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A quality control study on involved node radiotherapy in the EORTC/LYSA/FIL H10 Trial on stages I/II Hodgkin lymphoma; lessons learned.

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**Title:**

# A quality control study on involved node radiotherapy in the EORTC/LYSA/FIL H10 Trial on stages I/II Hodgkin lymphoma; lessons learned.

**Short Running Title**

Involved node radiotherapy quality control

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**Conflict of interest:**

**Aleman - leadership:**

- Chair of radiotherapy subcommittee of the EORTC lymphoma group
- Chair of the Dutch Platform for Radiotherapy in haematological malignancies
- Member of the Steering Committee of the International Lymphoma Radiation Oncology Group

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- International Lymphoma Radiation Oncology Group - vice chair
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- Danish Lymphoma Group- executive committee member

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Data will be shared according to the EORTC data release policy

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**Abstract:**

**Purpose**: Involved Node Radiotherapy (INRT) was introduced in the EORTC/LYSA/FIL H10 trial, a large multicenter trial in early stage Hodgkin Lymphoma (HL). The current study aimed to evaluate the quality of INRT in this trial.

**Methods and Materials**: A retrospective, descriptive study was initiated to evaluate INRT in a representative sample encompassing approximately 10% of all irradiated patients in the H10 trial. Sampling was stratified by academic group, year of treatment, size of treatment center and treatment arm and it was done proportional to the size of the strata. The sample was completed for all patients with known recurrences to enable future research on relapse pattern. Radiotherapy principle, delineation and coverage of the target volume and applied technique and dose were evaluated using the EORTC Radiotherapy Quality Assurance (RTQA) platform. Each case was reviewed by two reviewers and, in case of disagreement, also by an adjudicator for a consensus evaluation.

**Results**: Data was retrieved for 66 out of 1294 irradiated patients (5.1%). Data collection and analysis were hampered by changes in archiving of diagnostic imaging and treatment planning systems during the running period of the trial, more than anticipated. Review could be performed in 61 patients. The INRT principle was applied in 86.6%. Overall, 88.5% of cases were treated according to protocol. Unacceptable variations were predominately due to geographical misses of the target volume delineations. The rate of unacceptable variations decreased during trial recruitment.

**Conclusions**: The principle of INRT was applied in most of the reviewed patients. Almost 90% of the evaluated patients were treated according to the protocol. The current results

should, however, be interpreted with caution because the number of patients evaluated was limited. In future trials, individual case reviews should be done in a prospective fashion. RTQA tailored to the clinical trial objectives is strongly recommended.

**Introduction:**

The outcome of standard treatment for patients with clinical stage I/II Hodgkin lymphoma (HL) consisting of the combination of chemotherapy (mostly ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine)) followed by radiotherapy (RT) is excellent.[1] Both radiotherapy and chemotherapy may, however, cause long-term toxicity.[2, 3] Therefore, possibilities to reduce chemotherapy and radiotherapy as much as possible without compromising HL cure rates, have been and are still being studied systematically. [1, 4-8]

Over the last decades effective chemotherapy regimens have been developed, enabling reduction from extended field radiotherapy to involved field radiotherapy (IFRT).[9] IFRT was defined based on lymph node regions according to the Ann Arbor staging diagram, which was not designed to construct radiation fields. Since consolidating radiation therapy to involved lymph nodes after a limited number of chemotherapy cycles was still considered to be a necessity, the European Organisation for Research and Treatment of Cancer (EORTC) lymphoma group developed the involved node radiotherapy (INRT) principle. INRT encompasses irradiation of only initially macroscopically involved nodes as defined by pre-chemotherapy imaging.[10] INRT was applied for the first time in an international study performed by the EORTC Lymphoma Group, the Lymphoma Study Association (LYSA), formerly GELA (Groupe d'Étude de Lymphomes Adulte) and the Intergruppo Italiano Linfomi, now called Fondazione Italiana Linfomi (FIL), the H10 study.[5] The H10 trial was designed to evaluate whether radiotherapy could be omitted without compromising progression-free survival in patients attaining a negative early PET scan after two cycles of ABVD as compared with standard combined-modality treatment.

