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Guideline 6-20 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Management of Early-Stage Hodgkin Lymphoma

Members of the Hematology Disease Site Group

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(See Section 6: Document Assessment and Review for details)

Guideline 6-20 Version 2 is comprised of 6 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/171

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PUBLICATIONS RELATED TO THIS REPORT

Part of the evidentiary basis for this guideline has been published as a journal article in:

1. Crump M, Herst J, Baldassarre F, Sussman J, MacEachern J, Hodgson D et al. Evidence-based focused review of the role of radiation therapy in the treatment of early-stage Hodgkin lymphoma. Blood. 2015 Mar 12;125(11):1708-16. Epub 2015 Jan 20.

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version December 8, 2015	2003 to 2015	Full Report	Web publication	NA
Current Version 2 May 26, 2023	2015 to 2022	New data found in Section 6: Document Assessment and Review	Updated Web publication	2015 recommendations are **ENDORSED**

Management of Early-Stage Hodgkin Lymphoma

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To make recommendations on management strategies for patients with early-stage Hodgkin lymphoma (HL).

TARGET POPULATION

Patients with early-stage Hodgkin Lymphoma.

INTENDED USERS

Clinicians involved in the management of patients with early-stage Hodgkin lymphoma, including radiation oncologists and clinical hematologists/oncologists.

RECOMMENDATIONS

Recommendation 1
Patients with early-stage classical Hodgkin lymphoma should not be treated with radiotherapy alone.

Qualifying Statements for Recommendation 1

May 2023:The recommendation pertaining to patients with early-stage nodular lymphocyte predominant Hodgkin lymphoma has been retired. See Section 6 for details.

No phase III clinical trials have focused exclusively on NLPHL, therefore, no strong evidence for one particular treatment strategy over another is currently available. In some settings (such as low bulk disease, older patients), expert opinion suggests that involved-field radiation alone may be appropriate.

Recommendation 2
Chemotherapy plus radiotherapy or chemotherapy alone are recommended treatment options for patients with early-stage nonbulky Hodgkin lymphoma.

Qualifying Statements for Recommendation 2

The decision on which treatment option to use should involve a patient-centred discussion with a hematologist/medical oncologist and a radiation oncologist. Patients should be aware of inferior progression-free survival (PFS) with chemotherapy alone, and of the possibility of late radiotherapy toxicity.

Recommendation 3
May 2023: The recommendation pertaining to involved field radiation therapy (IFRT) when delivered as part of a planned combined modality treatment approach has been retired because some aspects of the recommendation are out of date. See Section 6 for details.

Recommendation 4
The dose of involved field radiation should be 20 Gy for patients with favourable characteristics and between 30 to 36 Gy for patients with unfavourable characteristics (see Appendix 1 for definitions of favourable and unfavourable characteristics).

Recommendation 5
The Working Group does not recommend the use of a negative interim positron emission tomography scan alone to identify patients with early-stage HL for whom radiotherapy can be omitted without a reduction in PFS.

Qualifying Statements for Recommendation 5
May 2023: The working group does not recommend using results of an interim PET scan to identify patients in whom radiation can be omitted if treated with ABVD; however, a negative PET scan after 2 cycles of escBEACOPP + 2 cycles of ABVD (4 cycles of chemotherapy in total) for early unfavourable HL, identifies a group of patients in whom radiation can safely be omitted without a reduction in PFS. [see also recommendation 8].

Recommendation 6A
Patients with early-stage, favourable risk Hodgkin lymphoma who are being treated with combined modality therapy should receive two cycles of chemotherapy before radiotherapy.

Recommendation 6B
Patients with early-stage, unfavourable risk Hodgkin lymphoma, who are being treated with combined modality therapy, should receive four cycles of chemotherapy before radiotherapy.

Recommendation 7
Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) should be the regimen of choice when administered before radiotherapy, except under the circumstances that follow in Recommendation 8.

Recommendation 8
Patients with early-stage, unfavourable risk Hodgkin lymphoma may be considered for treatment with either four cycles of ABVD, or two cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (escBEACOPP) followed by two cycles of ABVD before radiotherapy.

Qualifying Statements for Recommendation 8
May 2023: Radiation can be safely omitted in patients with unfavourable early stage Hodgkin lymphoma who are PET negative after 2 cycles of escBEACOPP + 2 cycles of ABVD (4 cycles of chemotherapy in total).
Comparing 2 escBEACOPP/2ABVD +/- radiation to 4ABVD + radiation, the escBEACOPP approach improves FFTF and PFS but is associated with more short-term adverse effects. Overall survival rates at 112 months follow-up did not differ, but available data are not sufficiently mature to assess some of the late effects and long-term outcomes (particularly risks of secondary malignancies).

Management of Early-stage Hodgkin Lymphoma

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To make recommendations on management strategies for patients with early-stage Hodgkin lymphoma (HL).

TARGET POPULATION

Patients with early-stage Hodgkin lymphoma.

INTENDED USERS

Clinicians involved in the management of patients with early-stage Hodgkin lymphoma, including radiation oncologists and clinical hematologists/oncologists.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1

A) Patients with early-stage classical Hodgkin lymphoma should not be treated with radiotherapy alone.

Qualifying Statements for Recommendation 1

May 2023: The recommendation pertaining to patients with early-stage nodular lymphocyte predominant Hodgkin lymphoma has been removed. See Section 6 for details.

No phase III clinical trials have focused exclusively on NLPHL, therefore, no strong evidence for one particular treatment strategy over another is currently available. In some settings (such as low bulk disease, older patients), expert opinion suggests that involved-field radiation alone may be appropriate.

Key Evidence for Recommendation 1

The evidence for this recommendation comes from one of the comparisons that the members of the Working Group had identified as relevant: "chemotherapy plus radiotherapy versus radiotherapy alone," and from a guideline that was included in the systematic review [3].

The GHSG HD7 study [4] found, at seven years follow-up, no statistically significant difference in overall survival rate (92% in the radiotherapy arm versus 94% in the combination chemotherapy plus radiotherapy arm, p=0.43), but a better freedom-from-treatment-failure rate (FFTF) in favour of the combination treatment when compared with radiotherapy alone (67% versus 88% respectively, p<0.0001).

The SWOG 9284A study [5] measured quality of life and found it statistically significantly worse in the combination therapy arm at six months (p=0.001), but not statistically significantly different at one and two years (Tables 4F and 5F).

Existing guidelines recommend treating patients with NLPHL with radiotherapy only [3].

Interpretation of Evidence for Recommendation 1

Is there important uncertainty about how much people value the outcomes?

The members of the Working Group agreed that overall survival rate (OS), measures of disease control, and late adverse events were outcomes that clinicians and patients would value highly. Quality of life was considered an important outcome as well.

What is the overall certainty of this evidence?

The members of the Working Group considered the quality of the evidence presented for patients with early-stage HL as moderate, because of imprecision: each outcome measure is represented in only one study, and in each study the number of events can be considered relatively low.

The recommendation regarding patients with NLPHL is based on nonrandomized evidence.

Are the desirable anticipated effects large?

No statistically significant difference was identified for OS. However, patients treated with combination therapy experienced a significantly better FFTF at 87 months follow-up.

Are the undesirable anticipated effects small?

Late adverse events were not statistically significantly different among groups. Patients in the combination modality treatment experienced more short term symptoms, and a decrease in quality of life. However, at one year, patients in the two groups had similar quality of life outcomes.

Are the desirable effects large relative to undesirable effects?

FFTF has been shown to be significantly better with combination therapy than with radiotherapy alone. Quality of life has been shown to be initially worse with combination therapy and no different after one year.

Is this evidence generalizable to the entire target population?

The patients enrolled in the GHSG HD7 study [4] were in clinical stages I and II without risk factors, and the SWOG 9284A [5] study excluded patients with unfavourable prognosis. Many of the trials that compared the use of radiotherapy alone with combined modality (e.g., the study reported by Press et al., [6]) were conducted prior to the cut off limit for this systematic review. Therefore, it has become good practice not to use radiotherapy alone for patients with early-stage HL, except for specific cases such as patients with NLPHL.

Recommendation 2

Chemotherapy plus radiotherapy or chemotherapy alone are recommended treatment options for patients with early-stage non-bulky Hodgkin lymphoma.

Qualifying Statements for Recommendation 2

The decision on which treatment option to use should involve a patient-centred discussion with a hematologist/medical oncologist and a radiation oncologist. Patients should be aware of inferior progression-free survival (PFS) with chemotherapy alone, and of the possibility of late radiotherapy toxicity.

Key Evidence for Recommendation 2

The studies that support this recommendation belong to two of the comparisons that the members of the Working Group had identified as relevant: "chemotherapy alone versus chemotherapy and radiotherapy" and "small radiotherapy field plus chemotherapy versus large radiotherapy field" (see Tables 1A and 2A, 1D and 2D, Section 4).

The statement about patient-centred discussion for decision making is a good practice statement.

The EORTC H.6 study [7,8], the RAPID trial [9], and the EORTC-GELA H9 study [10] compared chemotherapy alone with combination chemotherapy and radiotherapy for the treatment of early-stage HL.

The EORTC H.6 study [7] compared doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) alone with an extended field radiation (sub-total nodal irradiation [STNI]) with or without chemotherapy in patients who were not at very low risk or very high risk. At 11.3 years median follow-up, OS was better with chemotherapy alone (94% versus 87%; hazard ratio [HR] for death in the chemotherapy alone group, 0.50; 95% confidence interval [CI], 0.25 to 0.99; p=0.04). The EORTC H.6 study [7] did not detect any statistically significant between-group differences for event-free survival (EFS) and PFS (respectively 85% versus 80%; HR, 0.88; 95% CI, 0.54 to 1.43; p=0.60; and 87% versus 92%; HR, 1.91; 95% CI, 0.99 to 3.69; p=0.05) at 11.3 years. More patients in the radiotherapy group suffered deaths for causes other than Hodgkin lymphoma (10 versus two), second cancers (23 versus 10), and cardiac events (26 versus 16) than patients in the chemotherapy only group (p values were not reported). Two trials belonging to this body of evidence, the RAPID trial [9] and the EORTC-GELA H9 trial [10], were published only in abstract form. Therefore they were not given equal weight to the H.6 trial and were not considered relevant to the recommendations.

Interpretation of Evidence for Recommendation 2

Is there important uncertainty about how much people value the outcomes?

The members of the Working Group discussed the value of outcomes including OS, EFS, and secondary cancers. The members of the Working Group agreed that OS and EFS are outcomes that most patients and clinicians would value highly.

What is the overall certainty of this evidence?

The body of evidence for this comparison consists of only one directly relevant study with full publication. The number of adverse events for this condition is generally low and radiotherapy technology has evolved over time, therefore the overall quality of this evidence has been considered moderate to low across the critical outcomes. The quality of this study was downgraded for indirectness because the radiotherapy treatment used in this body of evidence has been superseded by IFRT. When it comes to assessing imprecision, the quality of this evidence should have been downgraded twice because this body of evidence comprises only one study with less than 300 events, and because 12 years of follow-up are not enough to detect late adverse events caused by radiotherapy treatment. However, this study found that patients in the chemotherapy alone group had a significantly better OS, therefore the members of the Working Group decided to downgrade its quality only once. The members of the Working Group highlighted that the evidence to date is based on larger/extensive doses of radiation than are currently in use.

Are the desirable anticipated effects large?

Yes, the recommended treatments are largely effective for most patients for all critical outcomes.

Are the undesirable anticipated effects small?

It is desirable to prevent late adverse events, and this is obtained by reducing the radiotherapy field size and minimizing the chemotherapy dose. Treatment with larger fields or higher doses of chemotherapy may cause late adverse events such as second cancers or cardiac dysfunction. However, the included studies did not have follow-up periods long enough to detect all possible late adverse events. The recommended approach aims at minimizing adverse side-effects while still maintaining treatment efficacy.

Are the desirable effects large relative to undesirable effects?

There is a fine balance between desirable effects and undesirable effects for this comparison. Different patients and clinicians may weigh the overall survival benefit from

combination treatment versus chemotherapy alone against the increased risk of serious adverse events with combination treatment and come to different conclusions.

Is this evidence generalizable to the entire target population?

The radiotherapy intervention used in the EORTC H.6 study [7,8] is no longer used in current practice. The H.6 study excluded patients with bulky disease. It is therefore difficult to generalize this evidence to the entire population of patients with early-stage HL. This led to a weak recommendation and to the suggestion that clinicians reach treatment decisions through patient-centred discussion with multi-professional teams so that patients are aware of trade-offs and uncertainties if willing to opt for chemotherapy alone.

Recommendation 3

May 2023: The recommendation pertaining to involved field radiation therapy (IFRT) when delivered as part of a planned combined modality treatment approach has been removed. See Section 6 for details.

Recommendation 4

The dose of IFRT should be 20 Gy for patients with favourable characteristics and between 30 to 36 Gy for patients with unfavourable characteristics (see Appendix 1 for definitions of favourable and unfavourable characteristics).

Key Evidence for Recommendation 4

The studies on which this recommendation is based belong to three of the comparisons that the members of the Working Group identified as relevant: "low radiotherapy dose versus high radiotherapy dose," "small radiotherapy field versus large radiotherapy field," and "small radiotherapy field plus chemotherapy versus large radiotherapy field alone" (see Tables 1B, 1C. 1D and 2B, 2C, and 2D in Section 4).

The GHSG HD11 study [16], in a 2x2 factorial design, and the GHSG HD10 study [17], tested lower versus higher doses of radiotherapy as part of combination treatment in patients with unfavourable- and favourable-prognosis early-stage HL. When comparing IFRT doses of 30 Gy versus IFRT 20 Gy, these two studies did not find any statistically significant difference in OS. For FFTF, treatment with 20 Gy was found noninferior to treatment with 30 Gy in combination with ABVD in patients with favourable prognosis [17] (the group difference at five years: -0.5% [95% CI, -3.6 to 2.6], which excluded the 7% inferiority margin). For patients with unfavourable prognosis the treatment with 20 Gy was noninferior to 30 Gy when combined with four cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) (the group difference at five years: -0.8%; 95% CI, -5.8% to 4.2%), but its inferiority could not be excluded if combined with ABVD (difference 4.7%; 95% CI, -10.3% to 0.8%). No statistically significant difference was found in either study for late adverse events and death at 90 months follow-up (respectively 3.4% versus 4% and 6.5% versus 6.2%).

The GOELAMS H97E study [18] compared three cycles of ABVD plus 36 Gy radiation to involved sites and 24 Gy to adjacent sites with the same chemotherapy with 40 Gy and 30 Gy radiation, respectively, in patients with favourable prognosis. No statistically significant difference was detected in OS and FFTF; at 10 years follow-up the incidence of threatening or fatal events was 0% in the arm with the lower radiation dose versus 15.5±5.3% in the arm with higher radiation dose ($p<0.003$).

The EORTC-GELA H9 study [10] is not considered of equal weight to the other studies because it is a conference abstract publication, and it is not discussed any further.

Interpretation of Evidence for Recommendation 4

Is there important uncertainty about how much people value the outcomes?

The members of the Working Group agreed that OS, FFTF, PFS, and late adverse events are all outcomes that patients and clinicians would value as of critical importance.

What is the overall certainty of this evidence?

The overall quality of the evidence was considered moderate because of risk of bias, indirectness (favourable and unfavourable populations, different interventions such as range of radiation fields and chemotherapy treatments), and imprecision (few events).

Are the desirable anticipated effects large?

The evidence to date shows no substantial difference in terms of overall survival and disease progression with lower radiotherapy doses compared with higher doses.

Are the undesirable anticipated effects small?

Higher radiotherapy doses have been shown to be associated with important adverse effects at longer follow-up times [18]. The GHSG HD11 study [16], with its 2x2 factorial design, uncovered an interaction between radiotherapy and chemotherapy treatments; FFTF and PFS were lower for patients treated with a milder chemotherapy regimen and a lower radiotherapy dose (i.e., ABVD/20 Gy), while they were similar in arms where patients received a milder chemotherapy regimen with a higher radiotherapy dose (i.e., ABVD/30 Gy) or a stronger chemotherapy regimen with a higher or lower radiotherapy dose (i.e., BEACOPP/20 Gy or BEACOPP/30 Gy).

Are the desirable effects large relative to undesirable effects?

Most patients with Hodgkin disease are cured with current treatment strategies; the attention is on minimizing the adverse effects of therapy. The evidence supporting this recommendation suggests that this aim can be obtained by using smaller doses and smaller fields of radiotherapy than in the past.

Is this evidence generalizable to the entire target population?

The evidence in support to this recommendation includes a sample of patients with favourable and unfavourable prognosis and is representative of all age and gender groups.

Recommendation 5

The Working Group does not recommend the use of a negative interim positron emission tomography (PET) scan alone to identify patients with early-stage HL for whom radiotherapy can be omitted without a reduction in PFS.

Qualifying Statements for Recommendation 5

May 2023: The working group does not recommend using results of an interim PET scan to identify patients in whom radiation can be omitted; however, a negative PET scan after 2 cycles of escBEACOPP + 2 cycles of ABVD (4 cycles of chemotherapy in total) for early unfavourable HL, identifies a group of patients in whom radiation can safely be omitted without a reduction in PFS. [see also recommendation 8].

Key Evidence for Recommendation 5

The evidence supporting this recommendation comes from one of the comparisons that the members of the Working Group identified as relevant: "PET versus no PET for tailoring the therapeutic strategy," and includes the EORTC H10, H10F, and H10U studies [1] (see Tables 1E and 2E). The members of the Working Group decided to include the RAPID trial in this comparison even though it did not directly focus on the PET question.

The EORTC H10 study [1] tested whether IFRT could be omitted in patients with negative PET scans after two cycles of ABVD. The study had to be stopped early for futility after 32 adverse events in the patients whose PET scans were negative at a median follow-up of 1.1 years, and all patients were switched to combination treatment. PFS at 1.1 years was 100% for combination therapy, and 94.9% for chemotherapy only in patients whose PET scans were negative (estimated HR, 9.36; 79.6% CI, 2.45 to 35.73; p=0.017), while PFS was 97.3% versus 94.7% (estimated HR. 2.42; 80.4% CI, 1.35 to 4.36; p=0.026) for patients whose PET scans were positive. PET scanning was not considered a good tool to identify patients for whom IFRT could be omitted.

The RAPID trial [9] added to this body of evidence by failing to demonstrate that, in patients whose PET scans were negative, chemotherapy alone was noninferior to a combination modality treatment. At three years follow-up, PFS was 90.8% (95% CI, 86.9 to 94.8) in patients in the chemotherapy alone group versus 94.6% (95% CI, 91.5 to 97.7) in the radiotherapy group, rate ratio 1.57 (95% CI, 0.84 to 2.97). The lower boundary of the risk difference, -3.8%, (95% CI, -8.8% to 1.3%), exceeded the preestablished difference of -7% for noninferiority. OS was 93% for patients randomized to IFRT and 88.6% for those randomized to chemotherapy alone, p values not reported. See Tables 1E and 2E for detailed results and outcome-by-outcome quality assessment.

Among the ongoing trials, the randomized, blinded GHSG HD16 trial is still exploring this question. Results will be available in the next few years and this recommendation might be revised in the future.

Interpretation of Evidence for Recommendation 5

Is there important uncertainty about how much people value the outcomes?

The members of the Working Group agreed that PFS is an outcome that most patients and clinicians would value highly. Other outcomes that the members of the Working Group considered critical (such as OS), other measures of disease control (such as EFS or failure-free survival rate [FFS]), and long-term adverse events were not reported by the authors of the EORTC H10 study because it was stopped early and it is awaiting new data from further follow-up.

What is the overall certainty of this evidence?

The members of the Working Group rated the quality of the evidence of the EORTC H10 [1] trial as moderate because the primary end-point, short-term PFS, is a surrogate for long-term OS. Furthermore, this study was stopped early and therefore was likely underpowered. The results of the EORTC H10 and of the RAPID trials point in the same direction. The results of the ongoing GHSG HD16 study for patients with favourable prognosis and the GHSG HD17 study for patients with unfavourable prognosis are still pending.

Are the desirable anticipated effects large?

PET was thought of as a tool intended to individualize treatment for patients with early-stage HL. If radiotherapy treatment could be omitted without changing survival rates and disease progression outcomes in patients with no residual disease after a first set of chemotherapy cycles, second cancers associated with this treatment could be prevented.

Are the undesirable anticipated effects small?

Patients with no residual disease after a first set of chemotherapy cycles, according to the identified evidence, did not have a better PFS if left only on chemotherapy than if treated with chemotherapy and radiotherapy.

Are the desirable effects large relative to undesirable effects?

The included evidence failed to demonstrate noninferiority of chemotherapy alone and combination treatment in the subgroup of patients whose PET scans were negative after a first round of chemotherapy.

Is this evidence generalizable to the entire target population?

The EORTC H10 studies included patients with favourable and unfavourable prognoses, therefore the members of the Working Group believe this evidence can be generalized to the entire population.

