impairment of the GLS, despite only 5.8% had a significant alteration of the ejection fraction. Interestingly, 17.6% of the population had a clinically relevant heart failure, evaluated with the "six-minutes-walk-test". These results support the hypothesis that GLS might be a sensitive tool to identify patients at higher risk of heart failure after cancer treatments in the preclinical phase, as it manifests earlier variations compared to the more popular ejection fraction parameter.

In our interim analysis on 52 patients enrolled in the CARDIOCARE project, we observed a non-significant reduction of the GLS both after chemotherapy (-19.69% vs -19.29%) and after radiotherapy (-20-24% vs -19-59%).

Anyway, after a stratification for clinical and dosimetric factors, we noticed a significant reduction of GLS after CT in patients with B symptoms (p = 0-02, CI = -2.44 – -0.23) and PS ECOG ≥1 (p = 0.04, 95% CI -2.58 – -0.06) at baseline; moreover a marginal reduction was observed for patients aged >40 years (p = 0.056, 95% CI = -2.84 – +0.04), for patients with stage III-IV disease (p = 0.06, 95% CI = -1.91 – +0.07) and for patients who received more than 4 cycles of CT (p = 0.055, 95% CI = -1.75 – +0.02). Interestingly, patient in the CT-alone group had a more relevant reduction of GLS (p = 0.06, 95% CI = -1.70 – +0.06) after CT, compared to patients in the CMT group (-20.08_{preCT} vs -20.05_{postCT}, p = 0.94). The latter observation is probably justified by the higher dose of anthracyclines received by patients enrolled in the CT-alone group (Median cumulative dose: 493 mg for CT-alone vs 397 mg for CMT, respectively; p = 0.09). After a multivariate analysis, we noticed that age >40 (HR 7,2 95% CI 1.148 – 45.167) is the only parameter predictive for a preclinically relevant reduction of the GLS (>15%, according with the recommendation of the European Society of Cardiology[**11**]).

Interim results of CARDIOCARE project, therefore, suggest the adoption of a careful cardiac monitoring for patients with B symptoms, a poorer PS at baseline and receiving more than 4 cycles of CT, because of the higher chance of developing a GLS drop after systemic therapies. That is more relevant in patients aged >40, who even experienced higher risk of a preclinical cardiac damage compared to younger patients.

We also observed a significant post-RT reduction of GLS after stratification for the following doses received by the heart and by the cardiac substructures:

C. Maximum dose >11 Gy to the left ventricle (p = 0.002, 95% CI -2.14 – -0.58), >10 Gy to the interventricular septum (p = 0.006, 95% CI -2.34 – -0.51) and >8 Gy to the lateral wall of the left ventricle (p = 0.002, 95% CI -2.73 – -0.83);
D. Mean dose >4.5 Gy to the whole heart (p = 0.007, CI 95%: -2,81 – 0,59) and >2 Gy to the left ventricle (p = 0.006, CI 95%: -2,61 – -0,57), to the interventricular septum (p = 0.01, CI 95%: -2,98 – -0,53) and to the lateral wall of the left ventricle (p = 0.02, CI 95%: -3,20 – -0,35).

We have thus identified multiple dose parameters related to a significant reduction of GLS after RT. Anyway, we were not able to identify any correlation between the dose constraints and a GLS reduction >15%, probably because only 3 patients, to date, experienced a GLS fall above that limit. A cohort expansion and the completion of CARDIOCARE project will be essential to identify any dose parameter related to a pre-clinically relevant abrupt of GLS after RT.

In any case, these interim results are of some interest, given the lacking of information in literature regarding a prospective monitoring of CT and RT induced heart toxicity in lymphoma patients. Moreover, the identification of dose parameters related to a significant impairment of GLS is the first attempt to define a list of cardiac-related dose constraints to be integrated in the complex planning process of lymphomas with mediastinal involvement. Logically, our results need a clinical confirmation, which will be available only in many years with the correlation between the dose-related reduction of GLS and the detection of cardiac events. In the meantime, GLS seems to be a sensitive parameter of systolic dysfunction, especially when compared to the “obsolete” ejection

fraction, and may represent the best strategy to monitor cardiac function in lymphoma patients, particularly after mediastinal RT. That is particularly relevant for all patients treated in the recent years, given the sensible improvement of the RT offer in reason of dose/volume reduction and exploitation of modern technique, which has leaded to a drastic reduction of the heart volume receiving high doses of radiation. Effectively, in our study median dose to the whole heart and to the left ventricle were only 4.8 Gy and 2.2 Gy, respectively. These doses are much lower compared to those detected in previous large cohorts. Van Nimwegen et al [**15**], for instance, detected a median heart dose of 20.9 Gy and a median left ventricle dose of 14.5 Gy on a cohort of 2617 long term survivors treated between 1965 and 1995 for HL. Therefore, we reasonably expect a significant reduction of radiation-induced cardiac events in the next 2-3 decades, given the more favorable dosimetric profile of modern RT (4 to5 fold decrease of the dose received by the heart and by the left ventricle) compared to the older techniques. For that reason, high sensitive diagnostic tools as GLS may play a pivotal role to identify in an early/preclinical phase those – hopefully few – patients potentially at higher risk of cardiac events, even after low heart doses. To date, anyway, we don't know exactly the real clinical impact of the GLS downfall, due to the limited follow-up and to the prompt recovery of strain parameters after 3 months after the end of treatment in our study. On one hand the upturn of GLS parameters may be the reassuring proof of complete recovery from a subclinical cardiac damage, promptly restored after the completion of cancer treatments; on the other hand, the significant fluctuation of GLS after CT and RT confirms the hypothesis that cancer treatments have caused a cardiac damage, whose clinical impact in the long term still needs to be confirmed.