Since INRT was a new radiotherapy principle applying more limited radiotherapy than in the past, radiotherapy quality assurance was indicated. The organization of early retrospective

quality assurance and local workshops to educate radiation oncologists on the INRT principle was recommended. In most countries workshops were organized. In addition, in France prospective quality assurance was performed on the target volume delineations by the main radiotherapy coordinator of the trial (TG) in most patients. Data from these reviews were not systematically collected. Therefore, a retrospective review to evaluate the quality of INRT performed in the setting of the H10 trial was initiated. The primary aim of the current study was to evaluate whether INRT was performed according to the guidelines of the H10 trial focussing on adequate coverage of the target volumes. In addition, radiation techniques and treatment verification were evaluated.[11]

**Methods and materials:**

*H10 study information:*

The H10 study is a randomized trial to evaluate treatment adaptation based on early PET (ePET) after two cycles of ABVD in previously untreated stage I and II HL patients. The standard arm consisted of ABVD followed by INRT, regardless of ePET result. In the experimental arm, ePET negative patients received ABVD only, whereas ePET-positive patients switched to two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc) and INRT. Primary endpoint was progression-free survival (PFS).[5] Retrospective quality assurance of radiotherapy was described in the study protocol for the newly introduced INRT.[10] The trial was approved by the respective scientific boards and national ethics committees and was registered in clinicaltrials.gov (NCT00433433).

The H10 trial protocol (developed in 2005) strongly recommended the use of CT simulation when designing INRT fields, performing pre- and post-chemotherapy CT-scans in the radiotherapy treatment position and fusion of the pre- and post-chemotherapy CT scans (albeit with caution). Delineation of organs at risk (OARs) was not mandatory. Radiation could be delivered using parallel opposed fields, 3D-conformal radiotherapy or intensity modulated radiotherapy (IMRT). The choice of the technique was left to the discretion of the treating physician. The dose had to be specified according to the ICRU 50/62 recommendations.[12, 13] In case of a complete remission after chemotherapy, radiation was applied to a dose of 30 Gy/1.8-2.0 Gy fractions/5 fractions per week; in case of a partial remission a 6 Gy boost was applied to the areas in partial remission to a total dose of 36 Gy/1.8-2.0 Gy fractions/5 fractions per week. Of note, the remission status after chemotherapy was determined for each initially involved lymph node based on CT-scans. Furthermore, a diagnostic CT-scan was not required in the standard arm when patients were in complete remission after 2 cycles of ABVD. Portal imaging of all fields had to be performed consecutively, within the first two days of treatment and once a week thereafter.

*Representative sample for radiotherapy quality control:*

From November 2006 to June 2011, 1950 patients were enrolled in the H10 trial. Of those 1294 were treated with INRT. The aim of this retrospective and descriptive study was to evaluate INRT in a representative sample including ~10% of all irradiated patients. To obtain a representative sample, sampling was stratified by academic group (EORTC/LYSA/FIL), year of randomization and time of treatment with respect to study duration in three categories (November 2006–January 2009; January 2009–May 2010; May 2010–June 2011), size of treatment center by number of patients entered in the H10 study (small size: 1-9 patients;

medium-size: 10-19 patients; large-size: ≥20 patients), randomized treatment arm (Favorable prognosis – standard arm, Favorable prognosis – experimental arm, Unfavorable prognosis - standard arm, Unfavorable prognosis - experimental arm); sampling was performed proportional to the size of the strata. Because of the retrospective data collection, difficulties with retrieval of the data were anticipated for 1/3 of the patients. Furthermore, the sample was completed with all patients with known recurrences to enable future evaluation of pattern of relapse in relation to the field. Sampling was performed after the study database was locked in 2015 for the final analysis report.[5]

*Radiotherapy quality control procedure:*

Reviews were conducted using the Visualisation and Organisation of Data for Cancer Analysis™ (VODCA™) software integrated in the EORTC Radiotherapy Quality Assurance (RTQA) platform.[14] The VODCA software enabled digital data submission, archiving and review of volumetric RT data. The following anonymized data was collected for the current study: baseline diagnostic information (baseline diagnostic CT-scans and preferably also PET/CT scan), post chemotherapy CT scans and preferably also post chemotherapy PET/CT-scans, target volume delineations, information on radiotherapy technique, radiotherapy dose plans or radiotherapy treatment fields, information on treatment verification.

When uploading the information for the individual case review to the VODCA database, the sites were also requested to complete a webform on radiotherapy (for both elective and boost volumes when applicable) total dose, number of fractions, planning target volume (PTV) margins, RT technique, RT energy, number of beams and treatment verification. The information from the webform was available for the reviewers. In addition, the reviewers received information on localization of originally involved nodes from the clinical database.

A panel of reviewers with representatives from all three study groups was installed to perform the review. The reviewers had remote online access to previously specified diagnostic and radiotherapy information using the VODCA system through a terminal server, and they received relevant clinical data from EORTC headquarters.[14] Reviewers were blinded to factors that might influence the review such as the treating radiation oncologist and treatment center, academic group, treatment arm and treatment outcome. Each case was reviewed by two reviewers and in case of disagreement an adjudicator was invited to review the case, for a consensus. In cases where there still was no consensus, the case was discussed in a larger panel.

Disagreements between reviewers were evaluated. The analysis for the primary study question were performed based on the result of the consensus. Completeness of the information available for the review was also scored by the reviewers (see Supplemental material).