Recommendation 6

A) Patients with early-stage, favourable risk Hodgkin lymphoma who are being treated with combined modality therapy should receive two cycles of chemotherapy before radiotherapy.
B) Patients with early-stage, unfavourable risk Hodgkin lymphoma, who are being treated with combined modality therapy should receive four cycles of chemotherapy before radiotherapy.

Key Evidence for Recommendation 6

The studies that support this recommendation [11,17,19] belong to one of the comparisons that the members of the Working Group identified as relevant: "more cycles of a specific chemotherapy (e.g., ABVD) plus radiotherapy versus fewer cycles of the same chemotherapy plus radiotherapy" (see Tables 4I and 5I).

The study reported by Hamed et al. [19], the GHSG HD10 study [17], and the EORTC GELA H8U study [11] did not find any statistically significant difference in any of the outcomes but acute adverse effects: the patients who received more cycles of chemotherapy suffered more acute adverse events than those who received fewer (54% versus 30%, p=0.02 [19], and 51.7% versus 33.2%). In particular, the HD10 study [17] was completed with patients with favourable risk disease; when offered as part of combined modality therapy, an approach that included two cycles of chemotherapy (ABVD) was noninferior to an approach with four cycles with respect to FFTF (difference -1.9% [95% CI, −5.2 to 1.4], does not include the prespecified noninferiority margin of 7%). In the EORTC-GELA H8U study, patients with unfavourable disease treated with four cycles of chemotherapy had the same long-term outcomes as patients treated with six cycles [11].

Interpretation of Evidence for Recommendation 6

Is there important uncertainty about how much people value the outcomes?

The members of the Working Group agreed that OS, FFTF, relapse-free survival (RFS), PFS, EFS, and second cancers are outcomes that most patients and clinicians would value highly.

What is the overall certainty of this evidence?

The overall quality of this body of evidence was considered high.

Are the desirable anticipated effects large?

Treatment with a smaller number of chemotherapy cycles did not result in worse outcomes than treatment with a larger number of chemotherapy cycles in any of the included studies.

Are the undesirable anticipated effects small?

Grade 3 and 4 acute adverse events have been found to be statistically significantly higher in patients assigned to a higher number of chemotherapy cycles than in patients assigned to fewer cycles.

Are the desirable effects large relative to undesirable effects?

A statistically significant difference in grade 3 and 4 acute adverse effects in patients exposed to a higher number of chemotherapy cycles, with no statistically significant between-group difference in efficacy, led the members of the Working Group to prefer a smaller number of chemotherapy cycles in patients with favourable risk disease.

Is this evidence generalizable to the entire target population?

The three studies included patients of all age and gender groups representative of the target population, with favourable [17,19] and unfavourable [17] profiles, therefore the findings are generalizable to the entire population.

Recommendation 7

ABVD should be the regimen of choice when administered before radiotherapy, except under the circumstances that follow in recommendation 8.

Key Evidence for Recommendation 7

The studies which support this recommendation [16,20-23] belong to one of the comparisons that the members of the Working Group identified as relevant: "more intensive chemotherapy regimens (e.g., ABVD) plus radiotherapy versus less intensive chemotherapy regimens plus radiotherapy (e.g., etoposide, vincristine, epirubicin [EVE] or Stanford V) ." The Working Group members also listed the GHSG HD11 study [16] under a radiotherapy comparison: "low-dose compared with high dose radiotherapy" (see Tables 4H and 5H).

The study reported by Pavone et al. [20], the E2496 study [21,24], reported in abstract form, the H90-NM study [22], and the GHSG HD13 study [25] compared ABVD with less intensive regimens, both in combination with radiotherapy. Behringer et al. [23], in a subgroup analysis of the GHSG HD13 study, compared ABVD with three other, less intensive, regimens and compared fertility outcomes. The studies did not find a statistically significant difference in overall survival rate and in adverse effects.

The study reported by Pavone et al. [20] compared ABVD with EVE regimens and found a better FFS and RFS for ABVD than for EVE (respectively, 90% versus 73%, p= 0.005, and 95% versus 78%, p=0.002) but no statistically significant difference for response (see Table 4H). The E2496 study [21,24] compared ABVD with Stanford V regimens, and did not find any difference in any of the outcomes. The H90-NM study [22] found a better FFS in the ABVD modified arm compared with the epirubicin, blomycin, vinblastine, methotrexate (EBVM) modified arm (91.4%±2.1% versus 80%±3%; p<0.002), and a better EFS (84.6% ± 2.8% 74.9% ± 3.6%; p=0.016). In the GHSG HD13 study [25], regimens that did not include dacarbazine were inferior to ABVD with respect to FFTF. Noninferiority of AVD (with bleomycin excluded) to ABVD also could not be detected in this study.

The GHSG HD11 study [16] compared 4xABVD with 4xBEACOPP, in combination with 20 Gy or 30 Gy radiotherapy. The authors found, with respect to FFTF, that treatment with ABVD/20 Gy was inferior to treatment with BEACOPP/20 Gy and that treatment with ABVD/30 Gy was noninferior to treatment with BEACOPP/30 Gy. No statistically significant difference was found for OS, PFS, response and long-term adverse events (Tables 4H and 5H in Section 4)

The noninferiority GHSG HD13 trial [25] tested the role of bleomycin and dacarbazine in the ABVD regimen by omitting one (ABV), the other (AVD), or both (AV) drugs in patients

with favourable risk disease. At five years, the authors found that the dacarbazine-deleted regimen was not noninferior to ABVD (FFTF difference between ABVD versus ABV, -11% [95% CI, -18.3 to -4.7], [HR 2.06, 1.21 to 3.52]); ABVD versus AV:-15.2% [95% CI, -23.0 to -7.4], [HR 2.57, 1.51 to 4.40]). Noninferiority in FFTF could not be demonstrated for the comparison including the bleomycin-deleted regimen (difference between ABVD versus AVD, -3.9% (95% CI -7.7 to -0.1, HR 1.50 [95% CI, 1.00 to 2.26]) which included the predefined noninferiority margin of 1.72.

Behringer et al, [23] in a subgroup analysis of the GHSG HD14 study [26] reported that gonadal hormone levels and number of pregnancies in patients treated for early stage HL were inversely correlated with the intensity of treatment (see Table 4H in Section 4 for detailed results).

Interpretation of Evidence for Recommendation 7

Is there important uncertainty about how much people value the outcomes?

The members of the Working Group agreed that OS, measures of disease control, and late adverse events are outcomes that most patients and clinicians would value highly.

What is the overall certainty of this evidence?

The members of the Working Group considered the quality of the evidence presented as moderate because of imprecision; each outcome was represented by one study with a relatively low number of events. See Table 5H for more details about the quality for each outcome.

Are the desirable anticipated effects large?

ABVD was associated with similar or improved FFTF compared with alternative regimens.

Are the undesirable anticipated effects small?

ABVD was associated with fewer adverse effects compared with alternative or more intense regimens including EVE or Stanford V. ABVD was associated with moderately higher grade 3 to 4 adverse effects compared with AVD (bleomycin-omitted) or with therapies in which dacarbazine was omitted.

Are the desirable effects large relative to undesirable effects?

When compared with alternative or more intense regimens, ABVD offered similar (or improved) efficacy but fewer adverse effects. When compared with less intense regimens, ABVD offered improved efficacy but with reasonable levels of adverse effects. In both situations, ABVD was felt to be the favoured approach.

Is this evidence generalizable to the entire target population?

The evidence in support of this recommendation includes patients of all ages representative of the target population, with favourable and unfavourable prognostic profiles, therefore the members of the Working Group considered this evidence generalizable to the entire target population.

Recommendation 8

Patients with early-stage, unfavourable risk Hodgkin lymphoma may be considered for treatment with either four cycles of ABVD, or two cycles of escalated BEACOPP followed by two cycles of ABVD before radiotherapy.

Qualifying Statement for Recommendation 8

May 2023: Radiation can be safely omitted in patients with unfavourable early stage Hodgkin lymphoma who are PET negative after 2 cycles of escBEACOPP + 2 cycles of ABVD (4 cycles of chemotherapy in total).
Comparing 2 escBEACOPP/2ABVD +/- radiation to 4ABVD + radiation, the escBEACOPP approach improves FFTF and PFS but is associated with more short-term adverse effects. Overall survival rates at 112 months follow-up did not differ, but available data are not sufficiently mature to assess some of the late effects and long-term outcomes (particularly risks of secondary malignancies).

Key Evidence for Recommendation 8

The studies which support this recommendation [12,26,27] belong to one of the comparisons that the members of the Working Group identified as relevant: "Less intensive chemotherapy regimens plus radiotherapy versus more intensive regimens plus radiotherapy" (see Tables 4G and 5G).

The GHSG HD14 study [26] did not find a statistically significant difference in OS at five years follow-up (HR 1.12; 95% CI, 0.58 to 2.16; p=0.7308), while the EORTC-GELA H7U study [12], at 10 years follow-up, found a better OS for patients assigned to the more intensive chemotherapy regimen (79% for six cycles of EBPV+IFRT versus 87% for MOPP/ABV hybrid plus IFRT, p<0.001).

*May 2023: The GHSG HD17 trial [*See Section 6 for details*] showed* no significant difference between the 2+2 and the PET4 guided groups in PFS. PFS at 5yrs: 97·3% (95% CI, 94·5–98.7) vs. 95.1% (92.0–97.0). HR= 0.523 (95% CI 0.226 to 1.211).

5-year PFS was significantly higher in the PET-negative group than in the PET-positive subgroups (HR 3.03 [95% CI, 1.10 to 8·33], p=0.024

PET positivity, defined as a Deauville score of 4 or higher, was identified as a significant risk factor for poor progression-free survival. HR 10.47 (95% CI 4.00 to 27.38]), p<0·0001. See Section 6 for details.

In the GHSG HD16 trial PET-negative patients treated with chemotherapy alone had a significantly higher risk of local recurrences than patients on CMT therapy.
The 5-year cumulative incidence of in-field progression in the chemotherapy arm was 10.5% (95% CI, 6.5 to 14.6) vs. 2.4% (95% CI, 0.5 to 4.3) with CMT. p=0.0008).

There was no significant difference in out-field recurrences. Five-year incidence in the chemotherapy arm was 4.1% (95% CI, 1.7 to 6.6) vs 6.6% (95% CI, 3.0 to 10.3) in the CMT group. p=0.54. See Section 6 for details.

Interpretation of Evidence for Recommendation 8

Is there important uncertainty about how much people value the outcomes?

There is a balance between the improved FFTF and PFS associated with BEACOPP and the fewer adverse effects associated with ABVD therapy. Because OS does not differ, individual patient preferences are of value in decisions regarding the chemotherapy backbone in unfavourable early-stage HL.

What is the overall certainty of this evidence?

The overall quality of this body of evidence was considered high

Are the desirable anticipated effects large?

There is the potential for improved FFTF and PFS associated with BEACOPP compared with ABVD.

Are the undesirable anticipated effects small?

There is the potential for considerable excess adverse effects associated with BEACOPP compared with ABVD.

Are the desirable effects large relative to undesirable effects?

There is likely a trade-off between improved efficacy and adverse effects. Patient values and preferences should be considered.

Is this evidence generalizable to the entire target population?

The results are relevant to patients with unfavourable early-stage HL.

IMPLEMENTATION CONSIDERATIONS

Feasibility

The chemotherapies discussed in the recommendations are currently funded in Ontario. Access to systemic therapies and radiation (involved-field) is well-established in the province and the costs of such care are reasonable. Access to newer technologies, including PET scans and involved nodal radiation, may still be evolving; however, these are not currently an integral component of the recommended care.

Patient Considerations

Outcomes of interest include survival, consideration of balance between upfront disease control and long-term adverse effects, and quality of life. In particular, the recommendations include statements focused on patient-centred decisions.

Equity

We do not anticipate that the recommendations would increase inequities in care. A Cancer Care Ontario priority is to maintain universal (including geographic) access to cancer care.

Provider Considerations

We hope the opinions expressed reflect the views of the broad community of clinicians. This guideline is subject to external review.

System Considerations

The recommendations should not impact the current system of care.

Management of Early-Stage Hodgkin Lymphoma

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR THE GUIDELINE

The evolution of the evidence base has challenged the use of radiotherapy in the field of early-stage Hodgkin lymphoma (HL). As a result, in Ontario there is a variation in practice in the management of early-stage HL.

Guideline Developers

This guideline was undertaken by the Early-Stage Hodgkin Lymphoma guideline development group (Appendix 2), which was convened at the request of the Hematology Disease Site Group. The project was led by a small Working Group of the Early-Stage Hodgkin Lymphoma guideline development group which was responsible for reviewing the evidence base, drafting the guideline recommendations and responding to comments received during the document review process. The members of the Working Group had expertise in hematology, radiation oncology and health research methodology. Other members of the Disease Site Group served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all guideline development members are summarized in Appendix 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [28,29]. This process includes a systematic review, interpretation of the evidence by the members of the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [30] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original

evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

SEARCH FOR EXISTING GUIDELINES

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions.

A search for existing guidelines for possible adaptation or endorsement was conducted jointly to the search for systematic reviews (see Section 4 and Appendix 3 for search strategies).

One guideline [3] was included, however, the Working Group decided that it could not be endorsed because an Ontario focused evidence-based, document was needed. This guideline was used as the evidence-base for one of the recommendations.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

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Management of Early-Stage Hodgkin Lymphoma

Section 4: Systematic Review

INTRODUCTION

Hodgkin lymphoma is a malignant neoplasm of B-cell lymphoid derivation representing approximately 0.5% of cases of newly diagnosed cancer. Incidence rates vary geographically. In the western European and North American population the age-standardized incidence rate is 2.6 to 2.9 per 100,000 population [31,32]. Ninety per cent of these cases are classical Hodgkin lymphoma, while the remaining 10% are nodular lymphocyte-predominant Hodgkin lymphoma [31,33]. Approximately 55% of patients are diagnosed with early-stage Hodgkin lymphoma (Ann Arbor stages I and II) [34].

Radiation therapy has long been a mainstay in treatment of early-stage Hodgkin lymphoma. Clinical trials subsequently established the benefit of adding chemotherapy to radiotherapy (combined modality therapy). More recently, chemotherapy alone has emerged as an option for treatment of early-stage Hodgkin lymphoma [8].

Current five-year survival rates for patients with early-stage Hodgkin lymphoma are in the range of 90% [31]. With progressive improvements in disease control, attention has gradually shifted towards a greater appreciation of the long-term adverse effects of therapy, both chemotherapy and radiotherapy. Recent clinical trials have tended to focus on strategies that preserve the excellent results of treatment while minimizing the long-term adverse effects of therapy. Such strategies have included modification of the chemotherapy regimen, limitation of the dose and extent of radiotherapy, elimination of radiotherapy entirely, and the use of positron emission tomography (PET) to assist in stratification of patients to treatments of different intensity.

The Working Group of the Hematology Disease Site Group developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the members of the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. What are the optimum radiation dose and schedule and what are the best chemotherapy regimens for the treatment of patients with early-stage Hodgkin lymphoma (HL)?
2. What are the best strategies for the prevention of early and late adverse events in patients with early-stage HL?
3. What is the role of PET in guiding therapeutic decisions in the management of early-stage HL?
4. What are the best strategies for the treatment of subgroups of patients with early-stage HL, such as those with very favourable or unfavourable disease?

METHODS

This evidence review was developed using a planned two-stage method, summarized here and described in more detail below.

The members of the Working Group decided to answer the questions in two parts: the initial questions were answered considering first radiotherapy, and then chemotherapy treatment.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. Identified systematic reviews were evaluated based on their clinical content and relevance.

Literature Search Strategy

The literature was systematically searched using the electronic databases MEDLINE (Ovid, 2003 to June 19, 2015), EMBASE (Ovid, 2003 to 2015 Week 25), and the Cochrane Library (Central Register of Controlled Trials, Database of Systematic Reviews, and Database of Abstracts of Effects, 2003 to June 19, 2015). Appendix 3 shows the search strategies used for the MEDLINE and EMBASE databases. This search was adapted for the other databases.

In addition, abstracts from the American Society of Hematology (ASH) (2003 to 2015), the American Society of Clinical Oncology (ASCO) (2003 to 2015), the Lugano International Conference on Malignant Lymphoma, and the Cologne International Symposium on Hodgkin Lymphoma (2003 to 2012) were searched. Working Group members' files and reference lists of included articles were also searched. The database Clinicaltrials.gov was searched for ongoing trials.

Study Selection Criteria and Process

Studies were selected for inclusion in this systematic review if they were:

- Studies of patients treated for early-stage HL who were of age >15 years.
- Studies of systemic treatment for early-stage HL, including chemotherapy, biological agents, field and dose of radiation therapy (e.g., involved field or involved nodes radio therapy [IFRT or INRT]), or a combination of the above.
- Study designs including systematic reviews (SR) published from 2011 to current, and randomized controlled trials (RCTs) published from 2003 to current.
- Studies that reported on the following outcomes:
    - Overall survival (OS)
    - Disease control (e.g., progression free survival)
    - Response
    - Quality of life
    - Adverse events (early and late)
- Published in English.

Studies were excluded if they were:

- Systematic reviews published in abstract format only.
- Studies including patients receiving treatment for advanced stage HL
- Studies including early and advanced stage HL, and with no separate data for the early-stage population.
- Abstract publication of interim analyses (although these will be discussed in the section on ongoing trials).
- Narrative reviews.
- Non randomized trials.
- Studies of PET used for staging.
- RCTs with sample size < 30 patients.
- Studies including age groups other than 15 years and over, and with no separate results for the age group of interest.

The methodologist (FB) and three of the clinicians from the Working Group (JH, MCC, and MC) reviewed independently, in duplicate, the titles and abstracts identified by the search.

For those items that warranted full text review, two reviewers (FB, JH, MCC, and MC in teams of two) reviewed each item independently. Discrepancies were resolved by consensus.

Data Extraction and Assessment of Study Quality and Potential for Bias

The methodologist (FB) extracted data from the studies included after full text review, and completed evidence tables. One of the clinicians in the working group (MC) reviewed for correctness the tables of general characteristics, results, and adverse events.

The quality of the included studies was evaluated according to the Cochrane Risk of Bias tool [35] independently by the methodologist (FB) and by one of the clinicians in the Working Group (MC). The GRADEprofiler (GRADEpro) [36] tool was used to create the evidence profile and summary-of-findings tables [37] considering the quality of the evidence for each outcome. Discrepancies were resolved by consensus.

The members of the Working Group identified nine relevant comparisons that were used to extract the data and synthesize the evidence:

Radiotherapy question.

A. Chemotherapy alone versus chemotherapy + radiotherapy
B. Low radiotherapy dose versus high radiotherapy dose
C. Small radiotherapy field versus large radiotherapy field
D. Small radiotherapy field plus chemotherapy versus large radiotherapy field alone
E. Standard therapy versus tailored therapy using fluorodeoxyglucose PET (FDG-PET) scanning.

Chemotherapy question.

F. Chemotherapy plus radiotherapy versus radiotherapy alone
G. Less intensive chemotherapy regimens plus radiotherapy versus more intensive regimens plus radiotherapy
H. More intense chemotherapy plus radiotherapy versus less intensive regimens plus radiotherapy
I. More cycles of a specific chemotherapy plus radiotherapy versus fewer cycles of the same chemotherapy plus radiotherapy.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.2) provided by the Cochrane Collaboration [38]. For time-to-event outcomes, hazard ratios (HR), rather than the number of events at a certain time point, are the preferred statistic for meta-analysis, and are used as reported. If the HR and/or its standard error were not reported, they have been derived from other information reported in the study, if possible, using the methods described by Parmar et al. [39]. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in Review Manager have been used.

Statistical heterogeneity was calculated using the x^2 test for heterogeneity and the I^2 percentage. A probability level for the x^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% was considered indicative of statistical heterogeneity.

If data was not considered sufficiently clinically and statistically homogeneous, a narrative synthesis was performed.

RESULTS

General search results

The search of electronic databases, conference abstracts, the files of the Working Group members, and the reference lists of included articles resulted in 2233 citations after deduplication, of which 778 came from MEDLINE, 463 from EMBASE, 61 from the Cochrane Library, and 926 from other sources. That is, 787 citations from conference proceedings, (130 from ASCO, 608 from ASH, 23 from the Cologne International Symposium on Hodgkin Lymphoma, and 26 from the Lugano International Conference on Malignant Lymphoma, 138 from the Working Group's own files, and five citations from the reference lists of included articles.

The full text of 136 articles was retrieved and independently reviewed by two authors. We were unable to locate the full text of one publication. Eighty-nine articles were excluded: 21 were duplicate publications, six were abstracts of interim analyses, eight did not report on any outcomes of interest, 25 did not report on the population of interest, one did not report on any interventions of interest, 22 did not have the design of interest, six were systematic reviews with a search strategy older than two years or were abstract reports of systematic reviews. Three articles were used only as background information. Forty-four publications were included in this review. Appendix 4 shows the study flow chart.

Among 44 included publications were: one guideline [3], two systematic reviews of summary data [40,41], two meta-analyses of individual-patient data, one in abstract form [42], and one fully published [43]; seven pooled analyses/subgroup analyses or long-term follow-up of published RCTs reported in nine publications [23,44-51] and 32 publications of RCTs [1,4,5,7-22,24-27,52-59].

