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CLINICAL INVESTIGATION

A Quality Control Study on Involved Node Radiation Therapy in the European Organisation for Research and Treatment of Cancer/Lymphoma Study Association/ Fondazione Italiana Linfomi H10 Trial on Stages I and II Hodgkin Lymphoma: Lessons Learned

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Purpose: Involved node radiation therapy (INRT) was introduced in the European Organisation for Research and Treatment of Cancer/Lymphoma Study Association/Fondazione Italiana Linfomi H10 trial, a large multicenter trial in early-stage Hodgkin Lymphoma. The present study aimed to evaluate the quality of INRT in this trial.

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Data will be shared according to the European Organisation for Research and Treatment of Cancer data release policy (https://www.eortc.org/data-sharing/).

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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 the 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 patterns. Radiation therapy principle, target volume delineation and coverage, and applied technique and dose were evaluated using the EORTC Radiation Therapy Quality Assurance platform. Each case was reviewed by 2 reviewers and, in case of disagreement also by an adjudicator for a consensus evaluation.

Results: Data were retrieved for 66 of 1294 irradiated patients (5.1%). Data collection and analysis were hampered more than anticipated by changes in archiving of diagnostic imaging and treatment planning systems during the running period of the trial. A review could be performed on 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 geographic 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 present results should, however, be interpreted with caution because the number of patients evaluated was limited. Individual case reviews should be done in a prospective fashion in future trials. Radiation therapy Quality Assurance 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 radiation therapy (RT) is excellent.[1] Both radiation therapy and chemotherapy may, however, cause long-term toxicity.[2,3] Therefore, possibilities to reduce chemotherapy and radiation therapy as much as possible without compromising HL cure rates have been and are still being studied systematically.[1,4-8]

During the past decades, effective chemotherapy regimens have been developed, enabling reduction from extended field radiation therapy to involved field radiation therapy.[9] Involved field radiation therapy was defined based on lymph node regions according to the Ann Arbor staging diagram, which was not designed to construct radiation fields. Because consolidating radiation therapy to involved lymph nodes after a limited number of chemotherapy cycles was still considered necessary, the European Organisation for Research and Treatment of Cancer (EORTC) lymphoma group developed the involved node radiation therapy (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 radiation therapy could be omitted without compromising progression-free survival in patients attaining a negative early positron emission tomography (PET) scan after 2 cycles of ABVD compared with standard combined-modality treatment.

Because INRT was a new radiation therapy principle applying more limited radiation therapy than before, radiation therapy 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 radiation therapy coordinator of the trial (T.G.) 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 focusing on an 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 2 cycles of ABVD in previously untreated stage I and II patients with HL. The standard arm consisted of ABVD followed by INRT, regardless of the ePET result. In the experimental arm, ePET-negative patients received ABVD only, whereas ePET-positive patients switched to 2 cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc) and INRT. The primary endpoint was progression-free survival.[5] Retrospective quality assurance of radiation therapy 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 using computed tomography (CT) simulation when designing INRT fields, performing pre- and

postchemotherapy CT scans in the radiation therapy treatment position, and fusion of the pre- and postchemotherapy CT scans (albeit cautiously). Delineation of organs at risk (OARs) was not mandatory. Radiation could be delivered using parallel opposed fields, 3-dimensional (3D) conformal radiation therapy, or intensity-modulated radiation therapy. 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 complete remission after chemotherapy, radiation was applied to a dose of 30 Gy/1.8 to 2.0 Gy fractions/5 fractions per week; in case of partial remission, a 6 Gy boost was applied to the areas in partial remission to a total dose of 36 Gy/1.8 to 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 2 days of treatment and once a week thereafter.