The following parameters were scored in the overall grading of protocol violations: probability of geographical miss of the clinical target volume (CTV; both elective and boost CTV as applicable) (definitely, likely, possibly, unlikely) and the delivered dose to the planning target volume (PTV; both elective and boost PTV as applicable) (acceptable, acceptable variation, unacceptable variation). Overall grading was scored as either acceptable/per protocol treatment, acceptable variation or unacceptable variation. (See Supplemental material for more detailed information).

*Databases used for the analyses:*

Data from Clinical database as locked on 9th January 2015, data collected through webforms completed upon uploading the data to the VODCA platform and the data from the individual case reviews.

*Statistics:*

The random sampling as well as the statistical analyses were performed using version 9.4 of the SAS System for Windows, Copyright (c) 2016 by SAS Institute Inc, Cary, NC, USA. All statistical analyses are descriptive, consisting of frequency tables for categorical variables and summary statistics (median, range and quartiles) for continuous variables.

**Results:**

*Patient population eligible for review:*

The subset of patients to be reviewed consisted of a random sample of 165 patients extracted from the set of 1294 patients who received radiotherapy and a subgroup of 59 patients from the set of patients who received radiotherapy and subsequently had progression or relapsed disease, based on the clinical database locked in 2015 for the final analysis report. Because of some overlap between these two subsets, the total number of patients included in the sample was 219 (original sample population). In the feasibility survey, the participating centers expected to be able to contribute the data on 134 out of 219 cases. Finally, data were uploaded for 66 patients. Data was incomplete for five patients and therefore the final review encompassed 61 patients (Quality Control RadioTherapy (QCRT) population) (See Figure 1).

*Clinical and treatment characteristics:*

There were no marked differences in clinical and treatment characteristics nor in stratification factors except for study group when comparing the population of all irradiated patients, the original sample population and the QCRT patient population (see Table 1). 59.0%, 19.7% and 21.3% of the QCRT patient population came from EORTC lymphoma group, LYSA and FIL respectively, while these proportions were 21.3%, 56.3% and 22.5% in the population of all irradiated patients. 34.4%, 19.7%, 45.9% of the QCRT patient population came from small, medium and large size hospitals, respectively. 39.3%, 27.9%, 32.8% of the QCRT patient population were enrolled in the H10 study during the first, second and last third of the accrual period.

After the end of chemotherapy in the QCRT population 24 patients (39.3%) had a complete remission or an unconfirmed complete remission, 18 (29.5%) a partial remission, 1 (1.6%) had stable disease. In 18 patients (29.5%) CT-based evaluation was not performed (For detailed information see Table 1).

Radiotherapy treatment details are shown in table 2. The median interval between the end of chemotherapy and the start of radiotherapy was 27 days (interquartile range (IQR) 22-32 days). Seventy-seven% of included patients received (elective) radiotherapy to the mediastinum. A boost was applied to 33/61 patients (54.1%) according to the data from the clinical database. (Relatively) modern radiotherapy techniques were used in most reviewed cases (44.3% 3D-conformal RT, 31.1% IMRT and 3.3% 3D-respiratory gating).

*Individual case reviews:*

Sixty out of 61 patients were reviewed by at least two reviewers (See Table 3). For 12 patients, evaluation by an adjudicator was performed. Consistency and discrepancies between reviewers were evaluated (See Table 4). Agreement between reviewers in terms of overall grading was perfect in 25/54 (46.3%) of cases and good in 44/54 (81.5%) when a score of acceptable variation by one reviewer and acceptable-per-protocol by another reviewer (19 cases) was also considered as in agreement. Discrepancies between reviewers were observed in 18.5%, 20.4% and 35.2% for type of review, radiotherapy principle and radiotherapy technique, respectively.

The final evaluation, including the adjudicator review, showed that the quality of the radiotherapy was assessed as acceptable-per-protocol, acceptable variation or unacceptable variation for 37.7%, 50.8% and 11.5% of the cases, respectively. The results of this evaluation by study period, hospital size and primary group affiliation are presented in Table 5. The percentage of unacceptable variations decreased over time with 16.7%, 11.8% and 5.0% for the period from November 2006–January 2009, January 2009–May 2010 and May 2010–June 2011, respectively. The percentage of unacceptable variations by size of center by number of patients entered in the H10 study showed 23.8%, 8.3 and 3.6% of unacceptable variations for small-size, medium-size and large-size hospitals, respectively.

An evaluation of all 127 reviews (see Supplementary Table 2) showed that 80.3% were full reviews. Appropriate immobilization was used in 89% of reviewed cases. INRT principle was followed in 86.6% of cases.