The members of the Working Group decided not to use any of the systematic reviews captured by the searches as an evidentiary base, or to endorse any of the existing guidelines, because the differences in questions, definitions of the early-stage HL population or provincial context were enough to make their content unfit as a base for this Ontario-based guideline. The systematic reviews retrieved were used as a source of evidence.

Literature search results: Radiotherapy question

For the radiotherapy question, 17 RCTs, represented by 21 publications were included [1,7-18,52-59]. These trials were found to be highly clinically heterogeneous and therefore were synthesized in a narrative manner.

General Characteristics and Outcomes Radiotherapy Question

The general characteristics of the included RCTs relevant for the radiotherapy question are presented in Table 1. The summary results are reported in Tables 1A to 1E; the dose and schedule of radiotherapy and chemotherapy used in the studies included are summarized in Appendix 5, Table 1.

The studies are grouped according to five comparisons:

A. Radiotherapy in combination with chemotherapy versus chemotherapy alone
B. Low dose radiotherapy versus high-dose radiotherapy
C. Narrow versus large field radiotherapy
D. Narrow field radiotherapy plus chemotherapy versus large field radiotherapy
E. Standard therapy versus tailored therapy using PET.

For each of these comparisons, four members of the Working Group (MC, MCC, JH, FB) rated patient-important outcomes as "Critical", "Important," or "Not Important". Only outcomes considered critical were used for further, outcome by outcome, quality evaluation. For

comparison A, critical outcomes are OS and event-free survival (EFS). For comparison B, critical outcomes are OS and death, freedom from treatment failure (FFTF), progression-free survival (PFS), EFS, freedom from disease progression, late adverse events; for comparison C, outcomes considered critical were OS and death, freedom from treatment failure (FFTF), PFS, freedom from disease progression (FDP), late adverse events and adverse events from radiotherapy; for comparison D, outcomes considered critical are OS or death, EFS, late adverse events, and quality of life. For comparison E, PFS was considered a critical outcome. Details on how these decisions were made are reported in Appendix 6.

Table 1 presents the general characteristics of all included studies relevant to the radiotherapy question. Tables 1A to 1E present summary results.

Table 1. Radiotherapy question: General characteristics of included studies

Study name, author(s), year (ref) Funding	Population, Data collection period	Intervention(s)	Control(s)	Outcomes	Follow-up, median
A. Chemotherapy plus Radiotherapy compared with chemotherapy alone for early-stage Hodgkin lymphoma					
NCIC CTG/ECOG H.6 Meyer, 2012, 2005 [7,8] Macdonald, 2007 [57] **Funding:** Canadian Cancer Society, National Cancer Institute of Canada	Pts with favourable or unfavourable early HL, CS IA, and IIA. N=405 randomized; 399 available for analysis Arm A: 196 Arm B: 203 Age (years): median: Arm A 35; Arm B: 36.7 Gender: male Arm A: 54%; Arm B: 57% 1994 to2002	Arm A: ABVD only	Arm B: STNI with or without chemotherapy.	*OS EFS PFS Late AE	11.3 years
RAPID Radford, 2015 [9] **Funding:** Leukaemia and Lymphoma Research, the Lymphoma Research Trust, Teenage Cancer Trust, and the U.K. Department of Health	Pts with HL CS IA and IIA, no B symptoms, no bulk who had received 3 cycles of ABVD and had a negative PET scan. N =420 randomized 398 available for analysis Arm A: 209 Arm B: 211 Age (years): median 34 Gender: male 53.3% 2003 to 2010	Arm B: no further intervention	Arm A: IFRT	OS *PFS	60 months
EORTC-GELA H9F Thomas, 2007 [abs] [10] **Funding:** *nr*	Pts in CS I or II supradiaphragmatic, previously untreated, either favourable (H9F) or unfavourable (H9U) B HL, in complete remission. H9F N=619 [H9U N=808 randomized, 713 (in CR) in analysis] Age (years): *nr* Gender: *nr* 1997 to 2004	Arm C: No RT + 6xEBVP (arm stopped early because >20% events)	Arm A: 36 Gy IFRT +6xEBVP Arm B: 20 Gy IFRT + 6xEBVP	OS PFS EFS	H9F 60 months
B. Low dose compared with high dose radiotherapy					
	Pts with supradiaphragmatic HL CS I and II, with ≤2 affected lymph node areas and mediastinal mass ratio <0.33. n =197 randomized, 188 in analysis Arm A: 89 Arm B: 99 Age (years): median *nr*	Arm A: 3xABVD + 36 Gy radiation to initially involved sites and 24 Gy to adjacent sites, the upper infra-diaphragmatic area, and the spleen.	Arm B (control arm): 3 cycles ABVD + same irradiation as Arm A administered at doses of 40 Gy and 30 Gy, respectively.	OS *FFTF Late AE	75 months

Study name, author(s), year (ref) Funding	Population, Data collection period	Intervention(s)	Control(s)	Outcomes	Follow-up, median
	Gender: male 44%; Arm A: 45%, Arm B: 42% 1997 to 2004				
GHSG HD11 Eich, 2010 [16] **Funding:** Deutsche Krebshilfe and the Swiss Federal Government	Pts in CS IA, IB, IIA with risk factors, IIB (early unfavourable HL) N =1570 randomized, 1395 in analysis Arm A: 386 assigned, 356 in analysis Arm B: 395 assigned, 347 in analysis Arm C: 394 assigned, 341 in analysis Arm D: 395 assigned, 351 in analysis Age (years): median 33 (range 16 to 75) Gender: male 49% 1998 to 2003	Arm B:4xABVD+IFRT 20 Gy Arm C:4xBEACOPP+30 Gy IFRT Arm D: 4xBEACOPP+20 Gy IFRT	Arm A:4xABVD+IFRT 30 Gy	OS *FFTF PFS Response Late AE	91 months
GHSG HD10 Engert, 2010 [17] **Funding:** Deutsche Krebshilfe and the Swiss Federal Government	Pts in CS I,II no risk factors (early favourable HL) N=1370 randomized, 1190 in analysis Arm A: 346 assigned, 298 in analysis Arm B: 340 assigned, 298 in analysis Arm C: 341 assigned, 295 in analysis Arm D: 343 assigned, 299 in analysis Age (years): mean 38.8; <20: *nr*; >60: *nr* Gender: male 60.9% 1998 to 2003	Arm B 4xABVD+IFRT 20 Gy Arm C 2xABVD+IFRT 30 Gy Arm D 2xABVD+IFRT 20 Gy	Arm A 4 x ABVD+IFRT 30 Gy	OS *FFTF PFS Response Late AE	90 months
EORTC-GELA H9U Thomas, 2007 [abs] [10] **Funding:** *nr*	Pts in CS I or II supradiaphragmatic, previously untreated, unfavourable (H9U)B HL, in complete remission. H9U N =808 randomized, 713 (in CR) in analysis Age (years): *nr* Gender: *nr* H9U: 1998 to 2002	6xABVD 4xABVD + 30 Gy IFRT	4xBEACOPP +30 Gy IFRT	OS EFS	H9U 67 months
C. Smaller field compared with larger radiotherapy field					
GHSG HD8 Engert, 2003 [14], Eich, 2005 [59], Klimm, 2007 [58],	Pts in CS I, IIA, IIB with risk factors, and CS IIIA no risk factors. n=1204 pts randomized; 1064 available for analysis Arm A: 532 Arm B: 532	Arm B: COPP + ABVD 30 Gy IF + 10 Gy to bulk	Arm A: COPP + ABVD 30 Gy EF +10 Gy to bulk	OS *FFTF PFS Response Late AE	55 months

Study name, author(s), year (ref) Funding	Population, Data collection period	Intervention(s)	Control(s)	Outcomes	Follow-up, median
Engert, 2004 [abs] [55], Sasse, 2102 [56] **Funding:** Deutsche Krebshilfe and by the Swiss Group for Clinical Cancer Research	Age (years): median Arm A: 31.3, Arm B: 30.7; <20: 19.3%; >60: 16.4% Gender: male 53% 1993 to 1998				
Bonadonna, 2004 [13], Viviani, 2012 [abs] [54] **Funding:** Associazione Italiana Ricerca sul Cancro, Italy	Pts in CS IA, IB, and IIA N =140 randomized 136 available for analysis Arm A: 66 Arm B: 70 Age (yrs): median 29 Gender: male 43% 1990 to 1996	Arm B: ABVD + up to 40 Gy IFRT	Arm A: ABVD + 30.6 Gy STNI	OS *PFS EFS Response	116 months
EORTC GELA H8U Ferme, 2007 [11] **Funding:** French Ministry of Health, and French National League against Cancer	Pts in CS I or II supradiaphragmatic, previously untreated, unfavourable HL. H8U: N =996 randomized Arm A: 336 Arm B: 333 Arm C: 327 Age (years): median: Arm A: 33, Arm B: 32, Arm C: 31 Gender: male 45% 1993 to 1999	Arm A: 6xMOPP-ABV + IFRT Arm B: 4xMOPP-ABV + IFRT	Arm C: 4 cycles of MOPP-ABV + STNI	OS *EFS Response Late AE	89 months
D. Smaller radiotherapy field plus chemotherapy compared with larger field radiotherapy					
EORTC-GELA H7F Noordijk, 2006 [12] **Funding:** *nr*	Pts in CS I and II with favourable or unfavourable supradiaphragmatic previously untreated HL n =762 randomized 709 available for analysis Arm A: 160 Arm B: 163 Arm C: 193 Arm D: 193 Age (years): median 30 Gender: male 53% 1988 to 1993	Arm B: 6xEBVP + IFRT	Arm A: STNI	*OS *EFS Response Late AE	105 months

Study name, author(s), year (ref) Funding	Population, Data collection period	Intervention(s)	Control(s)	Outcomes	Follow-up, median
EORTC GELA H8F Ferme, 2007 [11], Heutte, 2009 [52] **Funding**: French Ministry of Health, and French National League against Cancer	Pts in CS I or II supradiaphragmatic, previously untreated, favourable HL. n=542 randomized Arm A: 272 Arm B: 270 Age (years): median 30 Gender: male 62.5% 1993 to 1999	Arm B: a combination of 3xMOPP-ABV + IFRT	Arm A: STNI	OS *EFS Response Late AE	92 months
NCRI LY07 Thistlethwaite, 2007 [abs] [15] **Funding:** *nr*	Pts in CS I or II supradiaphragmatic HL. N =226 randomized Arm A: 115 Arm B: 111 Age (yrs): median 30 Gender: male 63% 1996 to 2001	Arm B: minimal initial chemotherapy (i.e., 4 wks of VAPEC-B) + IFRT	Arm A: MFRT	OS PFS Response	84 months
E. PET used for tailoring the therapeutic strategy					
EORTC /Lysa/Fil H10F Raemaekers, 2014 [1] **Funding:** Fonds Cancer (Belgium), Dutch Cancer Society (Netherlands), Institut National du Cancer, Fondation Contre le Cancer, Assistance Publique Hôpitaux de Paris, and Société Française de Médecine Nucléaire et Imagerie Moléculaire (France), Associazione Angela Serra (Italy), and Chugai Pharmaceutical (Japan).	CS I or II supradiaphragmatic, previously untreated HL with favourable profile. N=444 randomized Arm A: N=188 Arm B: N=193 Age: Arm A (median years): 31 Arm B (median years): 29.5 Gender: Arm A (male): 56.9% Arm B (male): 50.3% 2006 to 2010[a]	Arm B: 2xABVD + PET. If PET negative, 2 x ABVD and no radiotherapy. If PET positive 2xBEACOPP + 30 Gy INRT	Arm A: 3xABVD + 30 Gy INRT (PET only for comparison)	*PFS	1.1 years

Study name, author(s), year (ref) Funding	Population, Data collection period	Intervention(s)	Control(s)	Outcomes	Follow-up, median
EORTC /Lysa/Fil H10U Raemaekers, 2014 [1] **Funding: as above**	CS I or II supradiaphragmatic, previously untreated HL with unfavourable profile. N=693 randomized Arm A: N=251 Arm B: N=268 Age: Arm A (median, years): 31 Arm B (median, years): 33 Gender: male 50.1% 2006 to 2010[a]	Arm B (intervention): 2xABVD + PET. If PET positive, 2xBEACOPP + 30 Gy INRT	Arm A: 4xABVD + 30 Gy INRT. PET performed to all pts after cycle 2 with no change in treatment	*PFS	1.1 years
RAPID Radford 2015 [9] **Funding:** Leukaemia and Lymphoma Research, the Lymphoma Research Trust, Teenage Cancer Trust, and the U.K. Department of Health	Pts with HL CS IA and IIA, no B symptoms, no bulk who had received 3 cycles of ABVD and a PET scan. N=420 randomized 398 available for analysis Arm A: 209 Arm B: 211 Age (years): median 34 Gender: male 53.3% 2003 to 2010	Arm B: no further intervention (If PET positive: One more cycle of ABVD and IFRT)	Arm A: IFRT	OS *PFS	60 months

*Primary outcome

ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; AE = adverse events; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; COPP = cyclophosphamide, vincristine, procarbazine, and prednisone; CR = complete remission; CS = clinical stage; EBVP = epirubicin, bleomycin, vinblastine, and prednisone; EF = extended field radiotherapy; EFS = event-free survival; F = favourable; FFTF = freedom from treatment failure; HL = Hodgkin lymphoma; IFRT = involved field radiotherapy; INRT = involved node radiotherapy; MFRT = multiple fraction radiotherapy; MOPP-ABV = sequential mechlorethamine, oncovin, procarbazine, prednisone and doxorubicin, bleomycin, vinblastine; N = sample size; NR = not reported; OS = overall survival; PET = positron emission tonography; PFS = progression free survival; Pts = patients; RT = radiotherapy; STNI = subtotal nodal irradiation; U = unfavourable; VAPEC-B = doxorubicin, cyclophosphamide, etoposide, vincristine, and bleomycin with prednisolone and prophylactic cotrimoxazole or ketoconazole.

Table 1A. Radiotherapy question: Summary results of included RCTs comparing chemotherapy + radiotherapy with chemotherapy alone for early-stage Hodgkin lymphoma

Study name, author(s), year (ref)	Intervention Control	OS median	EFS, median	PFS median	Late AE
NCIC CTG/ECOG H.6 Meyer, 2012, 2005 [7,8] Macdonald, 2007 [57]	Arm A: ABVD only Arm B: STNI with or without chemotherapy.	94% vs 87%; HR for death 0.50; 95% CI, 0.25 to 0.99; p=0.04	At 12 yrs 85% vs 80%, HR 0.88 (95% CI 0.54 to 1.43)	87% vs 92% HR 1.91 (95% CI 0.99 to 3.69, p=0.05)	Death: 6.1% vs 8.8% Second cancers: 5.1% vs 11.33
RAPID Radford 2015 [9]	Subgroup of patients who had received 3 cycles of ABVD and had PET negative scan for residual disease: Arm A: IFRT Arm B: no further intervention (If PET positive: One more cycle of ABVD and IFRT)	At 3 yrs: 97.1% (95% CI, 94.8 to 99.4) vs 99.0% (95% CI, 97.6 to 100), RR 0.51 (95% CI, 0.15 to 1.68) (p=0.27)	*nr*	At 3 yrs*: 94.6% (95% CI 91.5 to 97.7) vs 90.8% (95% CI, 86.9 to 94.8) RR 1.57 (95% CI 0.84 to 2.97), P=0.16. Risk difference -3.8 (95% CI, -8.8 to 1.3) (this exceeds the margin for noninferiority of -7%)	*nr*
EORTC-GELA H9F Thomas, 2007 [abs] [10]	Arm A: 36 Gy IFRT + 6xEBVP Arm B: 20 Gy IFRT + 6xEBVP Arm C: No RT + 6xEBVP (arm stopped early because >20% events)	At 4 years: 98% vs 98% vs 98%	At 4 years: Arm A: 87% Arm B: 84% Arm C: 70% p<0.001	*nr*	*nr*

* The results presented in the table are for the intention-to-treat population

Abs = abstract; ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; AE = adverse events; CI = confidence interval; EBVP = epirubicin, bleomycin, vinblastine, and prednisone; F = favourable; EFS = event free survival; HR = hazard ratio; IFRT = involved field radiotherapy; *nr* = not reported; OS = overall survival; PET = positron emission tonography; PFS = progression free survival; RR = rate ratio; RT = radiotherapy; STNI = subtotal nodal irradiation; vs = versus; yrs = years.

In addition to the studies presented in Table 1A, Hay et al. [43] conducted an exploratory individual patient-data comparison including 406 patients from the H.6 trial [7] treated with ABVD only, and 182 patients from the GHSG HD10 [17] and HD11 [16] studies treated with chemotherapy and radiotherapy combination treatment.

The authors estimated that time to progression (TTP) at eight years follow-up was superior for patients treated with the combination modality (93%) than those treated with chemotherapy only (87%), (HR 0.44; 95% CI, 0.24 to 0.78). As well, the PFS was better for patients allocated to combination treatment (89% vs 86% respectively, (HR 0.71; 95% CI, 0.42 to 1.18). The eight-year overall survival (OS) estimates were 95% in both groups.

Table 1B. Radiotherapy question: Summary results of included RCTs comparing low-dose with high-dose radiotherapy for early-stage Hodgkin lymphoma

Study name Authors, Year (ref)	Intervention Control	OS	FFTF	PFS	EFS	Late AE	Response
GOELAMS H 97E Arakelyan, 2010 [18]	Arm A (experimental): 3xABVD + 36 Gy radiation to initially involved sites and 24 Gy to adjacent sites, the upper infra-diaphragmatic area, and the spleen. Arm B (control arm): 3 cycles ABVD + same irradiation as Arm A administered at doses of 40 Gy and 30 Gy, respectively.	At10 yrs follow-up: 97.8% ±3.1% vs 95% ± 4.9%, p=NS	88.6%±11.4% vs *92.6%±5.9% p = NS	*nr*	*nr*	At 10 yrs follow-up: Life-threatening events: 0% vs 15.5% ±5.3%, p<0.003	*nr*
GHSG HD11 Eich, 2010 [16]	Arm A:4xABVD+IFRT 30 Gy (standard treatment) Arm B:4xABVD+IFRT 20 Gy Arm C:4xBEACOPP+30 Gy IFRT Arm D: 4 x BEACOPP+20 Gy IFRT	p=NS (P values *nr*)	4xBEACOPP arm: 20 Gy was noninferior to 30 Gy n=669, at 5 yrs, difference -0.8%; 95% CI -5.8% to 4.2%.(Treatment was noninferior) 4xABVD arm n=682, 20 Gy vs 30 Gy: -4.7%, 95% CI, -10.3% to 0.8% (Treatment was not noninferior) †B vs A: HR 1.39; 95% CI, 0.98 to 1.97; p=0.06.	†B vs A: HR 1.49; 95% CI, 1.04 to 2.15; p=0.03; (ABVD +20 Gy was not noninferior to the standard) †C and D vs A: NS	*nr*	Secondary neoplasias (Rt comparison): 3.4% vs 4.0 (p=NS) Death: 6.5% vs 6.2%	CR: 94.5% vs 93.8% p=NS
GHSG HD10 Engert, 2010 [17]	Arm A 4xABVD+IFRT 30 Gy Arm B 4xABVD+IFRT 20 Gy Arm C 2xABVD+IFRT 30 Gy Arm D 2xABVD+IFRT 20 Gy	A and C at 8 yrs: 94.9 (92.2 to 96.6) B and D: 95.6 (93.2 to 97.1) HR for death, 0.86;95% CI, 0.49 to 1.53, p=0.61	*At 5 yrs: A and C: 93.4% (95% CI 91.0 to 95.2) B and D: 92.9% (95% CI, 90.4 to 94.8), HR 1.00 (95% CI, 0.68 to 1.47). Group difference (B and D vs A and C) -0.5 % (95% CI, -3.6 to 2.6). The 7% inferiority of 20 Gy can be excluded.	A and C at 8 yrs: 88.1 (84.1–91.2) B and D: 88.9 (85.4 to 91.6)	*nr*	Secondary neoplasia: Arms A and C:5.4% Arms B and D:4.1% (P=0.34) Death: (Arms A and C 4.3%; Arms B and D: 3.7% (p=NS)	CR: A and C: 99% B and D: 97.4% (p=NS)
EORTC-GELA H9 Thomas, 2007 [abs] [10]	Arm A: 36 Gy IFRT + 6xEBVP Arm B: 20 Gy IFRT + 6xEBVP Arm C: No RT + 6xEBVP + 30 Gy IFRT (arm stopped early)	98% vs 98% vs 98%	*nr*	*nr*	87% vs 84% vs 70% (p<0.001)	*nr*	*nr*

†The single experimental arms (arms B, C, and D) were compared with the standard arm (arm A) in a Cox regression model, together with all candidate prognostic factors.

Abs = abstract; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; AE = adverse events; BEACOPP = bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, prednisone; CI = confidence interval; CR = complete response; EBVP = epirubicin, bleomycin, vinblastine, prednisone; EFS = event free survival; FFTF = freedom from treatment failure; HR = hazard ratio; IFRT = involved field radiotherapy; *nr* = not reported; NS = not significant; OS = overall survival; PFS = progression free survival; ref = reference; Rt = radiotherapy; vs = versus; yrs = years.