In conclusion, 2D-GLS seems a promising tool to detect early cardiotoxicity in lymphoma patients. Preliminary results suggest a correlation of both anthracyclines and radiation dose with preclinical heart damage. The completion of CARDIOCARE study, and a future correlation with clinical events are needed to support and strengthen these preliminary assumptions.

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Chapter 6 – Respiratory gating with continuous positive airway pressure (CPAP): a very promising approach to reduce heart toxicity and to deal with breath holding in mediastinal irradiation

6.1 BACKGROUND

As already stated, the combination of chemotherapy and modern radiotherapy leads to excellent cure rates, with 80-90% of the patients getting cured from their lymphoma. For this large group of long term survivors, late complications as cardiovascular events and second cancers may counterbalance the benefit of cancer therapies and represent a relevant issue [**1-10**]. However, current radiation therapy protocols may combine limited radiation volumes [**11-12**] with advanced planning and delivery techniques, such as intensity modulated RT (IMRT), tomotherapy and proton therapy. This innovative approach should be associated with less radiation-related morbidity through an improved sparing of normal tissues.

A further benefit could be obtained with the integration of "respiratory gating" strategies, as already shown in some retrospective modeling studies [**13-17**]. The most used techniques of respiratory gating are the "*deep inspiration breath hold*" (DIBH) and the "*breathing synchronized*" radiotherapy. DIBH, particularly, provides a proven dosimetric benefit, compared to free-breathing, in patients receiving mediastinal radiotherapy for Hodgkin lymphoma [**18**]. Unfortunately, DIBH is not easily available in all Radiation Oncological departments and, moreover, not all patients have a sufficient compliance to maintain a deep inspiration for the required time. Furthermore, modern RT techniques have lengthened the treatment time and patients need to repeat DIBH many times per single fraction of radiation, thus compromising the overall compliance.

Lastly, the reproducibility of deep inspiration is still debated and, despite the adoption of IGRT and "surface-guided" technologies, many concerns still remain regarding inter-fraction and intra-fraction

variations of the lungs volume. Consequently, the potential discrepancy between planned and received dose is still uncertain.

A strategy to increase "forcedly" and continuously the lungs volume, minimizing at the meantime their excursion, could be represented by the adoption of non-invasive mechanic ventilation with "*Continuous Positive Airway Pressure*" (CPAP). Indeed, the physiological effects of CPAP are: lung hyper-expansion, moving down and stabilization of the diaphragm and reduction of the tidal volume. A preliminary experience [**19**] has shown the feasibility of this particular "respiratory gating" on a cohort of 11 early stage lung cancer patients treated with stereotactic body radiation therapy. To date, no reports are available on the integration of this strategy within a modern RT technique for lymphoma patients with mediastinal involvement. With this background, we have recently launched this pilot project of comparative planning between free-breathing and CPAP assisted RT, with the hypothesis that the lung expansion induced by CPAP may create a favorable "thoracic conformation" by taking away the target of treatment from the organs at risk, and in particular from the heart.

6.2 MATERIAL AND METHODS

6.2.1. Study design

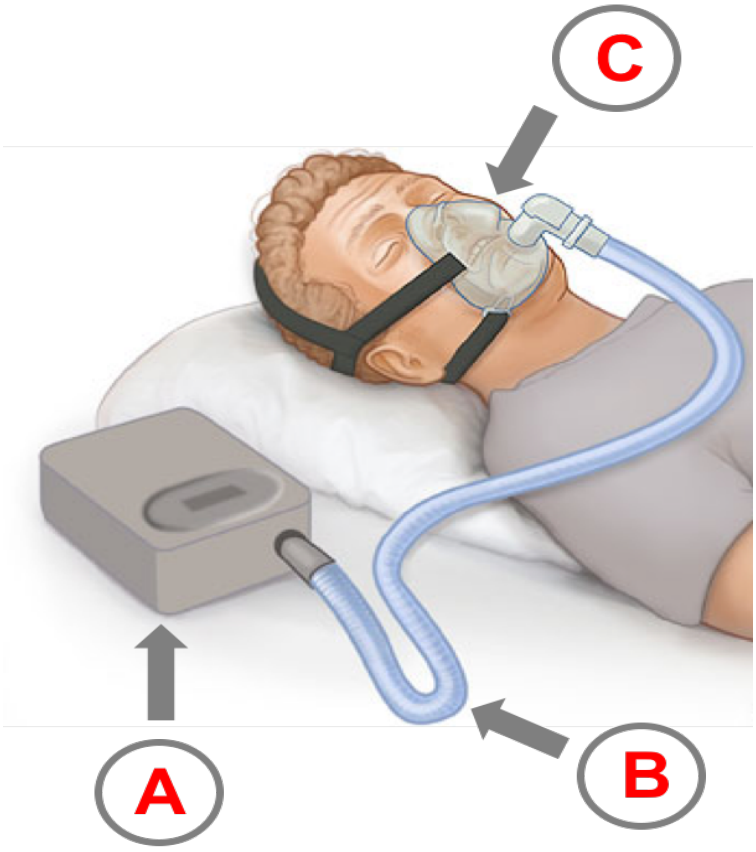
In this prospective observational study, we enroll patients with Hodgkin (HL) or non-Hodgkin (NHL) lymphomas with mediastinal involvement. All patients are candidate to mediastinal RT after the completion of a chemotherapy course, in according with the NCCN guidelines for the treatment of HL and NHL. The study was approved by our ethic committee (approval number CS2/581), and we enrolled the first patient in February 2018. To date, 14 patients have completed the treatment and were included in a preliminary analysis.