The probability of missing a part of the elective clinical target volume was scored as unlikely, possibly, likely or definitely in 81.1%, 7.9%, 4.7% and 4.7% of reviewed cases.

Furthermore, the probability of missing a part of the boost clinical target volume was scored as unlikely, possibly, likely or definitely in 87.5%, 4.2%, 1.4% and 6.9% of reviewed cases. Delivered dose to the elective PTV was scored as acceptable, acceptable variation or unacceptable variation in 65.4%, 27.6% and 3.1% of reviewed cases. In addition, delivered dose to the boost PTV was scored as acceptable, acceptable variation or unacceptable variation in 68.1%, 19.4% and 12.5% of reviewed cases.

In addition, 14 out of the 61 (23%) patients in the QCRT population had progression of disease compared to 59 out of the total of 1294 (4.6%) irradiated patients. In the QCRT population, 10 out of 14 relapses (71%) occurred in originally involved and irradiated areas and in 2 of those unacceptable variations from the study protocol were observed. Among all irradiated patients, 40 out of 59 relapses (68%) were observed in originally involved and irradiated areas.

Based on the information supplied by the centers when uploading the data to the VODCA platform, treatment verification was performed according to the study protocol in most patients. Portal imaging of all fields was applied within the first two days of treatment and once a week thereafter in 45.9% of patients, portal imaging once a week in 11.5%, daily on-line correction in 11.5% and other (but non-specified) treatment verification in 13.1% of patients. Information on treatment verification was missing in 18.0% of patients.



**Discussion:**

The quality of INRT in the context of a large, multicenter randomized trial [4,5] was evaluated for the first time in the current study. 11.5% of the evaluated patients had unacceptable protocol variations, These unacceptable variations were mostly caused by definite or likely misses in CTV delineation. The percentage of unacceptable protocol variations was lower

than we had anticipated since INRT was a new concept introduced at the beginning of the era of precise volume delineation in radiotherapy.[15, 16] Based on a previous study performed on behalf of the Radiotherapy Committee of the EORTC lymphoma group considerable, interobserver variation in delineation was expected.[15]

The findings of the current study are reassuring since insufficient coverage or underdosing of the target volumes could have caused local recurrences and therefore could have jeopardized the validity of the results of the H10 trial.[4,5] The rate of cases assessed as unacceptable variation seemed to decrease with increasing size of the hospital as well as with time so there appeared to be a learning curve for the application of the newly introduced INRT principle. Fairchild et al. have performed a literature review on compliance to radiotherapy protocol and treatment outcomes. They describe that there are conflicting data concerning a possible relationship between rates of protocol deviations and accrual rate of a trial.[17] Possible relationships between quality of radiotherapy and treatment outcomes have previously been reported. [17, 18] The German Hodgkin Study Group (GHSG) for instance already showed in 1996 that violations of the treatment protocol were correlated with a worse freedom from treatment failure[18] and stressed the importance of a quality assurance program.[19] A possible association between RTQA deviations and clinical outcomes was also examined in a meta-analysis of cooperative group clinical trials. A large variation in radiotherapy protocol deviations (8-71%, median 32%) was observed. Various definitions of protocol deviations were used. Deviations from radiotherapy protocols were associated with increased risks of treatment failure and overall mortality. Of note, most studies included in this meta-analysis utilized two-dimensional RT. The authors state that the applicability of their findings to newer radiotherapy techniques is unclear, but they believe that rigorous RTQA becomes even more critical as treatment complexity increases.

The current evaluation shows favorable results compared to a large retrospective study performed by the GSHG on patients included in their HD13/14 studies between 2003 and 2008. Based on the evaluation of simulation films, verification films, and radiotherapy case report forms, the RT treatment volume was considered to be according to the protocol guidelines in approximately 60% of patients.[16]

To enable a separate study on pattern of relapse in relation to radiotherapy volumes, we included all patients with relapsed disease in our sample population. As expected, this led to overrepresentation of patients with a relapse in the QCRT population; 14/61 (23%) of the patients in the QCRT population had progression of disease whereas only 59/1294 (4.6%) of all irradiated patients had progression of disease. Of note, based on the information on the case record forms, we did not find indications of a relationship between risk of relapse and quality of radiotherapy; unacceptable variations from the study protocol were observed in only two out of ten relapses in originally involved and irradiated areas.

The current study certainly has weaknesses. The main weakness is the number of patients evaluated, i.e. only approximately 5% instead of 10% of all irradiated patients. The data collection was hampered by the retrospective data request and the changes in radiology and treatment planning systems over time, significantly more than anticipated. Even though difficulties with the collection of data were anticipated, the number of patients collected with complete datasets was limited, so the conclusions need to be interpreted with caution. An important lesson learned from this study is that individual case reviews in the context of RTQA should either be done in a prospective or early retrospective fashion. Collection of data for early retrospective RTQA should be performed as soon as possible and preferably in DICOM format to enable the performance of additional data analyses. Furthermore, a description of the planned RTQA procedure should be included in the trial protocol.