Early adverse events:

The GHSG HD10 and HD11 studies reported on early adverse events related to radiotherapy treatment.

Patients experienced significantly more severe grade 3 or 4 adverse effects when treated with 30 Gy than with 20 Gy: 8.7% versus 2.9%, $P<0.001$ in the GHSG HD10 study [17], and 12% vs 5.7%, $p<0.001$ in the GHSG HD11 study [16].

Table 1C. Radiotherapy question: Summary results of RCTs comparing smaller with larger radiotherapy field.

Study name, Authors, Year (ref)	Intervention Control	OS	FFTF	PFS	EFS, median (months)	Late AE	Response
GHSG HD8							
Engert, 2003 [14], Eich, 2005 [59], Klimm, 2007 [58], Engert, 2004 [abs] [55], Sasse, 2102 [56]	Arm A: COPP + ABVD 30 Gy EF +10 Gy to bulk Arm B: COPP + ABVD 30 Gy IF + 10 Gy to bulk	90.8% vs 92.4%; difference EF-IF=-1.6 (95% CI, -5.6 to 2.5, p=*nr)*	85.8% vs 84.2% (difference 1.6%, upper boundary 5.9%) IFRT was not inferior to EFRT – margin at 6%	79.8% vs 80.0%, (95% CI, −5.2% to 5.6%; p=NS)	*nr*	SN: 4.6% vs 2.8%, P=0.191 Deaths: 8.1% vs 6.4% p=0.344	CR: 98.5% vs 97.2%
Bonadonna, 2004 [13], Viviani, 2012 [abs] [54]	Arm A: ABVD + 30.6 Gy STNI Arm B: ABVD + up to 40 Gy IFRT	96%, (95% CI, 91% to 100%) vs 94%, (95% CI, 89% to 100%)	*nr*	93% (95% CI, 83% to 100%) vs 94%, (95% CI, 88% to 100%)	At 12 yrs: 87%, (95% CI, 85% to 98%) vs 91%, (95% CI, 85% to 98%)	*nr*	CR: 100% vs 97%
EORTC GELA H8U Ferme, 2007 [11]	Arm A: 6xABV + IFRT Arm C: 4xMOPP-ABV + STNI	At 10 yrs 88% (95%CI 84 to 91) vs 85% (95% CI 78 to 90) vs 84% (95% CI 74 to 90)	*nr*	*nr*	*At 10 yrs: 82% (95% CI, 77% to 86%) vs 80% (95% CI, 75% to 85%) vs 80% (95% CI, 71% to 86%)	SN: 4% vs 5% vs 4% Death: 11% vs 11% vs 10%	75% vs 78% vs 78%

Abs = abstract; ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; AE = adverse events; CI = confidence interval; COPP = cyclophosphamide, vincristine, procarbazine, and prednisone; CR = complete remission; EF = extended field; EFS = event free survival; EFRT = extended field radiotherapy; FFTF = freedom from treatment failure; IF = involved field; IFRT = involved field radiotherapy; MOPP-ABV = mechlorethamine, oncovin, procarbazine, prednisone and doxorubicin, bleomycin, vinblastine; *nr* = not reported; NS = not significant; OS = overall survival; PFS = progression free survival; SN = second neoplasms; STNI = subtotal nodal irradiation; U = unfavourable.

Early Adverse Events

Nine per cent of patients in the EORTC-GELA H7F study's extended field radiotherapy group [12] experienced treatment related death (i.e., death during treatment) versus 0% of those in the involved field group (p values not reported).

In the GHSG HD8 study [14], patients allocated to extended field radiotherapy experienced significantly higher all-grades adverse effects: nausea (62.5% versus 29.1%; p<0.001), pharyngeal toxicity: 49.1% versuss 40.5%; p=0.001, leukopenia: 49.1% vs 33.3%; P<0.001, thrombocytopenia: 16.7% and 5.5%; P<0.001, gastrointestinal toxicity:17.5% vs 4.1%; P<0.001.

Table 1D. Radiotherapy question: Summary results of RCT comparing smaller radiotherapy field + chemotherapy with larger field radiotherapy.

Study name, Authors, Year (ref)	Intervention Control	OS	PFS	EFS, median	Late AE	Response
EORTC GELA H7F Noordijk, 2006 [12]	Arm A: STNI Arm B: 6 x EBVP + IFRT	At 10 yrs; 92% (95% CI, 85% to 95%) vs 92% (95% CI, 84% to 95%, p=0.79)	*nr*	At10 years: 78%, (95% CI, 70% to 83%) vs 88%, (95% CI, 82% to 92%; difference p=0.0113)	SN: 10-yr cumulative rate: 2.3%, (95% CI, 0.7% to 7.4%) vs 2.9%, (95% CI, 0.9% to 9.0%)	CR: 94% vs 91%, NS
EORTC-GELA H8F Ferme, 2007 [11], Heutte, 2009 [52]	Arm A: STNI Arm B: a combination of 3 cycles of MOPP-ABV + IFRT	At 10 years: 92% (95% CI, 87% to 95%) vs 97% (95% CI, 92% to 99%, p= 0.001)	*nr*	At 10 years 68% (95% CI, 64% to 76%) vs 93% (95% CI, 85% to 97%, p<0.001)	SN: 2% vs 2% Death: 7% vs 1%	CR: 73% vs 79%
NCRI LY07 Thistlethwaite, 2007 [abs] [15]	Arm A: MFRT Arm B: minimal initial chemotherapy (i.e., 4 wks of VAPEC-B) + IFRT	At 5 years: A: 93% B: 97% (HR=0.45, 95% CI, 0.17-1.20, p=0.11)	[A]At 5 years: A: 72% B: 88%, (HR=0.38, 95% CI, 0.23-0.65, p=0.0004)	*nr*	*nr*	CR at completion of treatment: A: 91% B: 90%

*Primary outcome

[A] The Authors also explored the association between Hansenclever score and treatment on PFS. They found an interaction between Hasenclever score (0,1 *vs* ³2) and treatment on PFS (*p*=0.058).

Abs = abstract; AE =adverse events; CI = confidence interval; CR = complete remission; EBVP = epirubicin, bleomycin, vinblastine, and prednisone; EFS = event free survival; F = favourable; HR = hazard ratio; IFRT = involved field irradiation; MFRT = multiple fraction radiotherapy; MOPP-ABV = sequential mechlorethamine, vincristine, procarbazine, and prednisone and doxorubicin, bleomycin, vinblastine; *nr* = not reported; NS = not significant; OS = overall survival; PFS = progression free survival; ref = reference; SN = second neoplasms; STNI = subtotal nodal irradiation; VAPEC= doxorubicin, cyclophosphamide, etoposide, vincristine, and bleomycin with prednisolone and prophylactic cotrimoxazole or ketoconazole; vs = versus; yrs = years.

Table 1E. Radiotherapy question: Summary results of RCTs testing the use of PET for tailoring the therapeutic strategy.

Study name, Authors, Year (ref)	Intervention Control	OS	PFS
EORTC /Lysa/Fil H10F Raemaekers, 2014 [1]	Arm A (control): 3xABVD + 30 Gy INRT (PET only for comparison) Arm B: 2xABVD + PET. If PET negative, 2xABVD and no radiotherapy. If PET positive 2xBEACOPP + 30 Gy INRT	*nr*	[A]At 1 yr: 100% vs 94.9% (1 vs 9 events). futility was declared p = 0.017 (<0.102), (one-sided significance level), Estimated HR 9.36; 79.6% CI, 2.45 to 35.73.
EORTC /Lysa/Fil H10U Raemaekers, 2014 [1]	Arm A (control): 4xABVD + 30 Gy INRT. PET performed to all pts after cycle 2 with no change in treatment Arm B (intervention): 2xABVD + PET. If PET positive, 2 x BEACOPP + 30 Gy INRT.	*nr*	[A]97.3% vs 94.7% (7 vs 16 events) futility was declared (p=0.026 [<0.098]), (one-sided significance level), Estimated HR 2.42; 84% CI, 1.35 to 4.36
RAPID Radford 2015 [9]	If PET negative: Arm A: IFRT Arm B: no further intervention If PET positive: One more cycle of ABVD and IFRT	At 3 yrs: 97% vs 99.5% (p values *nr*)	93.8% vs 90.7%, risk difference-2.9%, (95% CI, -10.7% to 1.4%; this exceeds the margin for noninferiority of -7%)

[A]The interim futility analysis was conducted among 1,124 of the 1,137 randomized patients.
ABVD = Doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CI = confidence interval; F = favourable; HR = hazard ratio; INRT = involved-node radiotherapy; IFRT = involved field radiotherapy; *nr* = not reported; OS = overall survival; PET = positron emission tomography; PFS = progression free survival; pts = patients; ref = reference; U = unfavourable; yrs = years.

Studies that discuss both radiotherapy and chemotherapy questions.

The study reported by Hamed et al. [19] (classified among the chemotherapy studies in the following paragraphs) reported that acute grade 3 or 4 adverse effects from radiotherapy treatment were observed more often among patients treated with 30 Gy than with patients treated with 20 Gy of IFRT: 16% versus 2.5%, p=0.03. The most common sites of grade 3 adverse effects were the skin, mucous membranes, and pharynx.

Study Design, Quality, and Outcomes

All included studies [1,7,9-18,53] were randomized controlled trials (RCTs). All but four, which were conference abstract publications [9,10,15,53], were represented by at least one fully published article.

Figures 1A and 1B show the results of quality assessment of the included studies performed using the Cochrane Risk of Bias tool [60]. Three studies declared that they were not blinded [7,17,25], and the other studies did not report blinding. The quality of the included studies was otherwise high.

The abstract of the EORTC-GELA H9F study reported by Thomas et al. [10] and the abstract report by Thistlethwaite, et al. [15] did not present enough data to evaluate study quality. As well, the abstract report by Specht et al. [53] presents the long term follow-up of an older study, and it does not report enough data to evaluate its quality. These abstracts, although presented at conferences some time ago, were never fully published. The results of the abstracts that are not included in the tables will be discussed in the text before the section on ongoing trials (see Table 3).

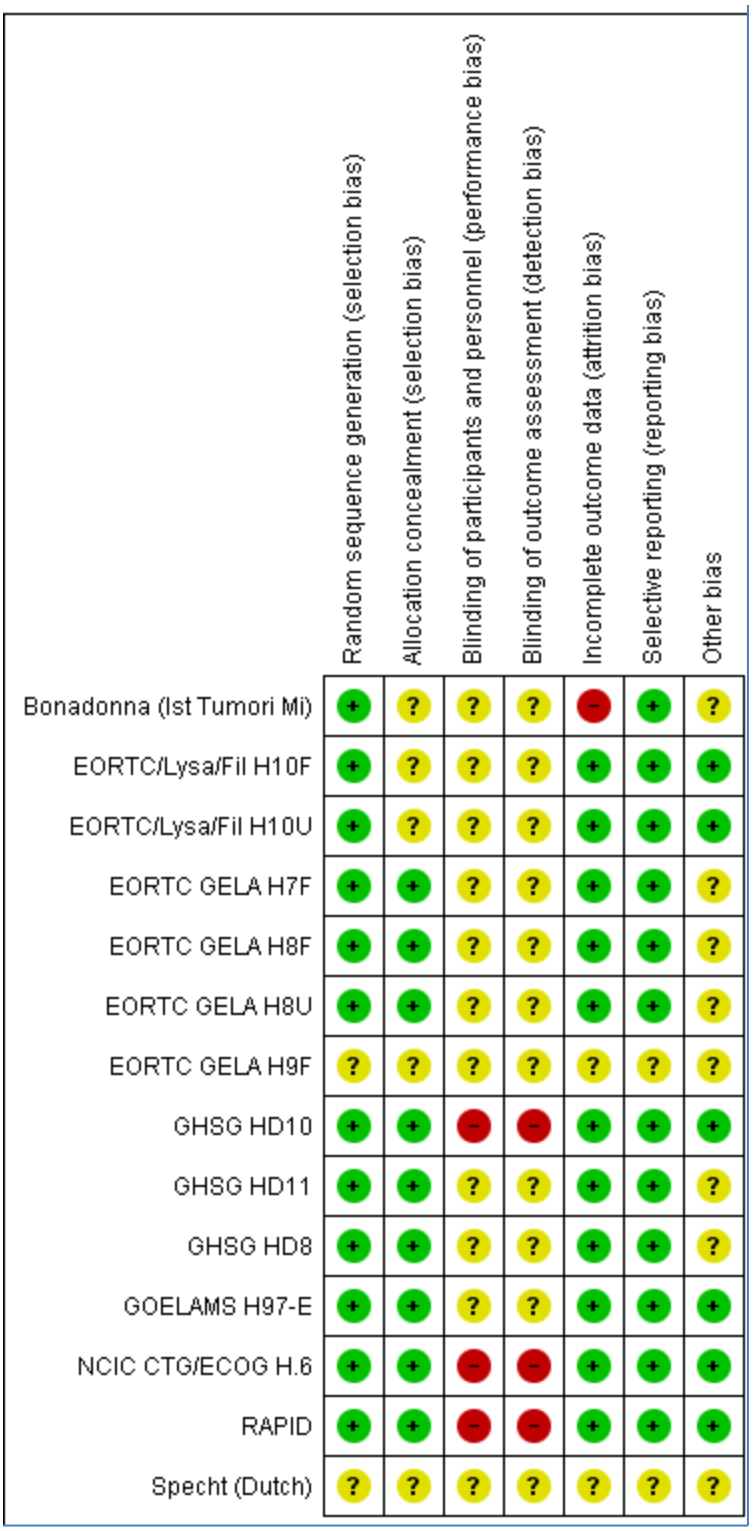

Figure 1A. Risk of bias summary [60] for randomized controlled trials of the radiotherapy management of early-stage Hodgkin lymphoma: review authors' judgements about each risk of bias item for each included study

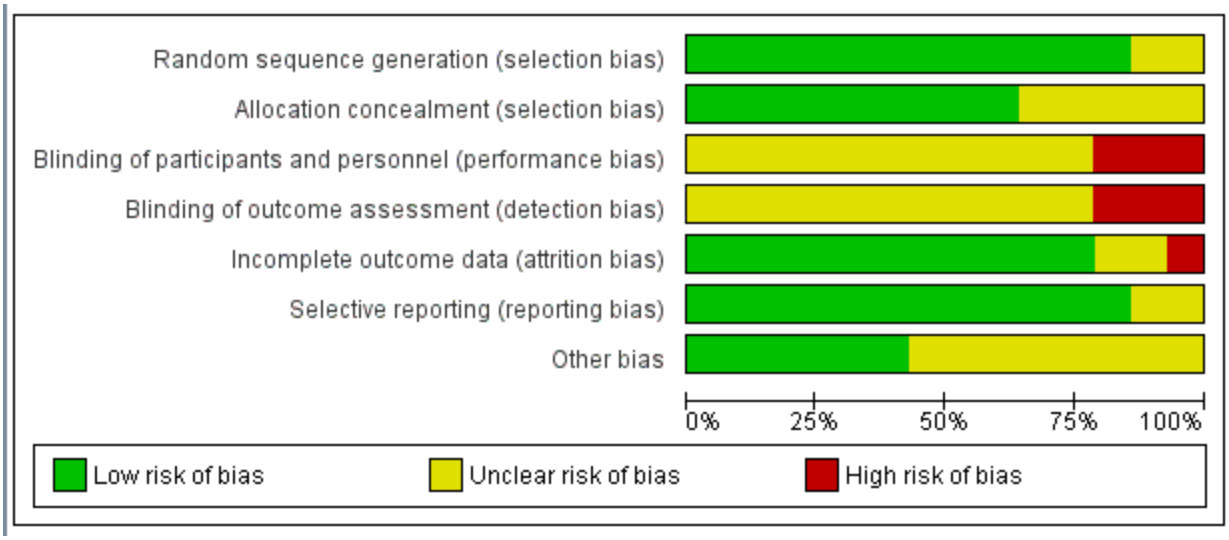

Figure 1B. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Quality was further rated outcome by outcome across studies according to the GRADE methodology [37]. The members of the Working Group considered the outcomes relevant to each comparison (Appendix 6) and classified them according to their importance. Only the critical and important outcomes are considered for quality assessment. For each critical outcome, the categories of "Risk of Bias," "Inconsistency," "Indirectness," "Imprecision," and "Other considerations" are examined. Tables 2A to 2E present the results of the outcome by outcome assessment and the summary results.

Radiotherapy Question Summary Results for Comparison A: RCTs of Chemotherapy Alone versus Chemotherapy plus Radiotherapy

One study, the NCIC CTG/ECOG H.6, represented by three publications [7,8,57] reported on this comparison. One study reported on this comparison on the subgroup of patients who had negative PET scans [9]. Meyer et al. [7,8,57] randomized 399 patients with early-stage HL to ABVD alone or to subtotal nodal irradiation (STNI) alone or with ABVD depending on whether they had a favourable or an unfavourable profile, and reported results at 4.2 and 11.3 years of follow-up. This study found a large beneficial treatment effect for OS at 11.3 years of follow-up (see Tables 1A and 2A for detailed numerical data), and the authors concluded that ABVD alone was associated with a higher rate of OS than STNI alone or in combination with chemotherapy because of a lower rate of death from other causes. Radford et al. [9] did not detect noninferiority for the chemotherapy only strategy in PFS.

The members of the Working Group considered OS, EFS, PFS, and late adverse events as critical outcomes and rated the quality of this body of evidence as moderate for OS and late adverse events, and low for EFS and PFS. In fact, despite the large beneficial effect for OS, this was only one study with less than 300 events; the radiotherapy procedure of this trial is no longer used in clinical practice, and Working Group members thought that 12 years of follow-up were not enough to assess long-term adverse events.

Overall Quality of Evidence for Comparison A: Chemotherapy Alone versus Chemotherapy plus Radiotherapy

The overall body of evidence for this comparison was considered to be of moderate quality.

Table 2A. Radiotherapy question: Quality and summary of findings of critical outcomes. RCTs of chemotherapy alone compared with chemotherapy plus radiotherapy

Quality assessment						№ of patients		Effect		Quality	Importance
№ of studies (participant)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy alone	Chemotherapy plus Radiotherapy	Relative (95% CI)	Absolute (95% CI)		
Overall Survival (follow-up: median 12 years; assessed with: survival)											
1 (399)	not serious [A]	not serious	serious[B]	serious[C]	strong association	184.24/196 (94.0%)	176.61/203 (87.0%)	**ECOG H.6** [7] at 12 yrs **HR 0.5** (95% CI, 0.25 to 0.99, p=0.04)	231 fewer per 1000 (from 3 fewer to 470 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Event-free-survival (follow-up: median 12 years; assessed with: disease progression or death)											
1 (399)	not serious	not serious	serious[B]	serious[C]	none	167/196 (85.2%)	162/203 (79.8%)	**ECOG H.6** [7] at 12 yrs **HR 0.88** (95% CI, 0.54 to 1.43, p=0.6)	43 fewer per 1000 (from 100 more to 220 fewer)	⊕⊕◯◯ LOW	CRITICAL
Progression-free-survival (follow-up: median 12 years; assessed with: disease progression)											
1 (399)	not serious	not serious	serious[B]	serious[C]	none	170.52/196 (87.0%)	186.76/203 (92.0%)	**ECOG H.6** [7] at 12 yrs **HR 1.91** (95% CI 0.99 to 3.69) p=0.05	72 more per 1000 (from 2 fewer to 80 more)	⊕⊕◯◯ LOW	CRITICAL
Late adverse events (follow-up: median 12 years; assessed with: death)											
1 (399)	not serious [A]	not serious	serious[B]	serious[D]	strong association	Death: 12/196 (6.1%) Second cancers: 5.1%	Death: 24/203 (11.8%) Second cancers: 11.33%	**ECOG H.6** [7] not estimable	not estimable	⊕⊕⊕◯ MODERATE	CRITICAL

[A] The trial was not blinded. However not likely to bias a hard outcome such as overall survival.
[B] The procedure has been superseeded by IFRT - reason for the study to be stopped early.
[C] Only one study, with less than 300 events.
[D] 12 years is not long enough to observe this kind of adverse events.
[E] DThe trial was not blinded.
[F] This study was considering only a subpopulation of patients who had a post-chemotherapy negative PET scan.
[G] This study had less than 300 events.
CI = confidence interval; HR = hazard ratio; IFRT = involved field radiotherapy; yr(s) = year(s)

Radiotherapy Question Summary Results for Comparison B. RCTs of Low Radiotherapy (RT) Dose versus High RT dose

Three studies, the GHSG HD10 [17], the GHSG HD11 [16], and the Groupe Ouest-Est d'Études des Leucémies et Autres Maladies du Sang (GOELAMS) H97E [18], represented by three publications, reported on this comparison. The population of the three studies comprised patients with early-stage, HL with favourable [17,18], or unfavourable [16] prognosis. Tables 1B and 2B present detailed numerical results.