Representative sample for radiation therapy 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 3 categories (November 2006 to January 2009; January 2009 to May 2010; May 2010 to June 2011), size of treatment center by the 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 proportionally to the size of the strata. Because of the retrospective data collection, difficulties with retrieving the data were anticipated for a third of the patients. Furthermore, the sample was completed with all patients with known recurrences to enable future evaluation of the 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]

Radiation therapy quality control procedure

Reviews were conducted using the Visualisation and Organisation of Data for Cancer Analysis (VODCA; Medical Software Solutions GmbH, Hagendorm, Switzerland) software integrated into the EORTC Radiation Therapy Quality Assurance (RTQA) platform.[14] The VODCA software enabled digital data submission, archiving, and review of volumetric RT data. The following anonymized data were collected for the current study: baseline diagnostic information (baseline diagnostic CT scans and preferably also PET/CT scan), postchemotherapy CT scans and preferably also postchemotherapy PET/CT scans, target volume delineations, information on radiation therapy technique, radiation therapy dose plans or radiation therapy 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 web form on radiation therapy (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 the localization of originally involved nodes from the clinical database.

A panel of reviewers with representatives from all 3 study groups was installed to perform the review. The reviewers had remote online access to previously specified diagnostic and radiation therapy information using the VODCA system through a terminal server, and they received relevant clinical data from EORTC headquarters.[14] Reviewers were masked from 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 2 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 was 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: the probability of geographic 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 acceptable/per protocol treatment, acceptable variation, or unacceptable variation (see Supplemental Material for more detailed information).

Databases used for the analyses

Data from the clinical database was locked on January 9, 2015, data collected through web forms was completed after uploading the data to the VODCA platform and the data from the individual case reviews.

Statistics

The random sampling and the statistical analyses were performed using version 9.4 of the SAS System for Windows (SAS Institute Inc, Cary, NC; 2016). 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 radiation therapy and a subgroup of 59 patients from the set of patients who received radiation therapy 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 2 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 were incomplete for 5 patients, and the final review encompassed 61 patients (quality control radiation therapy [QCRT]) population; Fig. 1).

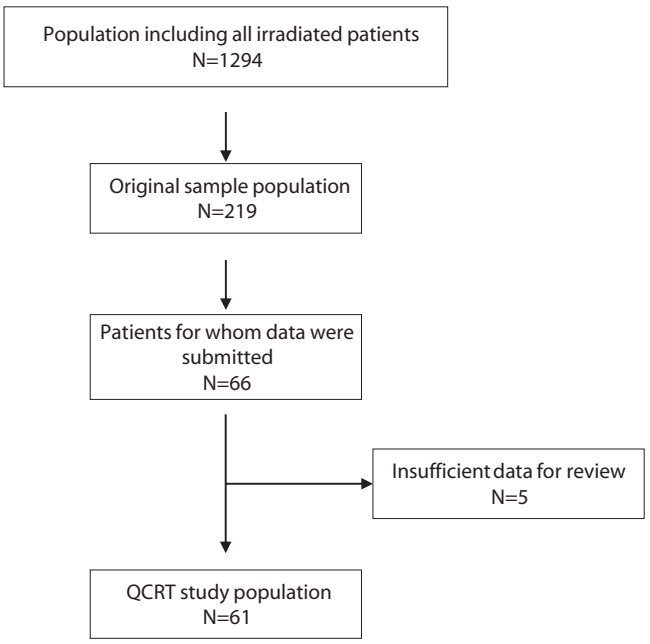

Fig. 1. Flowchart patient populations H10 quality control study. *Abbreviation*: QCRT = quality control radiation therapy.

Clinical and treatment characteristics

There were no marked differences in clinical and treatment characteristics nor stratification factors except for the study group when comparing the population of all irradiated patients, the original sample population, and the QCRT patient population (Table 1).

Fifty-nine %, 19.7%, and 21.3% of the QCRT patient population came from the EORTC lymphoma group, LYSA, and FIL, respectively, and these proportions were 21.3%, 56.3%, and 22.5% in the population of all irradiated patients. In addition, 34.4%, 19.7%, and 45.9% of the QCRT patient population came from small, medium, and large size hospitals, respectively. Furthermore, 39.3%, 27.9%, and 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%) had partial remission, and 1 (1.6%) had stable disease. In 18 patients (29.5%), CT-based evaluation was not performed (Table 1).

Radiation therapy treatment details are shown in Table 2. The median interval between the end of chemotherapy and the start of radiation therapy was 27 days (IQR, 22-32 days). Seventy-seven percent of included patients received (elective) radiation therapy to the mediastinum. According to the clinical database, a boost was applied to 33 of 61 patients (54.1%). Relatively modern radiation therapy techniques were used in most reviewed cases (44.3% 3D conformal RT; 31.1%, intensity modulated radiation therapy, and 3.3%, 3D respiratory gating).