Operatively, the study process is organized in the following 4 steps:

a) ***Phase 1*** *– CPAP training with a dedicated pulmonologist*

First, all patients have to test a facial or an orinasal CPAP mask, by choosing the most comfortable to the individual anatomy. At the same appointment, a spirometry is acquired in order to check for any contraindication to the utilization of the CPAP mask (e.g. severe restrictive pulmonary disease). Afterwards, all patients undergo a CPAP training, to test their ability to tolerate the final predetermined air pressure of 18 cmH2O (roughly 1,8 liters of air). To facilitate the compliance, each training begun with a pressure of 12 cmH2O and a ramp of 10 minutes to reach the maximum air pressure of 18 cmH2O. During the training, performed in sitting position, blood pressure and oxygen saturation are steadily monitored. This testing is essential for the patients in order to train their respiratory frequency and to avoid hyperventilation, potentially leading to a vasovagal syncope. The CPAP training is then repeated in our Radiation Oncology Department with the patient supine in treatment position, for a duration of 15 minutes in order to simulate a RT fraction. Figure 6.1 shows a CPAP equipment.

Figure 6.1 – CPAP equipment: A) air pump; B) tubing; C) facemask



b) ***Phase 2*** *– CT simulation for RT treatment*

A baseline CT with a slice thickness of 3 mm is acquired for treatment simulation. The treatment isocenter is placed by the treating Radiation Oncologist during this procedure. Every patient receives 2 different CT scan: the first one in free breathing and the second one with the CPAP equipment, in order to have 2 different image sets for a comparative planning. The CPAP scan is acquired with a "4D technique", in order to quantify precisely the modification of lung volume in the different phases of the respiratory cycle.

c) ***Phase 3*** *– Planning of RT treatment.*

In this phase, the treating Radiation Oncologist contours the target of treatment in accordance with the ISRT definition [**11-12**] and all the organs at risk (OARs), with a particular carefulness for the heart and cardiac structures [**20**] on both free breathing and CPAP scans.

Afterward a comparative planning (with the same IMRT/VMAT approach) is performed between the 2 scans, in order to select the best one, after a careful analysis of the dosimetric parameters for each OAR.

d) ***Phase 4*** – treatment delivery

RT treatment is given in free breathing or with the CPAP equipment on the basis of the comparative planning, selecting the best plan after the dosimetric comparison.

6.2.2 Inclusion and exclusion criteria

Inclusion criteria are:

- Age >15 years
- Histologically proven HL or PMBCL
- Mediastinal involvement
- Acquisition of the Informed consent

Exclusion criteria are:

- Age >50
- Previous mediastinal irradiation
- PS ECOG >1
- Moderate or severe restrictive pneumopathy at spirometry exam
- Poor compliance to maintain CPAP mask

6.2.3 Study purpose and statistical considerations

We designed this study with the purpose of evaluating the feasibility of a respiratory gating with CPAP, compared with a free-breathing, integrated to an IMRT/VMAT technique for the treatment of HL or PMBCL patients.

Primary Endpoints are:

- To look for a reduction of the doses received by OARs with the CPAP equipment:
- To estimate the expansion of lungs volume with CPAP, compared to free-breathing.

Secondary endpoint is:

- Reduction of cardiac events and secondary cancer risk with CPAP, both evaluated with a dedicated risk modeling.

Dosimetric parameters and mean values of OED, LAR, and AER to the OAR with CPAP and free-breathing will be compared using Student paired t test, with a two-tailed significance level of .05. All statistical analyses will be performed using STATA vesion 13.1 statistical software.

6.3 RESULTS

To date, only 14 patients were enrolled to the study. The results presented refers, thus, to a very preliminary analysis. Table 6.1 shows the population characteristics.