In the current study RTQA was planned in a representative selection of patients. This still seems a valid approach. Performing individual case reviews in all patients included in a trial may be very time consuming and is not always indicated.[20]

Over the last decades, the field of RTQA has evolved. Several groups including the Radiation Therapy Oncology Group (RTOG, now part of the NRG Oncology cooperative group), EORTC, American College of Radiology (ACR), and National Cancer Institute (NCI), have organized conferences and performed studies that stress the need for RTQA and made recommendations for trials concerning RTQA practices.[20-27] For instance EORTC quality assurance procedures nowadays include all or, depending on the trial objectives, a combination of the following: collection of the equipment, procedure and personnel at participating technical facilities, a dummy run with or without a delineation exercise, complex dosimetry check to validate whether modern radiotherapy techniques are being correctly used and either a limited or extensive individual case review .[14] Furthermore, the Global Quality Assurance of Radiation Therapy Clinal Trials Harmonization Group has proposed naming conventions and organ at risk delineation, which can be used in future clinical trials involving radiation therapy facilitating intergroup trial collaboration and simplifying exchange and interpretation of RTQA results.[24,28] Also, an expert panel from the GHSG recently developed guidelines and criteria to analyse "modern" field designs and treatment techniques.[29] In addition, in a conference sponsored by the National Cancer Institute, four recommendations were made for RTQA in clinical trials: 1) Develop a tiered system and tailor intensity of QA to clinical trial objectives; 2) Establish a case QA repository; 3) Develop an evidence base for clinical trial QA; and 4) Explore the feasibility of consolidating clinical trial QA in the United States.[20]

Since one of the aims of the H10 trial was to reduce late treatment-related toxicity, it would have been interesting to be able to evaluate overtreatment in terms of radiation volume and radiation dose. Performing a CT-planning and delineation of OARs were not mandatory and therefore an estimation of excessive radiation exposure was deemed to be impossible. Contrary to our expectations, the current evaluation showed that delineation of OARs was performed in most cases. Nowadays, delineation of OARs is usually obligatory, especially in trials aiming at reduction of late effects in young patients. The development of standard atlases for OARs has already improved the quality of OAR delineation (for instance, heart and different cardiac substructures).[30] It is expected that automated delineation developed through machine learning techniques will further facilitate OAR delineation leading to more consistent delineations which will enable studying normal tissue toxicity on a larger scale. In the future we should aim at quantification of doses to OARs, especially in patients with a long life expectancy like HL patients. Preferably, this should not only be done in the context of clinical trials, but also in routine daily practice.

Although the importance of RTQA is long recognized[22, 23], more attention to RTQA is needed. A recent study investigating the utilization of RTQA among randomized controlled trials involving radiotherapy that enrolled patients between 1991 and 2020, showed that there is a lack of RTQA utilization and transparency in RT clinical trials.[26] The authors state that it is imperative for RT trials to include increased QA for safe, consistent, and high-quality RT planning and delivery.

**Conclusion:**

The current study shows that the newly introduced principle of INRT was applied in most patients. The current results should, however, be interpreted with caution because the

number of patients evaluated was limited. For future studies, RTQA tailored to the clinical trial objectives, using harmonized naming conventions and organ at risk delineation, is strongly recommended. If individual case reviews are indicated, they should be done in a prospective or early retrospective way.

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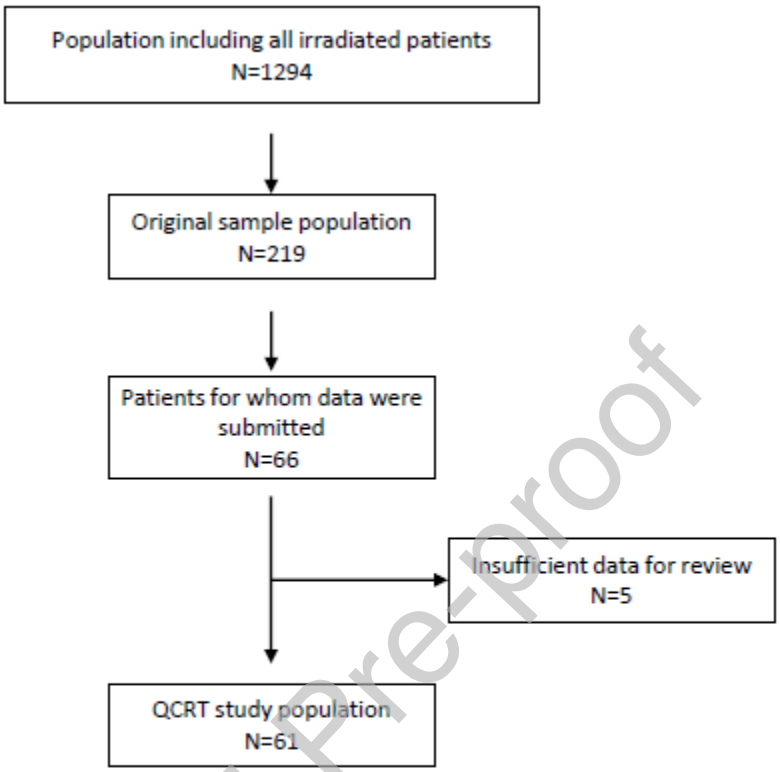
**Figure captions:**