The authors compared a 20 Gy with 30 Gy radiotherapy dose with two of four cycles of chemotherapy, ABVD [16,17], or BEACOPP [16], or they compared a reduced dose of 36 Gy to involved sites with a standard dose of 40 Gy in addition to ABVD [18].

No statistically significant between-group difference was detected for OS, by any of the studies.

All of the studies were planned with FFTF as primary outcome. In the GHSG HD10 study [17], at eight years follow-up, inferiority of 20 Gy versus 30 Gy radiotherapy could be excluded for FFTF. In the GHSG HD11 study [16], inferiority of 20 Gy could not be excluded at five years after treatment with four cycles of ABVD, but 20 Gy was not inferior to 30 Gy after treatment with four cycles of BEACOPP. The GOELAMS H97E study [18] did not detect any difference in FFTF between groups at 10 years follow-up.

For PFS, the GHSG HD10 did not report p values and hazard ratios, while in the GHSG HD11 trial, when the two radiotherapy dosages were compared in the groups treated with ABVD, inferiority of the 20 Gy treatment could not be excluded.

The authors of the included studies concluded that in early-stage HL with favourable diagnosis, treatment with two or three cycles of ABVD plus a low dose of IFRT (20 Gy [17] or 36 Gy [18]) is as effective as, and less toxic than four cycles of ABVD plus 30 Gy of IFRT [17,18]. For patients with unfavourable prognosis, the authors of the included studies concluded that the best treatment should be four cycles of ABVD plus 30 Gy of IFRT [16].

The members of the Working Group considered the body of evidence for OS, FFTF, and PFS of high quality, and the body of evidence for late adverse events of moderate quality. Working Group members considered eight years of follow-up insufficient to detect late adverse events related to radiotherapy.

Other outcomes

The following results are for outcomes that the Working Group members considered less than critical:

Response

The GHSG HD11 study [16] and GHSG HD10 study, [17] found a difference that was not statistically significant between low dose and high dose radiotherapy: complete response (CR) was 93.7% versus 94.5% (p=not significant) and 97.4% versus 99% (p=not significant) respectively.

Acute Adverse Effects

Engert et al. [17] reported that in the GHSG HD10 study, grade 3 or 4 acute toxicity was observed more often in patients who received 30 Gy than in patients who received 20 Gy (8.7% versus 2.9%, $p<0.001$). In the GHSG HD11 study, adverse effects were reported more frequently in the groups more heavily treated [16].

Overall Quality of Evidence for Comparison B: RCTs of Low Radiotherapy (RT) dose versus High RT dose

The overall body of evidence for this comparison was considered of high quality.

Table 2B. Summary of findings and quality for critical outcomes. RCTs of low radiotherapy dose compared with high radiotherapy dose.

Quality assessment						Effect[A]		Quality	Importance
№ of studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low Rt dose	High Rt dose		
Overall Survival (assessed with: deaths)									
3 (2773)	not serious	not serious	not serious	not serious	none	**GHSG HD10** [17] at 8 yrs		⊕⊕⊕⊕ HIGH	CRITICAL
						Arms B and D (20Gy): 95.6% (95% CI, 93.2% to 97.1%) HR for death, 0.86, (95% CI, 0.49 to 1.53, p=0.61)	Arms A and C: 94.9% (95% CI, 92.2% to 96.6%)		
						GHSG HD11 [16] at 5 yrs			
						NS	*nr* (p values NS)		
						GOELAMS H 97E [18] at 10 yrs			
						97.8% ± 3.1%	95% ± 4.9% (p values NS)		
Freedom from treatment failure (assessed with: time from the start of chemotherapy to progression during radiotherapy, lack of complete remission at the end of treatment, relapse, or death from any cause)									
3 (2117)	not serious	not serious	not serious	not serious	none	**GHSG HD10** [17] at 8 yrs		⊕⊕⊕⊕ HIGH	CRITICAL
						*Arms B and D (20 Gy): 88.6%, (95% CI, 85.1% to 91.3%)	Arms A and C (30 Gy): 87.8%, (95% CI, 83.8% to 90.9%) HR 1.00, (95% CI, 0.68 to 1.47)		
						Group difference (B and D vs A and C) -0.5 % (95% CI,-3.6 to 2.6). The 7% inferiority of 20 Gy can be excluded.			
						GHSG HD11 [16] at 5 yrs			
						*Arms C and D (after 4 cycles of BEACOPP): 20 Gy was not inferior to 30 Gy; difference -0.8%, (95% CI, -5.8% to 4.2%) Arms A and B (after 4 cycles of ABVD): Inferiority of 20 Gy cannot be excluded: difference -4.7%, (95% CI, -10.3% to 0.8%) †B vs A: HR 1.39, (95% CI, 0.98 to 1.97, p=0.06)			

Quality assessment						Effect[A]		Quality	Importance
№ of studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low Rt dose	High Rt dose		
						GOELAMS H 97E [18] at 10 yrs			
						*88.6%±11.4%	92.6%±5.9% (p values NS)		
Progression Free Survival (follow-up: median 82 months; assessed with: survival until progression, relapse, or death from any cause)									
2 (2940)	not serious	not serious	not serious	not serious	none	**GHSG HD10** [17] at 8 yrs		⊕⊕⊕⊕ HIGH	CRITICAL
						B and D: 88.9% (95% CI, 85.4% to 91.6%)	A and C: 88.1% (95% CI, 84.1% to 91.2%) HR and p values *nr*		
						GHSG HD11 [16]			
						†B vs A: HR 1.49, (95% CI, 1.04 to 2.15, p=0.03); ABVD +20 Gy vs ABVD + 30 Gy: inferiority of 20 Gy regimen could not be excluded †C and D vs A: NS			
Late Adverse Events (assessed with: radiotherapy related long term adverse events,i.e., secondary neoplasias)									
2 (2940)	not serious	not serious	not serious	not serious	none	**GHSG HD11 [16]**		⊕⊕⊕○ MODERATE	CRITICAL
						Secondary neoplasia (median follow-up 82 months)			
						3.4%	4.0 (p values NS)		
						Death (median follow-up 91 months)			
						6.5%	6.2%		
						GHSG HD10 [17]			
						Secondary neoplasia (median follow-up 7.5 yrs)			
						Arms B and D:4.1%	Arms A and C:5.4%		
						Death (median follow-up 7.5 yrs)			
						Arms B and D: 3.7%	Arms A and C 4.3%;(p=0.34)		

* Primary outcome;
†The individual experimental arms (arms B, C, and D) were compared with the standard arm (arm A) in a Cox regression model, together with all candidate prognostic factors.
[A]The statistical pooling of the results was not performed owing to the heterogeneity of the included studies, therefore results are presented separately for each study

BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; CI = confidence interval; HR = hazard ratio; Gy = gray; nr=not reported; OS = overall survival; RT = radiotherapy; yrs=years.

Abstract publication:

The study by Thomas et al. [10] reports the findings of the EORTC GELA H9F (favourable) and H9U (unfavourable) studies. The H9U is not relevant to this section because it answers a chemotherapy question solely, and it will be discussed later. In the H9F study 619 patients were randomized to 36 Gy IFRT plus six cycles epirubicin, bleomycin, vinblastine, and prednisone (EBVP) (Arm A) or to 20 Gy IFRT plus six cycles EBVP (Arm B) or no RT plus six cycles EBVP (Arm C: stopped early).

At four years, EFS rates were 87% in the 36 Gy and 84% in the 20 Gy arm; they were 70% in the 0 Gy arm ($p<0.001$), and the OS rate was 98% in all three arms. The authors' conclusion was that for patients with favourable early-stage HL who had achieved complete remission after six cycles of EBVP, the omission of IFRT results in unacceptable failure rates, while an IFRT dose reduction from 36 Gy to 20 Gy gives equivalent results. Among the included studies, this was the only one providing data on EFS.

Radiotherapy Question Summary Results for Comparison C: Smaller Compared with Larger Radiotherapy Field

Three studies, the GHSG HD8, the EORTC-GELA H8U, and the Bonadonna study, represented by eight publications [11,13,14,54-56,58,59], reported on this comparison. The population of these two studies included patients with early-stage HL with favourable [14] and unfavourable [11,13,14] prognosis. Tables 1C and 2 C present detailed numerical results.

In the included studies patients were treated with two cycles of cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) and ABVD plus 30 Gy extended field radiotherapy (EFRT) or 30 Gy IFRT [14], with ABVD plus STNI or IFRT [13] and with four cycles of sequential mechlorethamine, oncovin, procarbazine, prednisone and doxorubicin, bleomycin, vinblastine (MOPP-ABV) plus IFRT or STNI [11]. The GHSG HD8 trial was planned with FFTF as the primary outcome, the EORTC-GELA H8U trial was planned with EFS as the primary outcome, while the Bonadonna study did not present a power calculation and stated that the study was underpowered to test for noninferiority.

None of the three studies reported a statistically significant between-group difference for overall survival.

The GHSG HD8 study found that IFRT was noninferior to EF and found no statistically significant difference in late adverse events at 55 months.

The members of the Working Group considered the body of evidence for OS, FFTF, and late adverse events of moderate quality because of risk of bias, indirectness, and imprecision; the body of evidence for EFS was considered of low quality because of high risk of bias.

Overall quality of evidence for Comparison C: smaller compared with larger radiotherapy field

The overall body of evidence was considered of moderate quality because of risk of bias, indirectness and inconsistency.

Table 2C. Radiotherapy question: Quality and summary of findings for critical outcomes. RCTs of smaller compared with larger radiotherapy field.

Quality assessment						Summary of findings		Quality	Importance
№ of studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Smaller radiotherapy field	Larger radiotherapy field		
Overall survival (assessed with: death from any cause)									
3 (2194)	not serious[1]	not serious	serious[2]	not serious	none	**GHSG HD8** [14] at 5 yrs		⊕⊕⊕◯ MODERATE	CRITICAL
						92.4%	90.8% difference EF-IF=-1.6; (95% CI, -5.6 to 2.5; p=NS)		
						Bonadonna et al. [13]			
						94% (95% CI, 89% to 100%)	96% (95% CI, 91% to 100%)		
						EORTC GELA H8U [11] at 10 yrs:			
						6x chemo + IFRT: 88% (95% CI, 84% to 91%) 4 x chemo + IFRT: 85% (95% CI, 78% to 90%)	4x chemo + STNI 84% (95% CI, 74% to 90%, p=0.93)		
Freedom from treatment failure (follow-up: median 5 years; assessed with: time from the start of radiotherapy to the first of: progression during radiotherapy, lack of complete remission at the end of treatment, relapse or death from any cause)									
1 (1064)	serious[1]	not serious	not serious	serious[3]	none	**GHSG HD8** [14] at 5 yrs		⊕⊕⊕◯ MODERATE	CRITICAL
						*84.2%	85.8% difference 1.6%, IF was not inferior to EF – margin at 6%		
Progression free survival (assessed with: Time from start of therapy until progression, relapse or death from any cause[A])									
2 (1198)	serious[4,5]	not serious	serious[2]	not serious	none	**GHSG HD8** [14] at 5 yrs		⊕⊕◯◯ LOW	CRITICAL
						[A] 80.0%	79.8% (95% CI, −5.2% to 5.6%, p=NS)		
						Bonadonna et al. [13]			

Quality assessment						Summary of findings		Quality	Importance
№ of studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Smaller radiotherapy field	Larger radiotherapy field		
						93% (95% CI, 83% to 100%)	94% (95% CI, 88% to 100) %, p values *nr*		
Event Free Survival (assessed with: progressive disease, relapse, or death from any cause)									
2 (1132)	serious[4,5]	not serious	not serious	not serious	none	**Bonadonna et al. [13]** at 12 yrs		⊕⊕◯◯ LOW	CRITICAL
						91%, (95% CI, 85% to 98%)	87%, (95% CI, 85% to 98%)		
						EORTC-GELA H8U [11] at 10 yrs:			
						*82% (95% CI, 77% to 86%) 80% (95% CI, 75% to 85%)	80% (95% CI, 71% to 86%; p values *nr*)		
Late adverse events (assessed with: second cancers and fertility long term outcomes)									
2 (2060)	not serious	not serious	not serious	serious[6]	none	**GHSG HD8** [14] median follow-up 55 months		⊕⊕⊕◯ MODERATE	CRITICAL
						2.8%	4.6% (p= 0.191)		
						EORTC-GELA H8U [11] at 10 yrs:			
						4.5% (95% CI, 2.5% to 7.9%) 7.1% (95% CI, 4.3% to 11.6%)	8.8% (95% CI, 4.3% to 17.3%; p=0.63)		

*Primary outcome
[A] data from Sasse et al., 2012 [56]
[1] All the studies were not blinded. Not serious for overall survival.
[2] Indirectness due to different populations (favourable and unfavourable), interventions (range of radiation fields), and chemotherapy backbones.
[3] Only one study with less than 300 events.
[4] Incomplete outcome data in the study reported by Bonadonna et al [13].
[5] Bonadonna et al [13] did a per protocol analysis after 8 months.
[6] 10 years of follow-up are not enough to detect late adverse events from radiotherapy.
Chemo= chemotherapy; CI = confidence interval; EF = extended field; IF = involved field; IFRT = involved field radiotherapy; *nr* = not reported; NS = not significant; STNI = subtotal nodal irradiation; U = unfavourable; yrs = years. yrs = years

Radiotherapy Question Summary Results for Comparison D: Narrow Radiotherapy Field plus Chemotherapy versus Large Radiotherapy Field

Two studies, the EORTC GELA H7F and the EORTC GELA H8F, represented by two publications [11,12], reported on this comparison. The population of the two studies comprised patients with early-stage HL with favourable prognosis [11,12]. Treatment included IFRT plus six cycles of EBVP compared with STNI [12], and a combination of MOPP-ABV and IFRT compared with STNI. Tables 1D and 2 D present detailed numerical results.

The two studies reported contrasting results for OS: at 10 years follow-up: no statistically significant between-group difference [12] versus a statistically significant benefit for patients in the combination group [11]. For EFS, both studies detected a statistically significant advantage for the combination therapy, and neither study detected a statistically significant between-group difference for second cancers at 10 years follow-up.

Overall Quality of Evidence for Comparison D: Narrow Radiotherapy Field plus Chemotherapy versus Large Radiotherapy Field

The members of the Working Group rated the quality of the evidence as moderate for all outcomes. See notes in Table 2D for explanations.

Table 2D. Radiotherapy question: Quality and summary of findings for critical outcomes. RCTs of smaller radiotherapy field plus chemotherapy compared with larger radiotherapy field alone.

Quality assessment						Summary of findings		Quality	Importance
№ of studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Narrower radiotherapy field + chemotherapy	Larger radiotherapy field		
Overall Survival (assessed with: death from any cause)									
2 (1247)	not serious	not serious	serious[1]	not serious	none	**EORTC-GELA H7F** [12] at 10 yrs:		⊕⊕⊕◯ MODERATE	CRITICAL
						*92% (95% CI, 84% to 95%)	92% (95% CI, 85% to 95%; p=0.79)		
						EORTC-GELA H8F [11] at 10 yrs:			
						*97% (95% CI, 92% to 99%)	92% (95% CI, 87% to 95%; p=0.001)		
Event free survival (assessed with: progressive disease, relapse, or death from any cause)									
2 (1247)	not serious	not serious	serious[1]	not serious	none	**EORTC GELA H7F** [12] at 10 yrs:		⊕⊕⊕◯ MODERATE	CRITICAL
						*88% (95% CI, 82% to 92%);	78% (95% CI, 70% to 83%) difference was significant (p=0.0113)		
						EORTC-GELA H8F [11] at 10 yrs			
						*93% (95% CI, 85% to 97%)	68% (95% CI, 64% to 76%; p<0.001)		
Late adverse effects (assessed with: Cumulative probability of second cancers at10 yrs)									
2 (1247)	not serious	not serious	not serious	serious[2]	none	**EORTC-GELA H7F** [12] at 10 yrs**:**		⊕⊕⊕◯ MODERATE	CRITICAL
						2.9% (95% CI. 0.9 to 9.0)	2.3% (95% CI. 0.7 to 7.4)		
						EORTC-GELA H8F [11] at 10 yrs			
						3.2% (95% CI, 1.2% to 8.0%)	3.4% (95% CI, 1.3% to 8.4%)		

*Primary outcome

1. Differences in populations, and interventions
2. 10 years follow-up are not enough to detect adverse events due to radiotherapy treatment.

CI = confidence interval; F = favourable; yr = year

Abstract Publications

Thistlethwaite et al. 2007 [15] randomized patients to mantle field radiotherapy (MFRT) (Arm A) or minimal initial chemotherapy with doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, and prednisolone plus involved field radiation therapy (IFRT). Outcomes were OS, PFS, CR, and interaction between Hansenclever score and treatment. At a median follow-up of 84 months, the five-year PFS was 72% in arm A and 88% in arm B (HR 0.38; 95% CI, 0.23 to 0.65; p=0.0004). The five-year OS was 93% in arm A and 97% in arm B (HR 0.45; 95% CI, 0.17 to 1.20; p=0.11). The hazard ratio (HR) was 0.26, p<0.001 in patients with Hasenclever score of 0,1 and 0.87, p=0.79 in patients with a score ≥2. In arm B, a Hasenclever score of 0,1 was associated with five year PFS of 92% and OS of 99% whereas a score ≥2 was associated with a five year PFS of 77% and OS of 96%. The authors reported they found an interaction between Hasenclever score (0,1 versus ≥2) and treatment on PFS (p=0.058).

Specht et al. [53] report the 25-year follow-up of an RCT that included 327 patients with HL in pathological stages I or II treated with (S)TNI or MFRT with six cycles of mechloretamine, vincristine, procarbazine, and prednisone. Outcomes were survival and second cancers. The authors found that after the first 15 years survival was better for patients treated with combination therapy than with radiotherapy only (p<0.02). The authors estimated survival rate at 30 years would be 62% for combination therapy and 50% with radiotherapy only.

Radiotherapy Question Summary Results for Comparison E: RCTs of PET Used for Response-Adaptive Therapeutic Strategy

Three studies, the EORTC H10F, the EORTC H10U [1], and the RAPID trial [9], represented by two publications, reported on this comparison. Tables 1E and 2E present detailed numerical results.

The population of the EORTC trial comprised patients with early-stage HL with favourable and unfavourable prognoses. Patients with favourable prognosis were randomized to two cycles of ABVD and the standard treatment (one cycle ABVD and 30 Gy INRT), or to the tailored treatment according to PET results: if their PET scan was negative they received two cycles of ABVD; if their PET scan was positive they received two cycles of escalated BEACOPP and 30 Gy INRT. Patients with unfavourable prognosis were randomized to two cycles of ABVD and the standard treatment (four cycles of ABVD and 30 Gy INRT) or to the tailored treatment according to PET results: if their PET scan was negative they received four cycles of ABVD, and if their PET scan was positive they received two cycles of escalated BEACOPP and 30 Gy INRT.

This study was stopped early because of futility, and detected a strong association for PFS in favour of the combined treatment in the PET tailored arm.

The RAPID noninferiority trial included a subgroup of patients with favourable disease who had received three cycles of ABVD and had a negative PET scan for residual disease. Patients were randomized to IFRT (conventional treatment) or no further treatment. This study failed to detect noninferiority of the experimental treatment.

Overall quality of evidence for Comparison E: RCTs of PET used for Response Adaptive Therapeutic Strategy

The Working group members considered the quality of the evidence presented by this body of evidence as high.

Table 2E. Radiotherapy question summary of findings and quality for critical outcomes. RCTs of PET used for tailoring the therapeutic strategy.

Quality assessment						Summary of findings		Quality	Importance
№ of studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PET tailored strategy	standard treatment		
Progression free survival (assessed with: Disease progression or death from any cause)*									
3 (1557)	not serious	not serious	not serious	not serious	strong association	**EORTC /Lysa/Fil H10F** [1]		⊕⊕⊕⊕ HIGH	CRITICAL
						94.9%	100%[A]		
						EORTC /Lysa/Fil H10U [1]			
						94.7%	97.3%		
						RAPID [9]			
						90.7%	93.8% (95% CI, -10.7% to 1.4%)[B]		
Overall survival									
1 (420)	not serious	not serious	not serious	not serious	none	**RAPID** [9]		⊕⊕⊕⊕ HIGH	CRITICAL
						99.5%	97% (p values *nr*)		

*Primary outcome
[A]The study was stopped for futility
[B]The lower boundary of the CI exceeded the pre-determined margin of noninferiority of -7%.
F = favourable; PET = positron emission tomography; RCT = randomized controlled trial; u = unfavourable.

Ongoing, Unpublished, or Incomplete Studies

Table 3 shows the characteristics of an important ongoing trial identified by our search.

Table 3. General Characteristics of ongoing trials.