Table 6.1 – Population characteristics

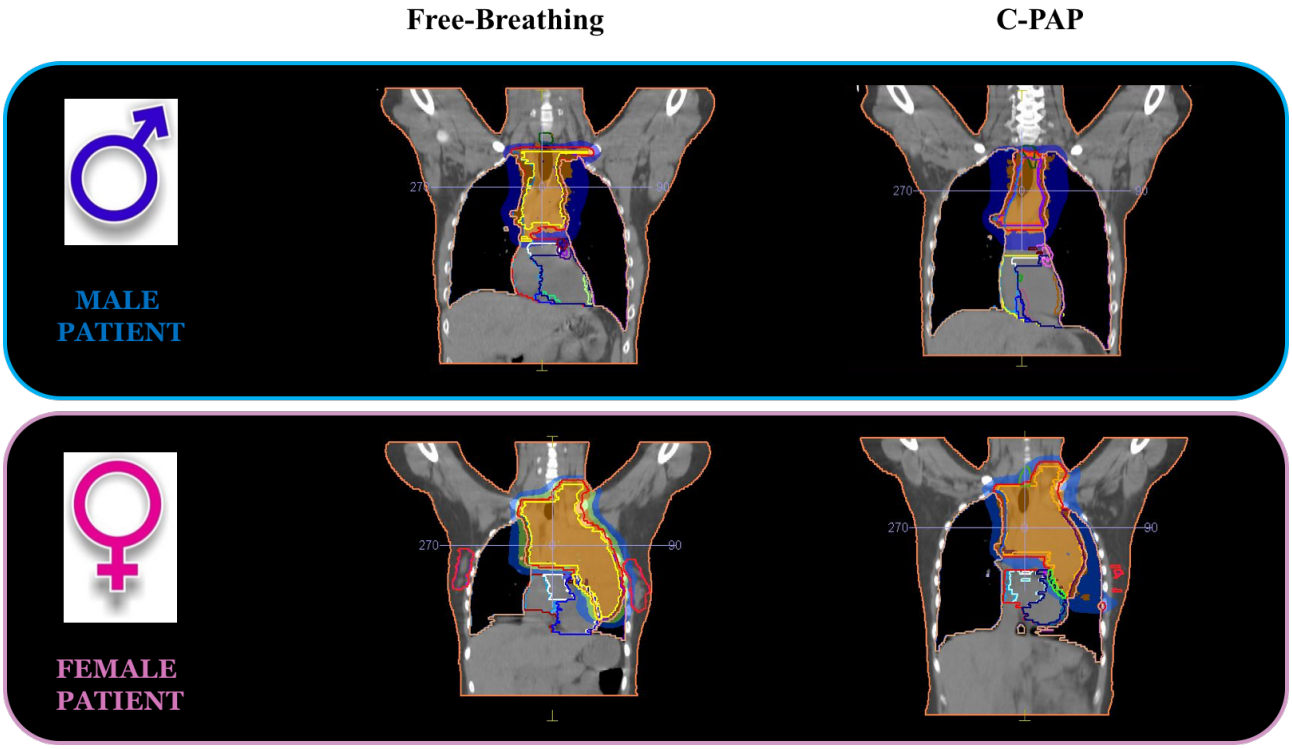
Characteristics	*Population N=14 (%)*
Gender	
Male	5 (35,7%)
Female	9 (64,3%)
Median age	29,4 (range 16-38)
PS ECOG	
0	14 (100%)
≥1	0 (0%)
Histology	
HL	12 (85,7%)
PMBCL	2 (14,3%)
Stage (Ann Arbor)	
I	0 (0%)
II	12 (85,7%)
III	0 (0%)
IV	2 (14,3%)
B symtpoms	
Yes	8 (57%)
No	6 (42,8%)
Bulky lesion	
Yes	9 (64.3%)
No	5 (35.7%)

All patients, but one, had a dosimetric benefit with the CPAP at the plan comparison and thus received the treatment with that equipment. Table 6.2 shows the dosimetric comparison of all OARs between free-breathing and CPAP. Particularly, the intersection between the PTV and the heart volume, and consequently the heart exposure, was significantly lower with CPAP ($p = 0,0024$). Even all coronaries received a lower dose with CPAP compared to free-breathin. Moreover, the lung expansion obtained with CPAP resulted in significantly lower Lung V20 ($p = 0,0046$) and Lung V5 ($p = 0,0005$). Figure 6.2 shows the different dosimetric distribution between CPAP and free breathing in a male and in a female patient.