Figure 1. Flowchart patient populations H10 quality control study






**H10 QCRT Tables**

**Table 1. Clinical and treatment characteristics (based on data from the clinical database)**

| | **All irradiated patients population (N=1294) N(%)** | **Original sample population (N=219) N(%)** | **QCRT population (N=61) N(%)** |
|---|---|---|---|
| **Characteristic** | | | |
| Age, years | | | |
| Median | 30 | 29 | 31 |
| Range | 15 - 70 | 15 - 68 | 18 - 64 |
| Male sex | 644 (49.8) | 112 (51.1) | 34 (55.7) |

| | | | |
|---|---|---|---|
| Ann Arbor clinical stage | | | |
| I | 274 (21.2) | 51 (23.3) | 12 (19.7) |
| II | 1019 (78.7) | 168 (76.7) | 49 (80.3) |
| IV‡ | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| Number of nodal areas | | | |
| Median | 2.0 | 2.0 | 2.0 |
| Range | 1.0 - 5.0 | 1.0 - 5.0 | 1.0 - 5.0 |
| Treatment group according to investigator | | | |
| Favorable | 514 (39.7) | 76 (34.7) | 26 (42.6) |
| Unfavorable | 780 (60.3) | 143 (65.3) | 35 (57.4) |
| Bulky disease | | | |
| No | 549 (42.4) | 82 (37.4) | 22 (36.1) |
| Yes | 386 (29.8) | 76 (34.7) | 19 (31.1) |
| Missing | 359 (27.7) | 61 (27.9) | 20 (32.8) |
| Bulky mediastinum | | | |
| No | 933 (72.1) | 148 (67.6) | 44 (72.1) |
| Yes | 360 (27.8) | 71 (32.4) | 17 (27.9) |
| Missing | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| Baseline FDG-PET available before entry trial | 1243 (96.1) | 211 (96.3) | 60 (98.4) |
| Lymphoma study group | | | |
| EORTC lymphoma group | 276 (21.3) | 51 (23.3) | 36 (59.0) |
| LYSA | 727 (56.2) | 120 (54.8) | 12 (19.7) |
| FIL | 291 (22.5) | 48 (21.9) | 13 (21.3) |
| Size of center | | | |
| Small-size hospital (1-9 patients) | 435 (33.6) | 74 (33.8) | 21 (34.4) |
| Medium-size hospital (10-19 patients) | 406 (31.4) | 73 (33.3) | 12 (19.7) |
| Large-size hospital (>=20 patients) | 453 (35.0) | 72 (32.9) | 28 (45.9) |
| Time of randomization wrt start of study* | | | |
| 1st third of study period | 431 (33.3) | 80 (36.5) | 24 (39.3) |
| 2nd third of study period | 434 (33.5) | 73 (33.3) | 17 (27.9) |
| 3rd third of study period | 429 (33.2) | 66 (30.1) | 20 (32.8) |
| | | | |
| ePET negative treated per initial protocol† | | | |
| Favorable, 3 ABVD+INRT | 223 (17.2) | 28 (12.8) | 7 (11.5) |
| Favorable, 4 ABVD | 5 (0.4) | 3 (1.4) | 0 (0.0) |
| Unfavorable, 4 ABVD+INRT | 280 (21.6) | 46 (21.0) | 13 (21.3) |
| Unfavorable, 6 ABVD | 8 (0.6) | 1 (0.5) | 0 (0.0) |
| ePET negative treated per safety amendment† | | | |
| Favorable, 3 ABVD+INRT | 178 (13.8) | 26 (11.9) | 12 (19.7) |
| Unfavorable, 4 ABVD+INRT | 294 (22.7) | 41 (18.7) | 8 (13.1) |
| ePET positive, favorable and unfavorable | | | |
| 3 or 4 ABVD+INRT | 167 (12.9) | 41 (18.7) | 9 (14.8) |
| 2 ABVD+2 BEACOPPesc+INRT | 139 (10.7) | 33 (15.1) | 12 (19.7) |
| Remission status after chemotherapy | | | |
| Complete Remission | 277 (21.4) | 44 (20.1) | 11 (18.0) |
| Complete Remission unconfirmed | 180 (13.9) | 45 (20.5) | 13 (21.3) |
| Partial Remission | 287 (22.2) | 61 (27.9) | 18 (29.5) |
| Stable disease | 24 (1.9) | 5 (2.3) | 1 (1.6) |
| No CT-based evaluation§ | 526 (40.6) | 64 (29.2) | 18 ‖ (29.5) |
| Not evaluable (only PET-scan or CT- | 75 (5.8) | 11 (5.0) | 3 (4.9) |