Study name. Registry number. Status	Author, Funding source	Study Objective, Design, Follow-up	Population	Intervention and Control	Outcomes	Expected completion date
HD 16 NCT00736320 Recruiting patients	Engert, 2013 [61] Kobe, 2012 [abs] [62] **Funding**: German Cancer Aid (Deutsche Krebshilfe)	To individualize treatment through adaptation to early response and treating with additional radiotherapy only pts who demonstrate an inadequate response as identified by PET **Design:** noninferiority trial	1100 pts with early-stage HL (Stage IA, IB, IIA, IIB without risk factor)	2xABVD all patients; FDG-PET stratification for pts who were PET positive: + 20 Gy IF-RT for PET negative pts: end of treatment	*PFS OS CR Proportion of pts with good or inadequate response to 2xABVD Late AE SN	November 2015

Abs = abstract; ABVD = Doxorubicin, bleomycin, vinblastine, and dacarbazine; AE = adverse events; CR = complete remission; FDG = fluorodeoxyglucose; Gy = gray; HL = Hodgkin lymphoma; IFRT = involved field radiotherapy; OS = overall survival; PET = positron emission tomography; PFS = progression free survival; Pts = patients; SN = secondary neoplasms.

Literature Search Results: Chemotherapy Question

For the chemotherapy question nine studies, represented by 11 publications were included [4,5,19-22,24-27,51].

In addition, three studies [11,12,17] that had been identified for the radiotherapy question also addressed a chemotherapy question. Their results are presented in the summary tables along with the others. These trials were found to be highly clinically heterogeneous and therefore were synthesized in a narrative manner.

General characteristics and outcomes:
Chemotherapy question

The general characteristics of the RCTs relevant for the chemotherapy question are reported in Table 4. The summary results are reported in Tables 4F to 4I. The chemotherapy doses and schedules used in the studies included are summarized in Appendix 5, Table 1.

The studies are grouped according to five comparisons:

F. Chemotherapy plus radiotherapy versus radiotherapy alone
G. Less intensive chemotherapy regimens plus radiotherapy versus more intensive regimens plus radiotherapy
H. More intensive chemotherapy plus radiotherapy versus less intensive regimens plus radiotherapy
I. More cycles of a specific chemotherapy plus radiotherapy versus fewer cycles of the same chemotherapy plus radiotherapy

For the three studies [11,12,17] that have also been listed in the sections on “radiotherapy question”, data regarding the chemotherapy question are extracted here.

Table 4. Chemotherapy question: General characteristics of included studies

Study name, author(s), year (ref), Funding	Population, Data collection period	Intervention(s)	Control(s)	Outcomes	Follow-up, median
F. Chemotherapy plus radiotherapy compared with radiotherapy alone					
GHSG HD7 **Engert, 2007 [4]** **Funding:** Deutsche Krebshilfe, and Swiss Group for Clinical Cancer Research.	CS/PS I or II, no risk factors N =650 randomized; 627 available for analysis Arm A: 311 Arm B: 316 Age (years): median 36; <20: 5%; >60: 10% Gender: male 59% 1993 to 1998	2xABVD + 30 Gy EF-RT+ 10 Gy IFRT	30 Gy EFRT + 10 Gy IFRT	OS *FFTF Late AE	87 months
SWOG 9284[A] **Ganz, 2003 [5]** **Funding:** National Cancer Institute (US), and Department of Health and Human Services (US)	CS IA, IEA, IIA and IIEA HL with favourable presentation N=247 randomized 244 available for analysis Arm A: 121 Arm B: 123 Age (median yrs): Arm A: 31.4 Arm B: 33.7 Gender (% male): Arm A: 59 Arm B: 58 1994 to 1996	Arm B: 3 cycles of doxorubicin and vinblastine + STLI	Arm A: STLI	QOL	2 yrs
G. Less intensive chemotherapy regimens + radiotherapy compared with more intensive regimens + radiotherapy					
GHSG HD14 Tresckow, 2012 [26], Sasse, 2014 [51] Behringer, 2012 [subgroup analysis] [27] **Funding:** Deutsche Krebshilfe, the Bundesministerium für Bildung und Forschung; and the Kompetenznetz Maligne Lymphome	CS IA, IB, or IIA with risk factors, IIB with elevated ESR and/or involvement of >3 lymph nodes (i.e., early-stage unfavourable HL) N=1655 randomized 1528 available for analysis Arm A: 835 assigned, 818 in analysis Arm B: 820 assigned, 805 in analysis Age (yrs): median 32, range 18 to 60 Gender: NR Subgroup: 263 female pts Arm A=ABVD: N=137, Arm B = 2+2: N=126, Age (yrs): at fertility assessment: Arm A: 32±7 (20–45) Arm B: 32±7 (20–44)	Arm B: 2xBEACOPP increased + 2xABVD + 30 Gy IFRT	Arm A: 4xABVD + 30 Gy IFRT	*FFTF PFS OS Response rate AE **Subgroup:** Fertility hormones, Menstrual cycle Offspring	43 months, estimate at 5 yrs 70 months

Study name, author(s), year (ref), Funding	Population, Data collection period	Intervention(s)	Control(s)	Outcomes	Follow-up, median
	2003 to 2008				
EORTC-GELA H7U Noordijk, 2006 [12] Also assessed in radiotherapy section **Funding:** *nr*	CS I and II with favourable or unfavourable previously untreated HL N =762 randomized 722 available for analysis, 389 for this analysis. Arm C: 194 Arm D: 195 Age (yrs): median 30 Gender: male 53% 1988 to 1993	Arm D: 6 cycles of MOPP/ABV hybrid + IFRT	Arm C: 6 cycles EBVP + IFRT	*EFS *OS Response rate Late AE	9 yrs
H. More intensive chemotherapy plus radiotherapy compared with less intensive regimens plus radiotherapy					
Pavone, 2008 [20] **Funding:** *nr*	Unfavourable CS IA and IIA N=189 randomized, 181 available for analysis Arm A: 92 Arm B: 89 Age (yrs): median 51 Gender: male 43% 1997-2001	Arm B: 4xEVE + IFRT	Arm A: 4xABVD + IFRT	*FFS RFS Response AE (early and late)	62 months
E2496 [A] Advani, 2010, 2011 [abs] [21,24] **Funding:** *nr*	CS I/II bulky mediastinal N =267 Arm A: 136 Arm B: 131 Age (yrs): median 30 Gender: male 43% Data collection period: *nr*	Arm B: 12 weeks of Stanford V, (weekly) + IFRT	Arm A: ABVD x 6–8 cycles (every 28 days) + modified 36 Gy IFRT	FFS RFS Response	5.5 years
H90-NM Le Maignan, 2004 [22] **Funding:** Association de recherche sur les maladies tumorales et virales (France)	Early/intermediate stage HL, CS IA to IIIB. Results unique to early HD are considered here. N = 393 randomized; 386 available for analysis Arm A: 200 Arm B: 186 Age (yrs): median 30.5 Gender: male 53.4% 1990 to 1996	Arm B: 3 cycles of EBVMm + tailored, high-dose RT	Arm A: 3 cycles of ABVDm + tailored, high-dose RT	FFP EFS OS Mortality (disease- and treatment-related)	98 months (range, 72 t o 140 months)

Study name, author(s), year (ref), Funding	Population, Data collection period	Intervention(s)	Control(s)	Outcomes	Follow-up, median
GHSG HD11 Eich, 2010 [16] **Funding:** Deutsche Krebshilfe and the Swiss Federal Government	Pts in CS IA, IB, IIA with risk factors, IIB (unfavourable) HL N =1570 randomized, 1395 in analysis Arm A: 386 assigned, 356 in analysis Arm B: 395 assigned, 347 in analysis Arm C: 394 assigned, 341 in analysis Arm D: 395 assigned, 351 in analysis Age (yrs): median 33 (range 16 to 75) Gender: male 49% 1998 to 2003	Arm C: 4xBEACOPP + 30 Gy IFRT; Arm D: 4xBEACOPP + 20 Gy IFRT	Arm A: 4xABVD + 30 Gy IFRT (standard treatment); Arm B: 4xABVD + 20 Gy IFRT	OS *FFTF PFS Response Late AE	91 months
GHSG HD13 Behringer, 2015 [25]; Behringer, 2013 [subgroup] [23] **Funding:** Deutsche Krebshilfe (106164) and partly by the Swiss State Secretariat for Education and Research	Pts with early-stage, favourable HL N=1710 randomized, 1502 qualified, and 1392 in per protocol analysis Age (yrs): median 39 (range 18 to 75) Gender: male 60% 2003 to 2009	2xABV[B] + 30 Gy IFRT 2xAVD + 30 Gy IFRT 2xAV[B] + 30 Gy IFRT	2xABVD + 30 Gy IFRT	OS *FFTF PFS Response AE Hormones Menstrual cycle Offspring	5 yrs
I. More cycles of a specific chemotherapy + radiotherapy compared with fewer cycles of the same chemotherapy + radiotherapy					
Hamed, 2012 [19] **Funding:** *nr*	Newly diagnosed, favourable HL, CS I or II. N =98 randomized 90 available for analysis Arm A: 50 Arm B: 48 Age (yrs): median 26 Gender: male 66.7% 2008 to 2010	Arm A: 4xABVD + 30 Gy IFRT	Arm B: 2xABVD + 20 Gy IFRT	OS RFS AE	30 months
GHSG HD10 Engert, 2010 [17] **also in RT section** Also assessed in radiotherapy sectionalso in RT section	CS I,II no risk factors (early favourable HL) N =1370 randomized 1190 in analysis Arm A: 346 assigned, 298 in analysis Arm B: 340 assigned, 298 in analysis Arm C: 341 assigned, 295 in analysis Arm D: 343 assigned, 299 in analysis Age (years): mean 38.8; <20: NR; >60: NR	Arm C: 2xABVD + 30 Gy IFRT Arm D: 2xABVD + 20 Gy IFRT	Arm A: 4xABVD + 30 Gy IFRT Arm B: 4xABVD + 20 Gy IFRT	OS *FFTF PFS Late AE Response	7.5 years

Study name, author(s), year (ref), Funding	Population, Data collection period	Intervention(s)	Control(s)	Outcomes	Follow-up, median
Funding: Deutsche Krebshilfe and the Swiss Federal Government	Gender: male 60.9% 1998 to 2003				
EORTC GELA H8U Ferme, 2007 [11] **also in RT section** **Funding:** French Ministry of Health (Programme Hospitalier de Recherche Clinique 1994) and French National League against Cancer	CS I or II supradiaphragmatic, previously untreated, HL, either favourable (H8F) or unfavourable (H8U)B N =996 Arm A: 336 Arm B: 333 Arm C: 327 Age (yrs): median: Arm A: 33, Arm B: 32, Arm C: 31 Gender: male 45% 1993 to 1999	Arm B: 4 cycles of MOPP-ABV + IFRT	Arm A: 6 cycles of MOPP-ABV + IFRT	OS *EFS Late AE Response	92 months

*Primary outcome

Abs = abstract; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; AE = adverse events; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CI = confidence interval; CS = clinical stage; EBVMm = epirubicin, bleomycin, vinblastine, and methotrexate, modified; EBVP = epirubicin, bleomycin, vinblastine, and prednisone; EFRT = extended field radiotherapy; EFS = event-free survival; ESR = erythrocyte sedimentation rate; EVE = etoposide, vincristine, epirubicin; F = favourable; FFP = freedom from progression; FFS = failure-free survival rate; FFTF = freedom from treatment failure; HL = Hodgkin lymphoma; IFRT = involved field radiotherapy; MOPP-ABV = sequential mechlorethamine, oncovin, procarbazine, prednisone and doxorubicin, bleomycin, vinblastine; nr = not reported; OS = overall survival; PFS = progression-free survival; PS = pathological stage; pts = patients; QOL = quality of life; ref = reference; RFS = relapse free survival; RT = radiotherapy; STLI = subtotal lymphoid irradiation; STNI = subtotal nodal irradiation; U = unfavourable; yrs = years.

Table 4F. Chemotherapy question: Summary results of included RCTs comparing chemotherapy + radiotherapy with radiotherapy alone.

Study name, author(s), year (ref)	Intervention Control	OS	FFTF	QOL	Late AE
GHSG HD7 **Engert, 2007 [4]**	Arm A: 30 Gy EFRT + 10 Gy IFRT Arm B: 2xABVD + 30 Gy EF-RT+ 10 Gy IFRT	At 7 yrs: Arm A: 92% (95% CI, 88% to 95%) Arm B: 94% (95% CI, 91% to 97%, p=0.43)	Arm A: 67% (95% CI, 61% to 73%) Arm B: 88% (95% CI, 84% to 92%; p<0.0001)	*nr*	Second cancers: Arm A: 7% Arm B: 6%
SWOG 9284A[A] **Ganz, 2003 [5]**	Arm A: STLI Arm B: 3 cycles of doxorubicin and vinblastine + STLI	*nr*	*nr*	[B] SDS: percentage of patients scoring at or above an score of 25 : At 6 months:32.3% vs 60%; p<0.0001 1 yr: p=NS 2 yrs: p=NS MOS-36 Vitality scores: At 6 months: significantly worse in arm B: p=0.001 1 yr: p=NS 2 yrs: p=NS CARES-SF: At 6 months: significantly worse in arm B: p<0.015 1 yr: p=NS 2 yrs: p=*nr*	*nr*

[A] Data from a companion early study [6] that was published before our search cut off limit, and therefore not included, found that the failure-free survival was better with combination therapy (94%) than with radiotherapy only (81%). The Press study was stopped early for benefit, and therefore the sample of SWOG 9284 was reduced compared with the planned size.

[B] Quality of life was measured with the Symptom Distress Scale [63]: score range from 13 to 65 with higher scores meaning worse quality of life; with the Medical Outcomes Study 36-item Short-Form Health Survey (MOS SF-36) vitality scale and single item health perception [64]: score range from 0 to 100 with higher scores meaning higher energy and lower scores representing higher fatigue; and with the Cancer Rehabilitation Evaluation System–Short Form (CARES-SF) for intermediate and long-term quality of life [65].

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; AE = adverse events; CARES-SF = cancer rehabilitation evaluation system-short form; CI = confidence interval; EFRT = extended field radiotherapy; FFTF = freedom from treatment failure; IFRT = involved field radiotherapy; MOS = medical outcomes study; *nr* = not reported; NS = not significant; OS = overall survival; QOL = quality of life; ref = reference; SDS = Symptom Distress Scale; STLI = subtotal lymphoid irradiation; vs = versus; yr(s) = year(s).

Table 4G. Chemotherapy question: Summary results of included RCTs comparing less intensive chemotherapy regiments plus radiotherapy with more intensive regimens plus radiotherapy

Study name, author(s), year (ref)	Intervention Control	FFTF	PFS	EFS	OS	Response rate	AE
GHSG HD14 Tresckow, 2012 [26], Sasse, 2014 [51]	Arm A: 4xABVD + 30 Gy IFRT Arm B: 2xBEACOPP increased + 2xABVD + 30 Gy IFRT	At 5 yrs FFTF rates Arm A: 87.7% (95% CI, 84.8% to 90.6%) Arm B: 94.8% (95% CI, 93.1% to 96.6%) for a difference of 7.2% (95% CI, 3.8% to 10.5%) [A]HR 0.44 (95% CI, 0.30 to 0.66; p<0.001).	At 5 yrs: Arm A: 89.1 (95% CI, 86.3 to 91.9) Arm B: 95.4 (95% CI, 93.7 to 97.1) HR 0.45 (95% CI, 0.30 to 0.69; p<0.001)	*nr*	At 5 yrs: A: 96.8 (95% CI, 95.2 to 98.4) B: 97.2 (95% CI, 95.8 to 98.6) HR 1.12 (95% CI, 0.58 to 2.16; p=0.7308)	No difference in response rate: p=0.6272	Acute toxicity (grade 3 or 4) Arm A: 50.7% Arm B: 87.1% P <0.001 Treatment related death: Arm A: 0 Arm B: 0.5% p=*nr*
EORTC-GELA H7U Noordijk, 2006 [12] Also assessed in radiotherapy part	Arm C: 6 cycles EBVP + IFRT Arm D: 6 cycles of MOPP-ABV hybrid + IFRT	*nr*	*nr*	[B]At 1 yr: C: 80%; D: 95% At 2 yrs: C: 74%; D: 92% At 10 yrs: C: 68%; D: 88%, p<0.001	At 10 yrs: C: 79%; D: 87% p=0.0175	CR: C: 82% D: 86%	Second cancers: C: 8% D: 4% p *nr*

[A] The non-adjusted P value is presented in the table. P value was adjusted, two-sided, and established by a significant group sequential test in the third planned interim analysis (P=0.0451).
[B] This result significantly better for the patients in the MOPP-ABV group led the authors to stop the study in November 1992.
ABVD = doxorubicin, bleomycin, vinblastine, decarbazine; AE = adverse events; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CI = confidence interval; CR = complete response; EBVP = epirubicin, bleomycin, vinblastine and prednisone; EFS = event-free survival; FFTF = freedom from treatment failure; HL = Hodgkin lymphoma; HR = hazard ratio; IFRT = involved field radiotherapy; ; MOPP-ABV = sequential mechlorethamine, oncovin, procarbazine, prednisone and doxorubicin, bleomycin, vinblastine; PFS = progression-free survival; *nr*= not reported; OS = overall survival; PFS = progression-free survival; ref = reference; yrs = years.

Table 4G cont'd. Chemotherapy question: Summary results of included RCTs comparing less intensive chemotherapy regiments + radiotherapy with more intensive regimens + radiotherapy

Study name, author(s), year (ref)	Intervention Control	Hormones	Menstrual Cycle	Offspring/ fertility
GHSG HD14 Behringer, 2012 [subgroup] [27]	Arm A: 4xABVD + 30 Gy IFRT Arm B: 2xBEACOPP increased + 2 x ABVD + 30 Gy IFRT	*18 to 29 yrs old* AMH [µg/l] Arm A: 2.2; Arm B: 0.9; p≤0.001 FSH [U/l] Arm A: 3.0; Arm B: 4.3; p=NS *30 to 45 yrs old* AMH [µg/l] Arm A: 0.8; Arm B: 0.03; p≤0.001 FSH [U/l] Arm A: 4.4; Arm B: 11.9; p≤0.001	No difference between arms: Arm A: 86% Arm B: 84%	Arm A: 15% Arm B: 26% p=0.043

ABVD = doxorubicin, bleomycin, vinblastine, decarbazine; AMH = anti-Mullerian hormone; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; FSH = follicle-stimulating hormone; HR = hazard ratio; IFRT = involved field radiotherapy; NS = not significant; ref = reference; yr(s) = year(s).

Table 4H. Chemotherapy question: Summary results of included RCTs comparing more intensive chemotherapy regimens plus radiotherapy with less intensive regimens plus radiotherapy

Study name, author(s), year (ref)	Intervention Control	OS	FFS / RFS / FFTF	PFS / EFS	Response	AE
Pavone, 2008 [20]	Arm A: 4xABVD + IFRT Arm B: 4xEVE + IFRT	NS	**FFS:** *A: 90%; B: 73%; p= 0.005 **RFS:** At 5 yrs: A: 95%; B: 78%; p=0.002	*nr*	CR+Cru after chemo: A: 69%; B: 68% CR after IFRT: A: 94%; B: 92%, p=NS	Acute toxicity (grade 3 and 4): no between-group difference Long-term toxicity: none observed.
E2496 [A] Advani, 2010, 2011 [abs] [21,24]	Arm A: ABVD x 6–8 cycles (every 28 days) + modified 36 Gy IFRT Arm B: 12 weeks of Stanford V, (weekly) + IFRT	At 5 yrs: A: 95%; B: 92% p=0.31, HR 1.69, (95% CI, 0.60 to 4.75)	**FFS:** *At 5 yrs: A: 85% B: 77%, p=0.13, HR 1.56, (95% CI, 0.87 to 2.88) **RFS:** A: 13% B: 17%, p=NS	*nr*	CR+PR: A:82% B:86%, p=NS	No difference in hematologic toxicity between arms
H90-NM Le Maignan, 2004 [22]	Arm A: 3 cycles of ABVDm + tailored, high-dose RT Arm B: 3 cycles of EBVMm + tailored, high-dose RT	At 10 yrs: A: 90.4% ± 2.3% B: 90.3% ± 2.7%, p=NS	*nr*	**FFP** rate After CMT: A: 91.4% ± 2.1% B: 80% ± 3%, p<0.002 **EFS:** At 10 yrs: A: 84.6% ± 2.8% B: 74.9% ± 3.6%, p=0.016	After Chemo: CR: A: 79.5% B: 70.4% After Radiotherapy: A: 96% B: 94.6%	**Second cancers:** A: 4.2% ± 1.6% B: 5.8% ± 2.4%, P=0.92 **Cardiac compications**: p=NS TRM at 10 yrs: A: 7.5% ± 2.1% B: 5.5% ± 2.4%; p=NS
GHSG HD11 Eich, 2010 [16]	Arm A: 4 x ABVD + 30 Gy IFRT (standard treatment) vs Arm B: 4 x ABVD + 20 Gy IFRT vs Arm C: 4xBEACOPP + 30 Gy IFRT vs Arm D: 4xBEACOPP + 20 Gy IFRT	NS (P values NR)	**FFTF:** A vs C: 4xBEACOPP + 30 Gy vs 4xABVD + 30 Gy: 5-yr FFTF difference, 1.6%; 95% CI, -3.6% to 6.9%) (treatment with ABVD was noninferior) D vs B: 4xBEACOPP + 20 Gy vs 4xABVD + 20 Gy: 5-yr FFTF difference, 5.7%, (95% CI, 0.1% to 11.3%, treatment with ABVD was inferior)	**PFS:** †C: 4xBEACOPP /30 vs A: 4xABVD/30: HR 0.92 (95% CI, 0.63 to 1.34), p=0.66 **EFS:** *nr*	CR: 94.5% vs 93.8% p=NS	Secondary neoplasias (RT comparison): 3.4% vs 4.0 (p=NS) Death: 6.5% vs 6.2%
GHSG HD13 Behringer, 2015 [25]	30 Gy IFRT +: 2xABVD vs 2xABV vs[B] 2xAVD vs	ABVD: 97.6% (69.1 to 99.1) ABV: 94.1% (90.8 to 97.5)	*FFTF ABVD: 93.1% (90.7 to 95.5) ABV: 81.4% (75.8 to 87.1) AVD: 89.2% (86.3 to 92.2)	**PFS:** ABVD: 93.5% (91.1 to 95.9) ABV: 82.1% (76.6 to 87.7) AVD: 89.6% (86.7 to 92.5)	CR: ABVD: 97.2% AVD: 98.1% ABV: 95.5%	**At least 1 event:** ABVD: 33% ABV: 28% AVD: 26%

Study name, author(s), year (ref)	Intervention Control	OS	FFS / RFS / FFTF	PFS / EFS	Response	AE
	2 x AV[B]	AVD: 97.6% (96.2 to 99.0) AV: 98.1% (96.0 to 100.00) Difference compared with ABVD: ABV: -2.1 (-6.4 to 2.3), HR 1.35 (0.61 to 2.96) AV: 1.9 (-1.7 to 5.6), HR 1.02 (0.41 to 2.51) AVD: 0.0 (-2.1 to 2.1), HR 1.33 (0.67 to 2.63)	AV: 77.1% (70.5 to 83.7) Difference compared with ABVD: ABV: -11.5% (95% CI, -18.3 to -4.7), HR 2.06 (95% CI,1.21 to 3.52); AV: -15.2% (95% CI, -23 to -7.4) HR 2.57 (95% CI,1.51 to 4.40) AVD: -3.9% (95% CI, -7.7 to -0.1), HR 1.50 (1.00 to 2.26) (includes the predefined noninferiority margin of 1.72)	AV: 78.9% (72.5 to 85.3) Difference compared with ABVD: ABV: -11.3 (-17.9 to -4.7), HR 1.97 (1.15 TO 3.38) AV: -14.0 (-21 to -6.4), HR 2.31 (1.34 to 3.96) AVD: -3.9 (-7.6 to -0.1), HR 1.49 (0.98 to 2.26)	AV: 88.6%	AV: 27% ABVD vs AVD p=0.02

* Primary outcome.