Table 6.2 – dosimetric comparison between free-breathing and CPAP

Structure	*Free-breathing*	*CPAP*	*P*
Intersection PTV/heart (cc)	23,6 ± 16,5	10 ± 15,6	0,0024
D mean Heart (Gy)	6,3 ± 4,4	4,8 ± 5,1	0,0061
Lung Volume - PTV (cc)	2626,3 ± 918,6	4156,1 ± 1095,7	0,0002
Lung V20 Gy (%)	13,7 ± 4,4	11,5 ± 3,6	0,0046
Lung V5 Gy (%)	43,8 ± 11,8	37,7 ± 10,1	0,0005
D mean Left ventricle (Gy)	4,3 ± 4,7	3,3 ± 4,1	0,0061
D mean Septum (Gy)	5,1 ± 6	3,5 ± 5,3	0,0010
D mean Lateral wall (Gy)	4,5 ± 6,4	3,3 ± 4,8	0,0010
D mean Aortic valve (Gy)	11,8 ± 7,1	7,8 ± 6,4	0,0005
D mean Right coronary (Gy)	9,1 ± 6,1	7,2 ± 6,3	0,0681
D mean Circumflex (Gy)	9,4 ± 6,6	6,5 ± 5,8	0,0005
D mean Left descending (Gy)	11,6 ± 8,4	8,8 ± 7,6	0,0005
D mean Left Main (Gy)	13 ± 8,4	10,3 ± 8,4	0,0327

Figure 6.2 – Dosimetric comparison between CPAP and free-breathing in a male and in a female patient



We paid extreme attention to the contouring of all the structures in both free-breathing and CPAP scan and table 6.3 shows a comparison of target and OARs volumes in the 2 different situations. With the exception of lungs, the volume of all structures was similar between CPAP and free-breathing.

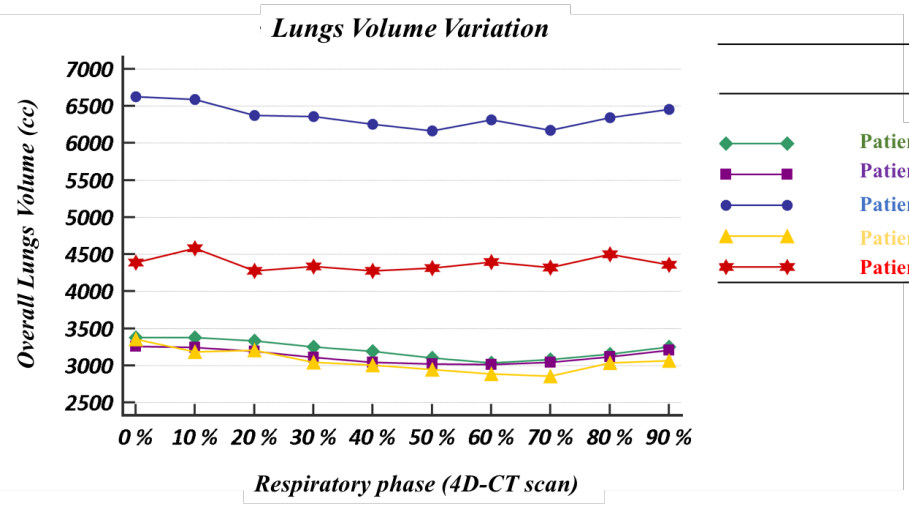
Table 6.3 – volume comparison of PTV and OARs between free-breathing and CPAP

Structure – Volume [cc]	***Free-breathing***	***CPAP***
PTV	642,9 ± 256,9	629,8 ± 257,8
Right lung	1501,4 ± 485,1	2309,7 ± 651,8
Left lung	1192,3 ± 403,5	1888,4 ± 530,7
Breasts	1048,5 ± 864,1	991,6 ± 628,9
Heart	561,2 ± 103,9	516,1 ± 96,9
Left ventricle	217,3 ± 56	202,4 ± 56,7
Right ventricle	143,9 ± 31,8	141,2 ± 34,9
Right coronary	1,8 ± 1	1,7 ± 1
Circumflex	1,6 ± 0,8	1,5 ± 0,8
Left descending	2,6 ± 0,9	2,8 ± 1
Left main trunk	0,5 ± 0,1	0,5 ± 0,2
Coronary tree (sum of all the coronaries)	6,5 ± 2,2	6,3 ± 2,4

We have also checked the lung excursion, by contouring the lung volumes in each single respiratory phase of the 4D CT scans acquired with the CPAP mask in 5 unselected "test" patients.

We noticed (Figure 6.3) that the lung excursions were limited with the CPAP mask, with a standard deviation from the average CT sequence, adopted for RT planning, ranging from 2 to 5% for each patient included in this particular analysis.

Figure 6.3 – Lung excursions during the respiratory phases with CPAP mask in 5 test patients. The table reports "average" lung volumes and standard deviation.



	Overall Lungs Volume [cc]
	C-PAP [mean ± SD]
Patient 1	3215 ± 124
Patient 2	3125 ± 95
Patient 3	6367 ± 156
Patient 4	3058 ± 154
Patient 5	4376 ± 98

6.4 CONSIDERATIONS

These very preliminary results support the continuation of our study in reason of a significant dosimetric benefit to the lungs and to the heart structures with CPAP, compared to free-breathing. This innovative respiratory gating technique seems promising and provides some advantages compared to the more popular DIBH:

1. No needs for repeated breath holding during a modern "long lasting" RT fraction;
2. No uncertainties concerning different lung expansions during repeated deep inspirations, because with the CPAP garrison the amount of air inflated is steady during all the treatment session;
3. Better patient compliance, provided the acceptance of the CPAP mask.