| | | | |
|---|---|---|---|
| scan not interpreted) | | | |
| No evaluation | 321 (24.8) | 41 (18.7) | 11 (18.0) |
| Missing information | 130 (10.0) | 12 (5.5) | 4 (6.6) |

* Time of treatment with respect to study duration, in three categories (November 2006– January 2009, January 2009– May 2010 and May 2010– June 2011)
† A safety amendment to close the ABVD only arms was issued in August 2010 [4]
‡ This patient was enrolled in the study despite not meeting the eligibility criteria
§ A diagnostic CT-scan was not required in the standard arm when patients were in CR after 2 cycles of ABVD.
‖ After 2 cycles of ABVD, CT-based evaluation was performed in 11 patients and showed CR/CRu in 8 patients. In the 10 patients that should have been evaluated after chemotherapy using a diagnostic CT-scan, 1 was evaluated with a PET-scan only, 1 patient had no clear interpretation of the CT and 8 were not evaluated.

wrt: with respect to; ePET: early PET-scan; EORTC: European Organisation for Research and Treatment of Cancer Lymphoma Group; LYSA: the Lymphoma Study Association ((LYSA) formerly GELA (Groupe d'Étude de Lymphomes Adulte); FIL:Fondazione Italiana Linfomi (FIL) formerly Intergruppo Italiano Linfomi

QCRT: quality control radiotherapy
ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine
BEACOPPesc: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone escalated

**Table 2: Radiotherapy treatment details**

| | **QCRT study population N=61** | |
|---|---|---|
| Median interval between last CT and start of RT in days (range; interquartile range) | 27 (1.0-98.0; 22.0-32.0) | |
| | | |
| Location of irradiated areas * | N | % |
| Left supraclavicular | 32 | 52.5 |
| Right supraclavicular | 25 | 41.0 |
| Left neck | 24 | 39.3 |
| Right neck | 19 | 31.1 |
| Left axilla | 12 | 19.7 |
| Right axilla | 9 | 14.8 |
| Mediastinum | 47 | 77.0 |
| Left hilum | 2 | 3.3 |
| Right hilum | 1 | 1.6 |
| Left submandibular | 1 | 1.6 |
| Other | 2 | 3.3 |
| | | |
| RT boost applied*§ | 33 | |
| | | |
| Application of RT boost by remission status * | | |
| Complete Remission | 3 | 27.3 |
| Complete Remission unconfirmed | 6 | 46.2 |
| Partial Remission | 15 | 83.3 |
| Stable disease | 1 | 100 |
| No CT-based evaluation | 8 | 44.4 |
| | | |
| RT dose by remission status after chemotherapy* | median (Q1-Q3) | N |
| Complete Remission | 30.0 (30.0-36.0) | 11 |
| Complete Remission unconfirmed | 32.4 (30.0-36.0) | 13 |
| Partial Remission | 36.0 (36.0-36.0) | 18 |
| Stable disease | 36.0 | 1 |
| No CT-based evaluation | 30.0 (30.0-36.0) | 18 |
| | | |
| RT technique * | N | % |
| Conventional | 12 | 19.7 |
| 3D-conformal | 27 | 44.3 |
| IMRT | 19 | 31.1 |
| 3D-respiratory gating | 2 | 3.3 |
| Unknown | 1 | 1.6 |
| | | |
| Treatment verification† | N | % |
| Portal imaging of all fields within the first two days of treatment and once a week thereafter | 28 | 45.9 |
| Once a week | 7 | 11.5 |
| Daily on-line correction | 7 | 11.5 |
| Other | 8 | 13.1 |
| Missing | 11 | 18.0 |

| | | |
|---|---|---|
| | | |

QCRT: quality control radiotherapy
IMRT: intensity modulated radiotherapy
RT: radiotherapy

Information in this table mostly based on data from the clinical database because there was less missing information in the clinical database.
* information from clinical database
† information from individual case review
§ location of boost (% of patients that received a boost): mediastinum (73.3%), left neck (30%) and right neck (30%).