[A] This is a subgroup of study E2496. The study enrolled 812 patients; of these 267 had locally advanced bulky mediastinal disease

[B] Randomization to the AV and ABV arms was stopped early (in 2005 and 2006) because of higher rates of HL related events (progressions, relapses, and HL-related deaths due to acute toxicity)

†The single experimental arms (arms B, C, and D) were compared with the standard arm (arm A) in a Cox regression model, together with all candidate prognostic factors.

ABV = doxorubicin, bleomycin, and vinblastine; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; ABVDm = ABVD and methylprednisolone; AE = adverse event; AV = doxorubicin and vinblastine; AVD = doxorubicin, vinblastine, and dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; chemo = chemotherapy; CI = confidence interval; CMT = combined modality treatment; CR =complete remission; CRu = unconfirmed complete response; CS = clinical stage; EBVM = epirubicin, bleomycin, vinblastine, methotrexate; EFS = event free survival (events were failures, relapses, and deaths in first CR for any cause); EVE = epirubicin, vinblastine, and etoposide; FFP = freedom from progression: events were failures to chemo or radiotherapy or relapses; FFS = failure free survival; FFTF = freedom from treatment failure; HL = Hodgkin lymphoma; HR = hazard ratio; IFRT = involved note radiotherapy; nr = not reported; NS = not statistically significant; OS = overall survival; PFS = progression-free survival; PR = partial remission; RFS = relapse free survival (patients who achieved CR); RT = radiotherapy; TRM = treatment –related mortality; vs = versus; yr(s) = year(s).

Table 4H Cont'd. Chemotherapy question: Summary results of included RCTs comparing more intensive chemotherapy regimens plus radiotherapy with less intensive regiments plus radiotherapy

Study name, author(s), year (ref)	Intervention Control	Population, Data collection period	Hormones	Menstrual Cycle	Offspring/ fertility	Follow-up, median
GHSG HD13[A] Behringer, 2013 [subgroup] [23]	2xABVD + 30 Gy IFRT vs 2xABV + 30 Gy IFRT vs 2xAVD + 30 Gy IFRT vs 2xAV + 30 Gy IFRT	Since 2000: CS IA no risk factors Since 2003: CS I, and II no risk factors Age (mean yrs): female: 35, male: 40 N= female: 56, male: 92 2000 to 2009	**Female survivors (**compares 18 to 29 yrs old with 30 to 45 yrs old): AMH and FSH: difference for women treated with fewer cycles (2 to 4 instead of 6 to 8) was significant regardless of age group ($p<0.001$). **Male survivors** (compares early-, intermediate- and advanced-stage HL) Inhibin B and FSH levels were significantly different for early-stage pts treated with fewer cycles (2 to 4 instead of 6 to 8) ($p<0.001$)	>90% had regular cycle after therapy regardless of age. Time to resumption of cycle was reached within 1 year.	**Female survivors** (compares early HL with advanced disease): Fewer pregnancies were reported in women after treatment for advanced stage HL (N=7) [not relevant to this analysis]. **Male surviors:** Inhibitin B and FSH levels corresponding to confirmed fertility (inhibin B/FSH ratio >23.5 ng/U) were only observed after ABVD or 2xABVD [or 2xABVD + 2xBEACOPP in HD15 of pts with intermediate disease [not relevant to this analysis]) (HD13: 51.2%)	>4 years

[A]Results presented here are only part of the results presented in the Behringer et al. [23] pooled analysis that contains results also for the HD14 (early-stage unfavourable) and HD15 (advanced HL) branches of the trial.

ABV = doxorubicin, bleomycin, and vinblastine; ABVD = =doxorubicin, bleomycin, vinblastine, dacarbazine; AMH=anti-Müllerian hormone; AV = doxorubicin and vinblastine; AVD = doxorubicin, vinblastine, and dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; CS = =clinical stage; FSH=follicle-stimulating hormone HL=Hodgkin lymphoma; IFRT = =involved field radiotherapy; pts = patients; yrs = years.

Table 4I. Chemotherapy question: Summary results of included RCTs comparing more cycles of a specific chemotherapy plus radiotherapy with fewer cycles of the same chemotherapy plus radiotherapy

Study name, author(s), year (ref)	Intervention, Control	OS	FFTF	RFS	PFS/EFS	AE	Response rate
Hamed, 2012 [19]	Arm A: 4xABVD + 30 Gy IFRT Arm B: 2xABVD + 20 Gy IFRT	Median: A: 28 months (range: 14 to 39 months) B: 27 months (range: 12-39 mo,p=0.16) At 2 yrs: A: 98% (95% CI, 88.5 to 99.8) B: 95% (95% CI, 83.4 to 98.5, p=0.43)	*nr*	*At 2 yrs: Median for pts in both groups: 28 months. A: 96% (95% CI, 86.5 to 98.8) B: 95% (95% CI, 83.4 to 98.5, p=0.8)	*nr*	**Acute toxicity (grade 3 and 4) after chemo:** A: 54% B:30%, p=0.02	*nr*
GHSG HD10 Engert, 2010 [17] Also assessed in RT section	Arm A: 4xABVD + 30 Gy IFRT vs Arm B: 4xABVD + 20 Gy IFRT vs Arm C: 2xABVD + 30 Gy IFRT vs Arm D: 2xABVD + 20 Gy IFRT	HR for death, 1.02 (95% CI, 0.61 to 1.72; p=0.93)	*At 5 yrs: A and B: 93.0% (95% CI, 90.5% to 94.8%) C and D: 91.1% (95% CI, 88.3% to 93.2%); p=0.39	*nr*	**PFS** HR 1.22 (95% CI, 0.85 to 1.77, p=0.28)	**Acute toxicity (at least 1 instance of grade 3 and 4) after chemo:** A + B: 51.7% C+ D: 33.2%, p<0.001 **Second cancers:** no between-group differences, P=0.89	NS
EORTC GELA H8U Ferme, 2007 [11] Also assessed in RT section	Arm A: 6 cycles of MOPP-ABV + IFRT Arm B: 4 cycles of MOPP-ABV + IFRT	At 10 yrs: A: 88% B: 85% p=NS	*nr*	*nr*	**EFS** at 5 yrs: A: 84% B: 88% p=NS At 10 yrs: A: 82% B: 80%, p=NS	**Second cancers:** Cumulative probability at 10 yrs: A: 4.5 (95% CI, 2.5 to 7.9) B: 7.1 (95% CI, 4.3 to11.6) p=NS	CR: A: 69% B: 64% p=0.38

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AE =adverse event; chemo = chemotherapy; CI = confidence interval; CR = complete response; EFS = event-free survival; FFTF = freedom from treatment failure; HR = hazard ratio; IFRT = involved field radiotherapy; MOPP-ABV = mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) followed by doxorubicin, bleomycin, vinblastine, and dacarbazine; *nr* = not reported; NS = not statistically significant; OS = overall survival; PFS = progression-free survival; RFS = relapse-free survival; RT = radiotherapy; U = unfavourable; vs =versus; yr(s) = year(s).

Study Design, Quality, and Outcomes

All included studies were RCTs. All the studies were represented by full text publications except for two abstracts reports by Advani et al. [21,24] representing a subgroup analysis of study E2496, and one abstract report by Thistlethwaite et al. [15].

Figures 2A and 2B show the results of quality assessment of the included studies performed using the Cochrane Risk of Bias tool [60]. One study was declared to be an open label study [17], one study was represented by two abstract publications and not enough information was available to rate quality [21,24], and one study was a pooled analysis [23] of studies GHSG HD13 and GHSG HD14. Not enough data were reported to rate the quality of the data on study GHSG HD13, which included the population of interest.

The abstract reported by Thistlethwaite et al. [15] did not present enough data to evaluate study quality.

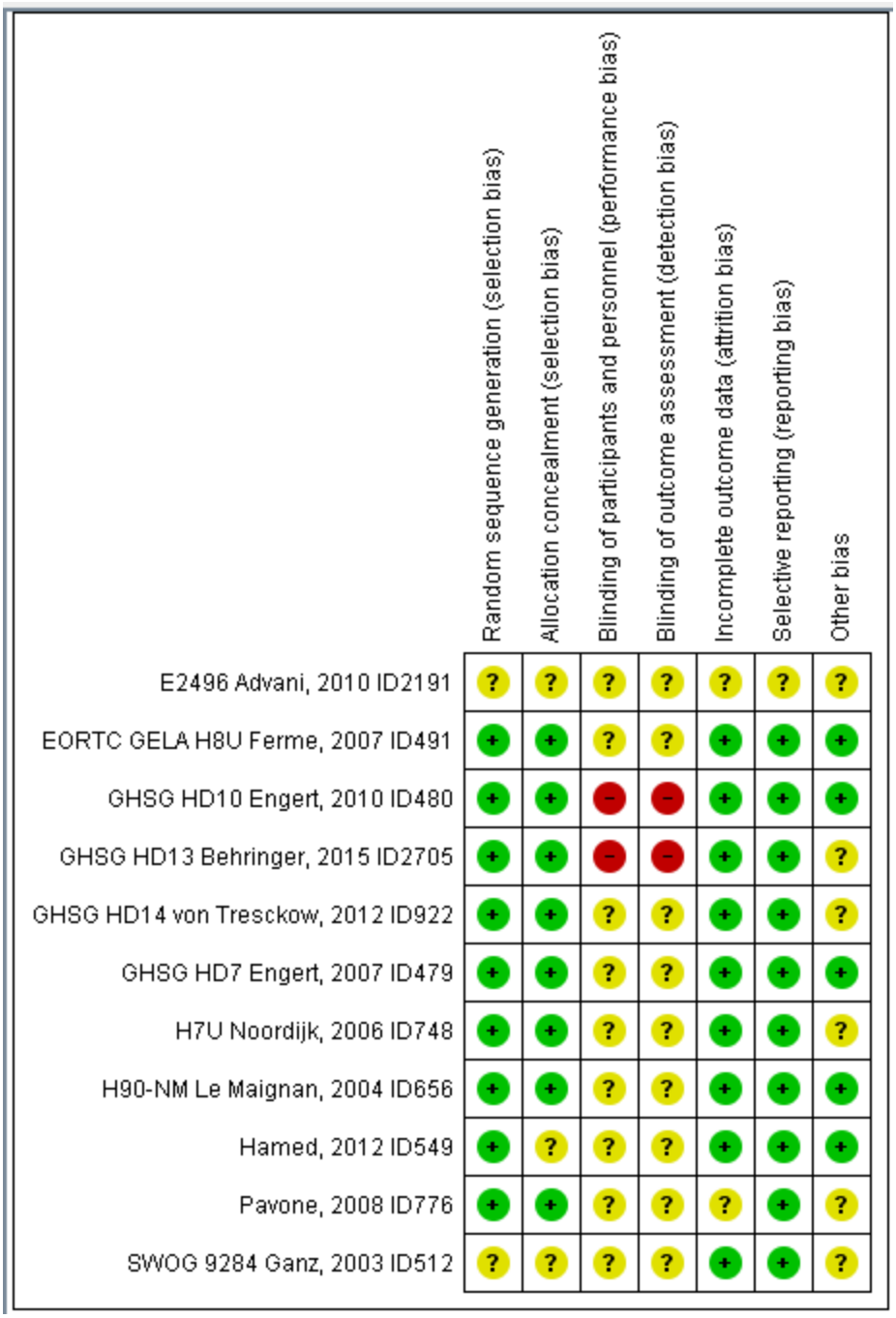

Figure 2A. Chemotherapy question. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

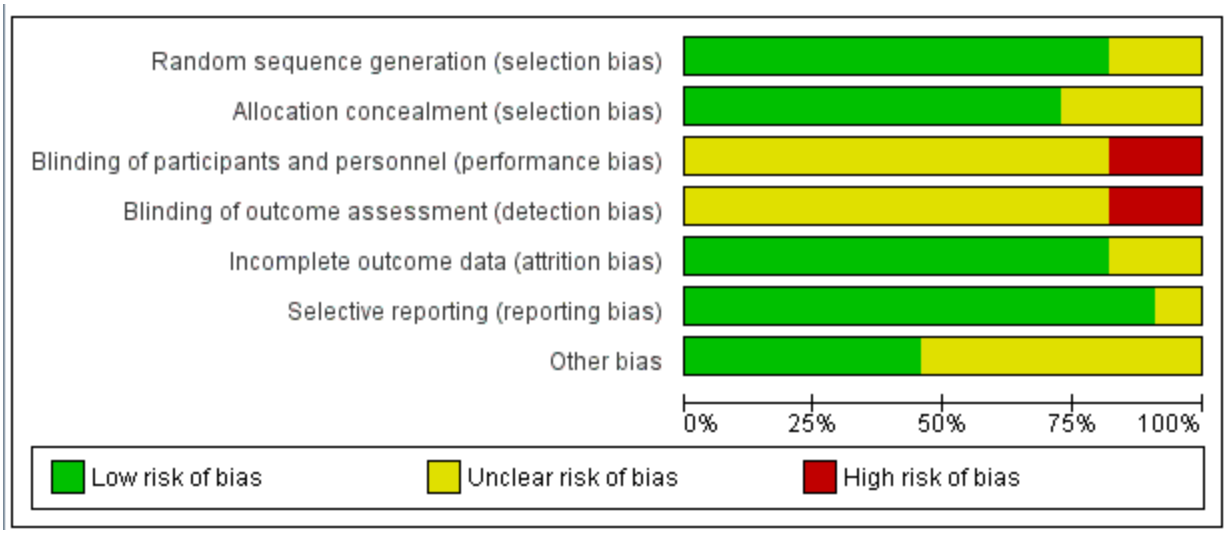

Figure 2B. Chemotherapy question. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Quality was further rated outcome by outcome across studies according to the GRADE methodology [37]. For each critical outcome, the categories: "Risk of Bias," "Inconsistency," "Indirectness," "Imprecision," and "Other considerations" were examined. Tables 5F to 5I present the outcome by outcome quality assessment and the summary results.

Chemotherapy Question Summary Results for: Comparison F. Rcts of Chemotherapy and Radiotherapy Compared with Radiotherapy Alone.

Two studies, the GSHG HD7 [4] and the SWOG 9133 [5], represented by two publications, addressed this comparison.

The members of the Working Group considered OS, measures of disease control, and late adverse events as critical for this comparison. Quality of life was considered an important outcome; other outcomes such as response rate and acute adverse effects were considered not important.

Among the outcomes that the members of the Working Group considered critical, the authors of the GSHG HD7 study [4] found no statistically significant between-group difference for OS and late adverse events; the authors found a significant benefit for the combination treatment for FFTF. The authors concluded that combination treatment is the treatment of choice for this population. The SWOG 9133 study [5] measured health-related quality of life and found worse scores at six months for patients in the group treated with combination chemotherapy and radiotherapy compared with patients in the group treated with radiotherapy alone, while at one and two years no statistically significant difference was detected. The authors concluded that patients treated with the combination therapy experience more treatment-related symptoms than patients treated with radiotherapy alone (see Tables 4F and 5 F for numerical results and quality assessment).

Tables 4F and 5F report detailed results and outcome by outcome quality assessment. In Table 5F a relative risk (RR) >1 represents better outcome for the combined modality treatment.

Overall Quality of Evidence for Comparison F: Chemotherapy and Radiotherapy Compared with Radiotherapy Alone

The members of the Working Group considered the quality of the evidence presented as moderate, because of imprecision: each outcome measure is represented in only one study, and in each study the number of events can be considered relatively low.

Other outcomes

The following results are for outcomes that the Working Group members considered less than critical or important:

Response:

The GSHG HD7 study [4] found no statistically significant difference for complete response (93.9% in the combination arm versus 94.6% in the radiotherapy only arm).

Acute adverse effects:

The GSHG HD7 study [4] did not report any statistical between-arm difference in grade 3 or 4 acute toxicity.

Table 5F. RCTs of chemotherapy plus radiotherapy compared with radiotherapy alone. Quality considerations

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies, Study name, [ref]	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy plus radiotherapy	radiotherapy alone	Relative (95% CI)	Absolute (95% CI)		
Overall Survival (follow-up: median 87 months; assessed with: percentage of patients alive at 7 years)												
1 **GHSG HD7** [4]	randomized trials	not serious	not serious	not serious	serious [1]	none	297/316 (94.0%)	286/311 (92.0%)	**RR 1.0220** (0.9789 to 1.0670)	20 more per 1000 (from 19 fewer to 62 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Freedom from treatment failure (follow-up: median 87 months; assessed with: time from random assignment to a recurrence)												
1 **GHSG HD7** [4]	randomized trials	not serious	not serious	not serious	serious [1]	none	278/316 (88.0%)	208/311 (66.9%)	**RR 1.3154** (1.2043 to 1.4367)	211 more per 1000 (from 137 more to 292 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Late adverse events (follow-up: median 87 months; assessed with: second malignancies)												
1 **GHSG HD7** [4]	randomized trials	not serious	not serious	not serious	serious [1]	none	18/316 (6%)	21/311 (6%)	**RR 1.1396** (0.6295 to 2.0631)	13 more per 1000 (from 24 fewer to 80 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of Life (assessed with: Symptom Distress Scale, MOS SF-36, CARES-SF)												
1 **SWOG 9284A** [5][2]	randomized trials	not serious	not serious	not serious	serious [1]	none	123	121	not estimable	not estimable	⊕⊕⊕◯ MODERATE	IMPORTANT

[1]Only one study with a small number of events;
[2]This study was closed early for benefit
CARES-SF = Cancer rehabilitation evaluation system-short form; CI = confidence interval; MOS-SF36 = medical outcomes study short form 36 questions; ref = reference; RR = rate ratio.

Chemotherapy Question Summary Results for Comparison G. Rcts of Less Intensive Chemotherapy Regimens plus Radiotherapy versus More Intensive Regimens plus Radiotherapy

Two studies, the GHSG HD14 [26], and the EORTC-GELA H7U [12], represented by three publications, addressed this comparison; both of these studies examined patients who had an unfavourable early-stage Hodgkin lymphoma, and who were of similar age, but the studies used dissimilar treatment regimens. Please refer to Tables 4G and 5G for detailed numerical results and outcome by outcome quality assessment.

The members of the Working Group considered OS, measures of disease control, and late adverse events as critical for this comparison. Quality of life was considered an important outcome and other outcomes, such as fertility were considered not important.