All fourteen patients enrolled to date had an excellent compliance with the CPAP mask. Only one out of fourteen (7%) hade no dosimetric benefit with CPAP and thus received the treatment in free-breathing position. That particular case refers to a young female patient with a huge disease volume to the left supraclavicular and axillary lymph-nodes plus minimal involvement to the upper

mediastinum and an isolated left diaphragmatic lymph node; in our opinion, the disease extent justifies the lacking of dosimetric benefit for CPAP, anyway the limited numbers enrolled to date and the absence of similar cases in our cohort do not allow us to generate a definitive hypothesis at this regard.

Overall, CPAP showed to be extremely effective, primarily, in reducing cardiac doses as demonstrated by the reduction of the intersection between PTV and heart volume, compared to free-breathing (10 cc vs 23.6 cc, $p = 0.0024$). In particular, coronary arteries and left ventricle obtained the major benefit from CPAP, and the sparing of these "noble" heart structure should translate in a lower risk of coronary events and heart failure in the long term. However, the actual data are not sufficient to calculate a reliable risk modeling ant thus a cohort expansion is needed to confirm our assumption.

In conclusion CPAP is an innovative technique for respiratory gating and seems to be promising in reducing the dose received by the heart structures (particularly coronaries and left ventricle) and lungs in a cohort of lymphoma patients with mediastinal involvement. Anyway, our preliminary results need to be confirmed by the continuation of the study and by a cohort expansion, integrating also an evaluation of the risk for second lung cancer and cardiovascular events in the long term with a dedicated risk modeling.

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List of Results

Published manuscripts

1. **Levis M**, De Luca V, Fiandra C, Veglia S, Fava A, Gatti M, Giorgi M, Bartoncini S, Cadoni F, Garabello D, Ragona R, Filippi AR, Ricardi U. *Plan optimization for mediastinal radiotherapy: estimation of coronary arteries motion with ECG-gated cardiac imaging and creation of compensatory expansion margins.* Radioth Oncol 2018;127:481-486

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4. **Levis M**, Piva C, Filippi AR, Botto B, Gavarotti P, Pregno P, Nicolosi M, Freilone R, Parvis G, Gottardi D, Vitolo U, Ricardi U. *Potential benefit of involved-field radiotherapy for patients with relapsed-refractory Hodgkin's lymphoma with incomplete response prior to autologous stem cell transplantation.* Clin Lymphoma Myel Leuk 2017;1:14-22

5. Filippi AR, Piva C, **Levis M**, Chiappella A, Caracciolo D, Bellò M, Bisi G, Vitolo U, Ricardi U. *Prognostic role of pre-radiation therapy ^{18}F-fluorodeoxyglucose positron emission tomography for primary mediastinal B-Cell lymphomas treated with R-CHOP or R-CHOP-Like chemotherapy plus radiation.* Int J Radiat Oncol Biol Phys 2016;95(4):1239-1243

6. Ricardi U, **Levis M**, Filippi AR. *Radiotherapy and Hodgkin: a never ending story*. Drugs and Cell Therapies in Hematology 2015;3:157-175

Selected abstracts

- **American Society for Radiation Oncology (ASTRO) 60° Congress** – to be held in San Antonio, USA, October 21st – 24th; Selected Oral Presentation: *"A Prospective, Observational Study Evaluating Early Subclinical Cardiotoxicity With Global Longitudinal Strain Imaging In Lymphoma Patients Treated With Chemotherapy +/- Mediastinal Radiotherapy: The CARDIOCARE Project."*

- **European Society of Radiotherapy and Oncology (ESTRO) 37° Congress** – Barcelona, Spain, April 20th – 24th 2018; Oral Presentation: *"Reduced cardiac risk in Hodgkin lymphoma patients treated with full-arc VMAT compared to b-VMAT"*

- **European Society of Radiotherapy and Oncology (ESTRO) 36° Congress** – Vienna, Austria, May 4th – 9th 2017; Poster viewing communication: *"Estimation of an internal risk volume for coronary arteries after motion evaluation with ECG-gated CT"*

- **European Society of Radiotherapy and Oncology (ESTRO) 35° Congress** – Torino, Italy, April 29th – May 3rd 2016; Poster viewing communication: *"Role of radiation therapy prior or after autologous stem cell rescue for refractory or relapsed Hodgkin's lymphoma"*

Curriculum Vitae

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Education and Training

- October 2001: admission at the Torino University School of Medicine
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- May 2010: admission to the Radiation Oncology Residency Program of Torino University
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Main Interests

- Hematological malignancies, Brain tumors, Lung cancer, Prostate Cancer, Oligometastatic disease, Long term complication and Survivorship care, IMRT, IGRT, SRS, SBRT

Memberships

- Council member – International Lymphoma Radiation Oncology Group (ILROG)
- Member – Fondazione Italiana Linfomi (FIL)
- Member – European Society for Therapeutic Radiology & Oncology (ESTRO)
- Member – Associazione Italiana Radioterapia Oncologica (AIRO)