Individual case reviews

Sixty out of 61 patients were reviewed by at least 2 reviewers (Table 3). For 12 patients, an evaluation by an adjudicator was performed. Consistency and discrepancies between reviewers were evaluated (Table 4). Agreement between reviewers in terms of overall grading was perfect in 25 of 54 (46.3%) of cases and good in 44 of 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 the type of review, radiation therapy principle, and radiation therapy technique, respectively.

The final evaluation, including the adjudicator review, showed that the quality of the radiation therapy 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 to January 2009, January 2009

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, y			
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)
No. 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)

(*Continued*)

Table 1 (*Continued*)

	All irradiated patients population (N = 1294) N (%)	Original sample population (N = 219) N (%)	QCRT population (N = 61) N (%)
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 CTscan not interpreted)	75 (5.8)	11 (5.0)	3 (4.9)
No evaluation	321 (24.8)	41 (18.7)	11 (18.0)
Missing information	130 (10.0)	12 (5.5)	4 (6.6)

Abbreviations: ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPPesc = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone escalated; CT = computed tomography; EORTC = European Organisation for Research and Treatment of Cancer Lymphoma Group; ePET = early PET-scan; LYSA = Lymphoma Study Association (formerly GELA [Groupe d'Étude de Lymphomes Adulte]); FIL = Fondazione Italiana Linfomi (formerly Intergruppo Italiano Linfomi); QCRT = quality control radiation therapy; WRT = with respect to.

[*] This patient was enrolled in the study despite not meeting the eligibility criteria.

[†] Time of treatment with respect to study duration, in 3 categories (November 2006 to January 2009, January 2009 to May 2010, and May 2010 to June 2011).

[‡] A safety amendment to close the ABVD-only arms was issued in August 2010.[4]

[§] 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. Of the 10 patients who 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.

to May 2010, and May 2010 to June 2011, respectively. The percentage of unacceptable variations by the size of the center by the number of patients entered in the H10 study showed 23.8%, 8.3%, and 3.6% of unacceptable variations for small-, medium-, and large-size hospitals, respectively.

An evaluation of all 127 reviews (Supplemental Table E2) showed that 80.3% were full reviews. Appropriate immobilization was used in 89% of reviewed cases. The 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, the 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 disease progression compared with 59 out of the total of 1294 (4.6%) irradiated patients (Supplemental Table E3). 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 (Supplemental Table E4). Among all irradiated patients, 40 out of 59 relapses (68%) were observed in originally involved and irradiated areas (Supplemental Table E3).

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 2 days of treatment and once a week thereafter in 45.9% of patients, portal imaging once a week in 11.5%, daily online correction in 11.5%, and other (but nonspecified) treatment verification in 13.1% of patients. Information on treatment verification was missing in 18.0% of patients.

Table 2 Radiation therapy treatment details

	QCRT study population N = 61	
Median interval between last CT and start of RT in days (range; IQR)	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 2 days of treatment and once a week thereafter	28	45.9
Once a week	7	11.5
Daily online correction	7	11.5
Other	8	13.1
Missing	11	18.0

Abbreviations: 3D = 3-dimensional; CT = computed tomography; IMRT = intensity modulated radiation therapy; QCRT = quality control radiation therapy; RT = radiation therapy.

Information is mostly based on data from the clinical database because there was less missing information in the clinical database.

* Information from clinical database.

† Location of boost (% of patients who received a boost): mediastinum (73.3%), left neck (30%), and right neck (30%).

‡ Information from individual case review.

Discussion

The quality of INRT in the context of a large, multicenter randomized trial[4,5] was evaluated for the first time in the present study. Of the evaluated patients, 11.5% 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 anticipated because INRT was a new concept introduced at the beginning of the era of precise volume delineation in radiation therapy.[15,16] Based on a previous study performed on behalf of the Radiation Therapy Committee of the EORTC lymphoma group, considerable interobserver variation in delineation was expected.[15]

Table 3 Final evaluation: Overall

	QCRT study population No. of patients (%)
No. 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)
No. 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)

Abbreviation: QCRT = quality control radiation therapy.