**Table 3. Final evaluation - overall**

| | **QCRT study population** Number of patients (%) |
|---|---|
| Number of reviews per patient (excluding adjudicator) | |
| 1 | 1 (1.6) |
| 2 | 60 (98.4)* |
| Need of adjudicator evaluation | |
| No | 49 (80.3) |
| Yes | 12 (19.7) |
| Number of reviewers (including adjudicator) | |
| 2 | 50 (82.0)* |
| 3 | 11 (18.0) |
| Overall grading | |
| Acceptable/per protocol | 23 (37.7) |
| Acceptable variation | 31 (50.8) |
| Unacceptable variation | 7 (11.5) |

*: Seven of these patients were reviewed by at least two reviewers together, therefore they are only counted as one single review

**Table 4. Consistency and discrepancies between reviewers**

| | **QCRT study population (N=61)** Number of patients (%) |
|---|---|
| Number of patients included in the assessment of consistency* | 54 (100%) |
| | |
| Consistency/discrepancies in type of review | |
| Full for all reviewers | 39 (72.2) |
| Limited for all reviewers | 5 (9.3) |
| Discrepancies across reviewers (+ adjudicator) | 10 (18.5) |
| Consistency/discrepancies in RT principle | |
| IFRT for all reviewers | 1 (1.9) |
| INRT for all reviewers | 42 (77.8) |
| Discrepancies across reviewers (+ adjudicator) | 11 (20.4) |
| Consistency/discrepancies in RT technique | |
| 3DCRT for all reviewers | 13 (24.1) |
| AP/PA for all reviewers | 14 (25.9) |
| IMRT for all reviewers | 8 (14.8) |
| Discrepancies across reviewers (+ adjudicator) | 19 (35.2) |
| Consistency/discrepancies in grade† | |
| Acceptable variation for all reviewers | 5 (9.3) |
| Acceptable - per protocol for all reviewers | 17 (31.4) |
| Unacceptable variation for all reviewers | 3 (5.6) |
| Discrepancies between reviewers | 29 (54.7) |
| Acceptable variation versus acceptable-per-protocol | 19 (35.2) |
| Acceptable variation versus unacceptable variation | 6 (11.1) |
| Acceptable - per protocol versus unacceptable variation | 2 (3.7) |
| Acceptable variation versus acceptable-per-protocol versus unacceptable variation | 2 (3.7) |

*: Seven patients were reviewed by at least two reviewers together because of technical issues with the VODCA system, therefore no assessment of consistency/discrepancy can be done for these cases

†: There was no adjudication done when the reviewers considered the case was “Acceptable Variation” or “Acceptable - per protocol”, even when the two reviewers were discrepant (18 cases).

**Table 5. Final evaluation by study period, hospital size and primary group affiliation**

| | **1st third of study period (N=24)** | **2nd third of study period (N=17)** | **3rd third of study period (N=20)** | **Total (N=61)** |
|---|---|---|---|---|
| | N (%) | N (%) | N (%) | N (%) |
| Final evaluation | | | | |
| Acceptable – per protocol | 7 (29.2) | 10 (58.8) | 6 (30.0) | 23 (37.7) |
| Acceptable variation | 13 (54.2) | 5 (29.4) | 13 (65.0) | 31 (50.8) |
| Unacceptable variation | 4 (16.7) | 2 (11.8) | 1 (5.0) | 7 (11.5) |
| | | | | |
| | **Small-size hospital (N=21)** | **Medium-size hospital (N=12)** | **Large-size hospital (N=28)** | **Total (N=61)** |
| | N (%) | N (%) | N (%) | N (%) |
| Final evaluation | | | | |
| Acceptable – per protocol | 6 (28.6) | 6 (50.0) | 11 (39.3) | 23 (37.7) |
| Acceptable variation | 10 (47.6) | 5 (41.7) | 16 (57.1) | 31 (50.8) |
| Unacceptable variation | 5 (23.8) | 1 (8.3) | 1 (3.6) | 7 (11.5) |
| | | | | |
| | **EORTC LYMG (N=36)** | **LYSA (N=12)** | **FIL (N=13)** | **Total (N=61)** |
| | N (%) | N (%) | N (%) | N (%) |
| Final evaluation | | | | |
| Acceptable – per protocol | 16 (44.4) | 2 (16.7) | 5 (38.5) | 23 (37.7) |
| Acceptable variation | 15 (41.7) | 9 (75.0) | 7 (53.8) | 31 (50.8) |
| Unacceptable variation | 5 (13.9) | 1 (8.3) | 1 (7.7) | 7 (11.5) |

EORTC: European Organisation for Research and Treatment of Cancer Lymphoma Group; LYSA: the Lymphoma Study Association ((LYSA) formerly GELA (Groupe d'Étude de Lymphomes Adulte); FIL:Fondazione Italiana Linfomi (FIL) formerly Intergruppo Italiano Linfomi