Invited National and International Talks

- June 2018: Teacher at the ESTRO Course "Combined drug-radiation treatment: biological basis, current applications and perspectives". *Lectures on: Brain tumors, non-small cell lung cancer, small cell lung cancer and lymphomas* (Chengdu, China).
- May 2018: Multidisciplinary management of patients affected with Hodgkin and Non-Hodgkin Lymphoma: *"Cardiac protection in the treatment of mediastinal lymphomas"* (Cagliari, Italy)
- April 2018: Selected Oral Presentation at ESTRO 37th annual meeting: *"Reduced cardiac risk in Hodgkin lymphoma patients treated with full-arc VMAT compared to b-VMAT"* (Barcelona, Spain)
- September 2017; The Young side of Lymphoma, under 40 meeting: *"Role of radiotherapy in the treatment of primary CNS lymphoma"* (Torino, Italy)
- June 2017: Teacher at the ESTRO Course "Combined drug-radiation treatment: biological basis, current applications and perspectives". *Lectures on: Brain tumors, non-small cell lung cancer, small cell lung cancer and lymphomas* (Bruxelles, Belgium).
- May 2017: Cardioncologia 2017 "Domande, risposte e…dubbi" (Torino, Italy)
- May 2017: Poster viewing communication at ESTRO 36th annual meeting: *"Estimation of an internal risk volume for coronary arteries after motion evaluation with ECG-gated CT"* (Vienna, Austria)
- January 2017: II level University Master Course "Diagnosis and therapy of hematologic malignancies" 6° week – *Radiotherapy in classical HL: early stage; Radiotherapy in classical HL: advanced stage* (Udine, Italy)
- November 2016: Brescia Meetings in Radiation Oncology, 2016 edition – The Heart of Oncology: *"Cardiac damage in Hodgkin's lymphoma: overview of ongoing studies"* (Brescia, Italy)

- November 2016: Fondazione Italiana Linfomi (FIL) National Meeting: *"Cardiotoxicity: potential prevention with modern radiotherapy"* (Roma, Italy)
- September 2016: The Young side of Lymphoma, under 40 meeting: *"Advanced stage Hodgkin Lymphoma. Mediastinal bulky and radiation induced cardiac toxicity"* (Reggio Emilia, Italy)
- May 2016: Oncological treatments and cardiotoxicity: *"Radiation therapy and risk of cardiac toxicity"* (Torino, Italy)
- May 2016: Poster viewing communication at ESTRO 35th annual meeting: *"Role of radiation therapy prior or after autologous stem cell rescue for refractory or relapsed Hodgkin's lymphoma"* (Torino, Italy)
- May 2015: Cardio-Oncological Meeting: *"Radiotherapy"* (Torino, Italy)
- November 2014: Fondazione Italiana Linfomi regional meeting: *"Radiation Therapy and potential heart damage"* (Torino, Italy)
- March 2014: Cardio-Oncological Meeting: *"Radiotherapy and potential cardiologic damage"* (Torino, Italy)
- November 2013: New therapies in Prostatic Cancer: Clinical Impact?: *"Adjuvant and salvage radiotherapy: role for hormonal therapy?"* (Torino, Italy)
- December 2012: III Regional Meeting AIRO Piemonte, Liguria e Valle D'Aosta: *"Risk-adapted stereotactic body radiotherapy (SBRT) for patients with early stage non-small cell lung cancer: experience at University of Torino"*. (Sestri Levante, Italy)

Publications

1. **Levis M**, De Luca V, Fiandra C, Veglia S, Fava A, Gatti M, Giorgi M, Bartoncini S, Cadoni F, Garabello D, Ragona R, Filippi AR, Ricardi U. *Plan optimization for mediastinal radiotherapy: estimation of coronary arteries motion with ECG-gated cardiac imaging and creation of compensatory expansion margins.* Radioth Oncol 2018;127:481-486
2. Andreis A, Budano C, **Levis M**, Garrone P, Usmiani T, D'Ascenzo F, De Filippo O, D'Amico M, Bergamasco L, Biancone L, Marra S, Colombo A, Gaita F. *Contrast-induced kidney injury: how does it affect long-term cardiac mortality?* J Cardiovasc Med 2017;18:908-915
3. Filippi AR, **Levis M**, Parikh R, Hoppe B. *Optimal therapy for early-stage Hodgkin's lymphoma: risk adapting, response adapting and role of radiotherapy*. Curr Oncol Rep 2017;19:34