* Seven of these patients were reviewed by at least 2 reviewers together; therefore, they are only counted as one single review.

Table 4 Consistency and discrepancies between reviewers

	QCRT study population (N = 61) No. of patients (%)
No. 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 vs unacceptable variation	2 (3.7)

Abbreviations: 3DCRT = 3-dimensional control radiation therapy; AP/PA =anteroposterior/posteroanterior; IFRT = involved field radiation therapy; IMRT = intensity modulated radiation therapy; INRT = involved node radiation therapy; QCRT = quality control radiation therapy; RT = radiation therapy.

* Seven patients were reviewed by at least 2 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 2 reviewers were discrepant (18 cases).

The present study's findings are reassuring because 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 the increasing size of the hospital and with time, and there appeared to be a learning curve for applying the newly introduced INRT principle. Fairchild et al have performed a literature review on compliance with radiation therapy protocol and treatment outcomes. They describe that there are conflicting data concerning a possible relationship between rates of protocol deviations and the accrual rate of a trial.[17] Possible relationships between the quality of radiation therapy 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 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 radiation therapy protocol deviations (8%-71%, median, 32%) was observed. Various definitions of protocol deviations were used. Deviations from radiation therapy protocols were associated with increased risks of treatment failure and overall mortality. Of note, most studies included in this meta-analysis used 2-dimensional RT. The authors state that the applicability of their findings to newer radiation therapy techniques is unclear, but they believe that rigorous RTQA becomes even more critical as treatment complexity increases.

The current evaluation shows favorable results compared with a large retrospective study performed by the GHSG on patients included in their HD13/14 studies between 2003

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

	1st third of study period (N = 24) N (%)	2nd third of study period (N = 17) N (%)	3rd third of study period (N = 20) N (%)	Total (N = 61) 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) N (%)	**Medium-size hospital (N = 12) N (%)**	**Large-size hospital (N = 28) N (%)**	**Total (N = 61) 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) N (%)	**LYSA (N = 12) N (%)**	**FIL (N = 13) N (%)**	**Total (N = 61) 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)

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

and 2008. Based on the evaluation of simulation films, verification films, and radiation therapy 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 the pattern of relapse in relation to radiation therapy volumes, we included all patients with relapsed disease in our sample population. As expected, this led to an overrepresentation of patients with a relapse in the QCRT population; 14 of 61 (23%) of the patients in the QCRT population had disease progression, whereas only 59 of 1294 (4.6%) of all irradiated patients had disease progression. Of note, based on the information on the case record forms, we did not find indications of a relationship between the risk of relapse and the quality of radiation therapy; unacceptable variations from the study protocol were observed in only 2 out of ten relapses in originally involved and irradiated areas.

The present study certainly has weaknesses. The main weakness is the number of patients evaluated (ie, 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 data collection were anticipated, the number of patients collected with complete data sets was limited, and the conclusions must be interpreted cautiously.

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. Data collection 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, the trial protocol should include a description of the planned RTQA procedure.

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

During the past decades, the field of RTQA has evolved. Several groups, including the Radiation Therapy Oncology Group (now part of the NRG Oncology cooperative group), EORTC, American College of Radiology, and National Cancer Institute, 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: the 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 radiation therapy 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 analyze "modern" field designs and treatment techniques.[29] In addition, in a conference sponsored by the National Cancer Institute, 4 recommendations were made for RTQA in clinical trials: (1) Develop a tiered system and tailor the 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]

Because one of the aims of the H10 trial was to reduce late treatment-related toxicity, it would have been interesting to evaluate overtreatment in terms of radiation volume and dose. Performing CT planning and delineating OARs were not mandatory; therefore, estimating excessive radiation exposure was deemed 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 to reduce 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, enabling studying normal tissue toxicity on a larger scale. In the future, we should aim to quantify doses of OARs, especially in patients with a long-life expectancy like HL patients. Preferably, this should be done in the context of clinical trials and routine daily practice.

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

Conclusion

The present study shows that the newly introduced principle of INRT was applied in most patients. The present 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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