4. Ricardi U, Filippi AR, Piva C, **Levis M**. *Extranodal Marginal Lymphoma*. In: Dabaja BS. and Ng A. Radiation Therapy in Hematologic Malignancies – An illustrated practical guide. Springer 2017, Cham, Switzerland pp 55-71
5. **Levis M**, Piva C, Filippi AR, Botto B, Gavarotti P, Pregno P, Nicolosi M, Freilone R, Parvis G, Gottardi D, Vitolo U, Ricardi U. *Potential benefit of involved-field radiotherapy for patients with relapsed-refractory Hodgkin's lymphoma with incomplete response prior to autologous stem cells transplantation.* Clin Lymphoma Myeloma Leuk 2017;1:14-22
6. Filippi AR, Piva C, **Levis M**, Chiappella A, Caracciolo D, Bellò M, Bisi G, Vitolo U, Ricardi U. *Prognostic role of pre-radiation therapy 18F-fluorodeoxyglucose positron emission tomography for primary mediastinal B-cell lymphomas treated with R-CHOP or R-CHOP-Like chemotherapy plus radiation*. Int J Radiat Oncol Biol Phys 2016;95(4):1239-1243
7. **Levis M**, Guarneri A, Giaj Levra N, Spratt DE, Bartoncini S, Munoz F, Trino E, Botticella A, Arcadipane F, Ricardi U. *Risk stratification system and pattern of relapse in patients treated with adjuvant radiotherapy after radical prostatectomy.* Tumori 2016;102(3):323-329
8. Ricardi U, **Levis M**, Filippi AR. *Radiotherapy and Hodgkin: a never ending story*. Drugs and Cell Therapies in Hematology 2015;3:157-175
9. Ferrero C, Badellino S, Filippi AR, Focaraccio L, Giaj Levra M, **Levis M**, Moretto F, Torchio R, Ricardi U, Novello S. *Pulmonary function and quality of life after VMAT-based stereotactic ablative radiotherapy for early stage inoperable NSCLC: a prospective study.* Lung Cancer 2015;89:350-356
10. Arcadipane F, Fiandra C, Franco P, Munoz F, Irgolini P, Trino E, **Levis M**, Guarneri A, Ricardi U. *Three-dimensional ultrasound-based target volume delination and consequent dose calculation in prostate cancer patients with bilateral hip replacement: a report of 4 cases*. Tumori 2015;101(5)e133-e137
11. Ricardi U, Franco P, Munoz F, **Levis M**, Fiandra C, Guarneri A, Moretto F, Bartoncini S, Arcadipane F, Badellino S, Piva C, Trino E, Ruggieri A, Filippi AR, Ragona R. *Three-dimensional ultrasound-based image-guided hypofractionated radiotherapy for intermediate-risk prostate cancer: results of a consecutive case series.* Cancer Invest 2015;33(2):23-28
12. Fiandra C, Filippi AR, Munoz F, Guarneri A, Moretto F, **Levis M**, Ragona R, Ricardi U. *Impact of observers' experience on daily prostate localization accuracy in ultrasound- based IGRT with the Clarity platform.* J Appl Clin Med Phys 2014;15(4):4795.
13. Botticella A, Guarneri A, Giaj Levra N, Munoz F, Filippi AR, Rondi N, Badellino S, Arcardipane F, **Levis M**, Ragona R, Ricardi U. *Biochemical and clinical outcomes after high-*

dose Salvage Radiotherapy as monotherapy for prostate cancer. J Cancer Res Clin Oncol, 2014;140(7):1111-1116.

14. Ricardi U, Frezza G, Filippi AR, Badellino S, **Levis M**, Navarria P, Salvi F, Marcenaro M, Trovò M, Guarneri A, Corvò R, Scorsetti M *Stereotactic Ablative Radiotherapy for stage I histologically proven non-small cell lung cancer: An Italian multicenter observational study.* Lung Cancer, 2014;84(3):248-253.
15. Filippi AR, Badellino S, Guarneri A, **Levis M**, Botticella A, Mantovani C, Ragona R, Racca P, Buffoni L, Novello S, Ricardi U. *Outcomes of single fraction stereotactic ablative radiotherapy for lung metastases.* Technol Cancer Res Treat, 2014; 13(1):37-45
16. Budano C, **Levis M**, D'Amico M, Usmiani T, Fava A, Sbarra P, Burdese M, Segoloni GP, Colombo A, Marra S. *Impact of contrast-induced acute kidney injury definition on clinical outcomes.* Amer Heart J, 2011; 161(5): 963-971
17. Scacciatella P, Ebrille E, Infantino V, Amato G, **Levis M**, Marra S. *Left main minimal plaque burden complicated by an acute massive thrombosis: diagnostic and therapeutic strategies*. J Cardiovasc Med, 2011; 12(9): 692-694
18. Alunni G, Giorgi M, Sartori C, Garrone P, Conrotto F, D'Amico M, Scacciatella P, Andriani M, **Levis M**, Marra S. *Real-time triplane echocardiography in aortic valve stenosis: validation, reliability and feasibility of a new method for valve area quantification*. Echocardiography, 2010; 27(6): 644-650
19. Scacciatella P, Amato G, Ebrille E, **Levis M**, Frisenda V, Pompilio G, Marra S. *Current perspectives in cell therapy in cardiology: an overview of ongoing trials*. G Ital Cardiol, 2010; 11(10): 769-774

Reviewer for the following Journals

International Journal Radiation Oncology Biology and Physics --- Radiotherapy and Oncology --- Radiation Oncology --- Acta Oncologica --- Cancer Medicine

Mario Levis

Torino, June 29th, 2018