Among the outcomes that the Working Group members considered critical, the GHSG HD14 study [26] reported a better FFTF and PFS with the more intensive regimen (two cycles of BEACOPP plus two cycles of ABVD and 30 Gy radiotherapy) compared with the less intensive regimen (four cycles of ABVD and 30 Gy radiotherapy). However, the authors estimated no statistically significant between-group difference in OS at five years follow-up.

A different pattern can be observed in the EORTC-GELA H7U study [12]: EFS, and OS at 10 years follow-up were significantly better for patients in the group treated with the more intensive regimen (MOPP-ABV hybrid and radiotherapy) than for those treated with the less intensive regimen (six cycles of epirubicin, bleomycin, vinblastine, and prednisone and radiotherapy), and this result led the authors to stop the study early.

The GHSG HD14 study [26] reported 17 cases of second cancer (2.2%) for patients in the less intensive regimen group and 15 cases (2.0%) for patients in the more intensive regimen group, while the EORTC-GELA H7U study [12] reported 16 cases (8%) of second malignancies in patients allocated to the less intensive regimen group, and eight cases (4%) in the more intensive regimen (p values not reported).

Behringer et al. [27], in a corollary study, examined fertility and offspring in women treated in the GHSG HD14 trial. The authors found a statistically significant between-group difference for hormone levels, and did not find any statistically significant between-group difference in menopausal symptoms.

Tables 4G and 5G report detailed results and outcome by outcome quality assessment; a HR <1 represents a better outcome for the more intensive regimens plus radiotherapy; a RR >1 represents a better outcome for the less intensive chemotherapy plus radiotherapy regimen.

Overall Quality of the Evidence for Comparison G

The overall quality of this body of evidence was considered moderate to low because of imprecision and sometimes because of inconsistency: each outcome measure is represented in only one study, in each study the number of events can be considered relatively low, and results pointing in different directions.

Other outcomes

Acute Adverse Events

The GHSG HD 14 study [26] reported a statistically significant increase of acute grade 3 and 4 adverse events, including four treatment-related deaths in the BEACOPP arm (see Table 4G for numerical results).

The authors of the EORTC-GELA H7U trial [12] reported 2% treatment-related deaths in patients treated with the more intensive regimen.

Response rate

The GHSG HD 14 study [26] did not find any statistically significant between-group difference in response rate (see Table 4G for numerical results).

The EORTC-GELA H7U trial [12] found a similar response rate in patients treated with the more intensive regimen (86%) and in patients treated with the less intensive regimen (82%).

Fertility outcomes

Behringer et al., in a subgroup analysis of the GHSG HD14 study [27], examined fertility outcomes such as hormone levels, menstrual cycle, and offspring. See Table 4G (cont'd) for the results.

Table 5G. Chemotherapy question: Quality of studies for critical outcomes. Comparison G. RCTs of less intensive chemotherapy regimens plus radiotherapy vs more intensive regimens plus radiotherapy. RCTs of chemotherapy plus radiotherapy compared with radiotherapy alone.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies, Study name [ref]	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Less intensive chemotherapy regimens (e.g., ABVD) plus radiotherapy	More intensive regimens (e.g., BEACOPP) plus radiotherapy	Relative (95% CI)	Absolute (95% CI)		
Overall survival (follow-up: median 5 yrs; assessed with: per centage alive at 5 yrs)												
2 **GHSG HD14** [26], **EORTC-GELA H7U** [12]	randomized trials	not serious	serious [1]	not serious	serious [2]	none	883/935 (94.4%)	912/937 (97.3%)	not estimable	not estimable	⊕⊕◯◯ LOW	CRITICAL
Freedom from treatment failure (follow-up: median 5 yrs; assessed with: percent that did not fail at 5 yrs)												
1 **GHSG HD14** [26]	randomized trials	not serious	not serious	not serious	serious [3]	none	671/765 (87.7%)	723/763 (94.8%)	**HR 0.44** (0.30 to 0.66)	221 fewer per 1000 (from 90 fewer to 360 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Progression-free survival												
1 **GHSG HD14** [26]	randomized trials	not serious	not serious	not serious	serious [3]	none	681/765 (89.1%)	728/763 (95.4%)	**HR 0.45** (0.30 to 0.69)	204 fewer per 1000 (from 73 fewer to 351 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Late adverse events (assessed with: any adverse event that occurs a long time after exposure)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies, Study name [ref]	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Less intensive chemotherapy regimens (e.g., ABVD) plus radiotherapy	More intensive regimens (e.g., BEACOPP) plus radiotherapy	Relative (95% CI)	Absolute (95% CI)		
1 EORTC-GELA H7U [12]	randomized trials	not serious	not serious	not serious	serious [3]	none	11/194 (5.7%)	4/195 (2.1%)	**RR 2.01** (95% CI 0.88 to 4.59)	41 more per 1000 (from 5 fewer to 147 more)	⊕⊕⊕◯ MODERATE	CRITICAL

[1] The included studies had different interventions and the results have opposite directions.
[2] Event rate is very low
[3] Only one study with a relatively small number of events.
ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; CI = confidence interval; HR = hazard ratio; ref = reference; RR = rate ratio; yrs = years.

.

Chemotherapy Question Summary Results for Comparison H. More intensive chemotherapy regimens plus radiotherapy versus Less Intensive Regimens.

Five studies, Pavone et al. [20], the E2496 study [21,24], the H90-NM study [22], the GHSG HD11 study [16], and the GHSG HD13 study [25] - represented by six publications, addressed this comparison. The study reported by Advani et al. [21] is an abstract and does not report enough information to assess the quality, therefore it was not included in the quality evaluation.

The Working Group members considered OS, measures of disease control, and late adverse events as critical for this comparison. Quality of life was considered an important outcome; other outcomes such as response rate and acute toxicity were considered not important.

Among the critical outcomes, the authors of the H90-NM study [22] found no statistically significant difference in OS at 10 years follow-up and the authors of the GHSG HD13 study [25], in patients with favourable disease, did not detect a statistically significant difference at five years follow-up. In patients with unfavourable disease, the study reported by Pavone et al. [20] found, at 5.2 years follow-up, statistically significantly better failure-free survival (FFS) and relapse-free survival (RFS) by treating with ABVD as compared with EVE, both in combination with IFRT (respectively, 90% versus 73%; p=0.005 and 95% versus 78%; p=0.002), while the authors of the E2496 study [21], at 5.5 years follow-up, found no statistically significant difference between six to eight cycles of ABVD and 12 weeks of Stanford V chemotherapy for FFS and RFS (respectively, 85% versus 77%, HR=1.56; p=0.13). The authors of the H90-NM study [22], at 10 years follow-up, found a statistically significantly better freedom from progression and EFS with ABVD than with epirubicin, bleomycin, vinblastine, and methotrexate (respectively, 91.4% versus 80%; p<0.002, and 84.6% versus 74.9%; p=0.016). The same authors did not find a between-treatments significant difference in long-term adverse events such as second cancers or cardiac complications. The authors of the GHSG HD11 and GHSG HD13 studies [16,25] failed to detect nonnferiority of treatments other than ABVD in patients with favourable or unfavourable disease.

Tables 4H and 5H report detailed results and outcome by outcome quality assessment; a RR>1 represents better outcome for the more intensive chemotherapy regimen, a RR<1 represents a better outcome for less intensive chemotherapy regimen.

Overall Quality of Evidence For Comparison H: More Intensive Chemotherapy Regimens plus Radiotherapy ersus Less Intensive Regimens

The Working Group members considered the quality of the evidence presented as moderate because of imprecision, mainly because of the low number of events in each study. See Table 5H for more details about the quality for each critical outcome.

Other outcomes

The following results are for outcomes that the Working Group members considered less than critical or important:

Response:

The studies reported by Pavone et al. [20], Advani et al. [21], and le Maignan et al. [22] did not report any significant between group difference in response rate.

Acute Adverse Effects:

The studies reported by Pavone et al. [20] and Advani et al [21] reported no difference in acute adverse effects between groups.

Gonadal function

Behringer et al. [23], in a pooled analysis, reported on gonadal function and fertility of female and male survivors who participated in studies GHSG HD13 and GHSG HD14. Only the results relative to patients with early-stage Hodgkin lymphoma are presented in Table 4H. Patients, both man and women, treated with fewer cycles of chemotherapy were more likely to have their fertility preserved. Fewer pregnancies were reported by women treated with more intensive regimens.

Table 5H. Chemotherapy question: Quality of studies for critical outcomes. Comparison H: More intensive chemotherapy plus radiotherapy versus less intense regimens plus radiotherapy

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies, Study name [ref]	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H. More intensive chemotherapy regimens (e.g., ABVD) plus radiotherapy	less intensive chemotherapy regimens (e.g., EVE or Stanford V) plus radiotherapy	Relative (95% CI)	Absolute (95% CI)		
Ten years survival (assessed with: per centage of patients alive at 10 years follow-up)												
1 **H90-NM** [22]	randomized trial	not serious	not serious	not serious	serious [1]	none	180.8/200 (90.4%)	168/186 (90.3%)	**RR 1.0020** (0.9389 to 1.0693)	2 more per 1000 (from 55 fewer to 63 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Freedom from treatment failure (assessed with: percent free from failure at 87 months follow-up: assessed with time from random assignment to a recurrence)												
1 **Pavone** et al., 2008 [20] **GHSG HD11** [16]	randomized trials	serious [2]	not serious	not serious	not serious	none	**Pavone** et al., 2008 [20]				⊕⊕⊕◯ MODERATE	CRITICAL
							82.8/92 (90%)	65/89 (73.0%)	**RR 1.2353** (0.0706 to1.4253) p=0.05	172 more per 1000 (from 311 more to 679 fewer)		
							GHSG HD11 [16] comparison 1: 4 x BEACOPP + 30 Gy IFRT vs 4 x ABVD + 30 Gy IFRT comparison 2: 4xBEACOPP/20 Gy vs 4xABVD/20Gy					
							comparison 1:4xBEACOPP/30 Gy vs 4xABVD/30Gy					
							394	386	HR 0.92, 95%CI 0.63 to 1.34, difference: 1.6% (-3.6 to 6.9), p=0.66			
							comparison 2: 4xBEACOPP/20 Gy vs 4xABVD/20Gy:					
							395	395	difference: 5.7% (0.1 to11.3), p=0.02			
							GHGS HD13 Behringer , 2015 **[25]**					

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies, Study name [ref]	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H. More intensive chemotherapy regimens (e.g., ABVD) plus radiotherapy	less intensive chemotherapy regimens (e.g., EVE or Stanford V) plus radiotherapy	Relative (95% CI)	Absolute (95% CI)		
							646	1064	ABV: -HR 2.06 (95% CI,1.21 to 3.52) AV: HR 2.57 (95% CI,1.51 to 4.40) AVD: HR 1.50 (1.00 to 2.26)	Difference compared with ABVD: ABV: -11.5% (95% CI, -18.3 to -4.7) AV: -15.2% (95% CI, -23 to -7.4) AVD: -3.9% (95% CI, -7.7 to -0.1) (includes the predefined noninferiority margin of 1.72)		
Five-year relapse free survival (assessed with: percentage free from relapse at 5 years follow-up)												
1 **Pavone** et al., 2008 [20]	randomized trials	serious [2]	not serious	not serious	serious [1]	none	87.4/92 (95.0%)	69.42/89 (78.0%)	**RR 1.2198** (1.0795 to 1.3782)	171 more per 1000 (from 62 more to 295 more)	⊕⊕◯◯ LOW	CRITICAL
98-month freedom from progression (assessed with: rate of people free from progression at 98 months follow-up)												
1 **H90-NM** [22]	randomized trials	not serious	not serious	not serious	serious [1]	none	182.8/200 (91.4%)	148.8/186 (80.0%)	**RR 1.1422** (1.0511 to 1.2412)	114 more per 1000 (from 41 more to 193 more)	⊕⊕⊕◯ MODERATE	CRITICAL
10 years event free survival (assessed with: Rate of patients surviving at 10 years follow-up without failure to respond to treatment)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies, Study name [ref]	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H. More intensive chemotherapy regimens (e.g., ABVD) plus radiotherapy	less intensive chemotherapy regimens (e.g., EVE or Stanford V) plus radiotherapy	Relative (95% CI)	Absolute (95% CI)		
1 **H90-NM** [22]	randomized trials	not serious	not serious	not serious	serious [1]	none	169.22/200 (84.6%)	139.314/186 (74.9%)	**RR 1.1307** (1.0206 to 1.2528)	98 more per 1000 (from 15 more to 189 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Late adverse events (assessed with: long term adverse events (second cancers) at 98 months follow-up)												
1 **H90-NM** [22]	randomized trials	not serious	not serious	not serious	serious [1]	none	8.4/200 (4.2%)	10.788/186 (5.8%)	**RR 0.6764** (0.2781 to 1.6447)	19 fewer per 1000 (from 37 more to 42 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

[1] Only one study with a small number of events
[2] The Pavone et al study [20] has no blinding and it is impossible to say if there is incomplete outcome reporting.
ABV = doxorubicin, belomycin, vinblastine; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AV = doxorubicin, vinblastine; AVD = doxorubicin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; CI = confidence interval; HR = hazard ratio; IFRT = involved field radiotherapy; ref = reference; RR = rate ratio; yrs = years.

Chemotherapy Question Summary Results for Comparison I: Rcts of More Cycles of a Specific Chemotherapy plus Radiotherapy versus Fewer Cycles of the Same Chemotherapy plus Radiotherapy

Three studies, Hamed et al. [19], GHSG HD10 [17], and EORTC-GELA H8U [11], represented by three publications, addressed this comparison. Two of the studies [17,19] had populations of patients with favourable prognosis, and one study [11] included patients with unfavourable prognosis. Tables 4I and 5I report detailed numerical results and outcome by outcome quality assessment. A RR>1 or a HR>1 represent a better outcome for the arm with more cycles of chemotherapy plus radiotherapy compared with the arm with fewer cycles.

The members of the Working Group considered OS, measures of disease control, and late adverse events as critical outcomes for this comparison. Acute adverse effects and response rate were considered not important.

None of the studies reported a statistically significant difference in OS at follow-ups that varied from 30 months to 10 years. As well, no difference was detected for FFTF [17], for RFS [19], for EFS [11], and for PFS [17].

Overall Quality of the Evidence for Comparison I

The overall quality of this body of evidence was considered moderate because of imprecision. See Table 5I for details on the outcome by outcome quality assessment.

Other outcomes

Acute Adverse Effects

The study reported by Hamed et al. [19] and the GHSG HD10U and GHSG HD10F studies [17] reported greater grade 3 and 4 acute adverse effects in patients allocated to the group treated with a higher number of chemotherapy cycles (respectively, 54% versus 30%; p=0.02, and 51.7% versus 33.2%; p<0.001).

Response rate

The GHSG HD10 and the EORTC-GELA H8U studies [11,17] reported no statistically significant between-group difference in response rate.

Table 5I. Chemotherapy question: Quality of studies for critical outcomes.
RCTs of more cycles of a specific chemotherapy plus radiotherapy versus fewer cycles of the same chemotherapy plus radiotherapy

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies, Study name [ref]	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	More cycles of a specific chemotherapy plus radiotherapy	Fewer cycles of the same chemotherapy plus radiotherapy	Relative (95% CI)	Absolute (95% CI)		
Overall Survival (assessed with: survival rate)												
3 **Hamed, 2012** [19] **GHSG HD10** [17], and **EORTC-GELA H8U** [11]	randomized trials	not serious	serious [1]	not serious	not serious	none	874.396/932 (93.8%)	1131.481/1254 (90.2%)	not estimable	not estimable	⊕⊕⊕◯ MODERATE	CRITICAL
Freedom from treatment failure (assessed with: rate of patients free from treatment failure)												
1 **GHSG HD10** [17]	randomized trials	not serious	not serious	not serious	not serious	none	527/596 (88.4%)	509/594 (85.7%)	**RR 1.0319** (0.9876 to 1.0782)	27 more per 1000 (from 11 fewer to 67 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Relapse-free survival (assessed with: rate of patients without relapse)												
1 **Hamed, 2012** [19]	randomized trials	not serious	not serious	not serious	not serious	none	48/50 (96.0%)	38/40 (95.0%)	**RR 1.0017** (0.9231 to 1.0871)	2 more per 1000 (from 73 fewer to 83 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Progression-free survival (assessed with: rate of patients free from progression)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies, Study name [ref]	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	More cycles of a specific chemotherapy plus radiotherapy	Fewer cycles of the same chemotherapy plus radiotherapy	Relative (95% CI)	Absolute (95% CI)		
1 **GHSG HD10** [17]	randomized trials	not serious	not serious	not serious	not serious	none	557.26/596 (93.5%)	541.728/594 (91.2%)	**HR 1.22** (0.85 to 1.77)	36 more per 1000 (from 39 fewer to 74 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Event Free Survival (assessed with: rate of people free from an event)												
1 **EORTC GELA H8U** [11]	randomized trials	not serious	not serious	not serious	not serious	none	275.52/336 (82.0%)	266.4/333 (80.0%)	**RR 1.0283** (0.9555 to 1.1067)	23 more per 1000 (from 36 fewer to 85 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Late adverse events (assessed with: rate of AE (second cancers))												
2 **EORTC GELA H8U** [11] **GHSG HD10** [17]	randomized trials	not serious	not serious	not serious	not serious	none	39/932 (4.2%)	60/1254 (4.8%)	not pooled	see note 1	⊕⊕⊕⊕ HIGH	CRITICAL

1 Studies use different treatments and controls
CI = confidence interval; HR = hazard ratio; ref = reference; RR = rate ratio.

DISCUSSION AND CONCLUSIONS

This document represents a review of the evidence, and an evidence-based guideline for management of early-stage Hodgkin lymphoma. While much of the evidence relates to combinations of different treatment modalities, the members of the Working Group have chosen to group the recommendations, key evidence, and interpretation of the evidence in two sections, relating to radiotherapy and chemotherapy. The recommendations presented here are based mainly on evidence relevant to adult patients, but there is a biological rationale to apply them to patients who are adolescents and young adults.

The first treatment introduced to clinical practice for early-stage Hodgkin lymphoma was radiotherapy, typically administered as an extended field. Radiotherapy as a single treatment modality is no longer used. A series of clinical trials, that were reported before the dates encompassed by our literature search, demonstrated superiority of an abbreviated course of chemotherapy prior to radiotherapy (combined modality therapy) over radiotherapy alone. Within the parameters of our literature search, the GHSG HD7 study [4] demonstrated an improvement in FFTF with the addition of two cycles of ABVD to 30 Gy EFRT plus 10 Gy IFRT.

Added as part of the 2023 Endorsement: Nodular lymphocyte-predominant Hodgkin lymphoma represents a distinct subset of patients with a unique pathology, biology, and natural history. Combined modality therapy is a reasonable treatment option for early-stage nodular lymphocyte predominant Hodgkin lymphoma. In selected patients (eg. low-bulk disease, advanced age, or with comorbidities) involved-field radiation therapy alone, or active surveillance may be appropriate. Although this recommendation is not based upon randomized clinical trials, it is supported by phase 2 data, it is often cited as a consensus of experts [3].

Radiotherapy, when used to treat early-stage Hodgkin lymphoma, was historically administered using an extended field. More limited radiation fields, generally administered as part of a combined modality approach, have now supplanted this technique. The EORTC H8 trial [11] demonstrated an improvement in EFS and OS with MOPP-ABV and IFRT when compared with STNI. The EORTC-GELA H7F trial [12] detected an improvement in EFS but not OS when six cycles of EBVP were followed by IFRT compared with STNI. In the study reported by Bonadonna [13], recurrence rates did not differ when four cycles of ABVD were followed by either IFRT or STNI. In the EORTC GELA H8 study [11], efficacy was maintained and toxicity was reduced when IFRT was used rather than EFRT (each in combination with COPP ABVD). In light of the equivalent efficacy and reduction in adverse effects, IFRT in combination with chemotherapy has supplanted EFRT (either alone or with chemotherapy).

Recent trends in radiotherapy for early-stage Hodgkin lymphoma have attempted to further reduce the field size, with a view to further decreasing the long-term adverse effects of treatment. INRT or involved-site radiation therapy (ISRT) are now being used in many institutions. While this approach is supported by expert consensus, there are no randomized trials comparing IFRT with INRT/ISRT.

With further appreciation of the important role of chemotherapy in the treatment of early-stage Hodgkin lymphoma, and gradual understanding of the long-term adverse effects of radiotherapy, the possible omission of radiotherapy from treatment has been investigated. The HD6 trial [7] compared chemotherapy alone (ABVD) with a strategy that incorporated radiotherapy (either alone or with chemotherapy depending on patient risk profile). Early reporting of this trial [8] identified a higher failure rate with omission of radiotherapy, without compromising overall survival. Long-term follow-up has, however, reported improved overall survival with omission of radiotherapy due to a higher risk of death from late adverse effects of radiotherapy such as second malignancies and cardiovascular toxicity. This trial demonstrated the important principle that where competing risks exist, long-term follow-up is crucial and progression-free-survival is not a valid surrogate for overall survival. The radiation

fields used in this study were extended field, representing the standard of care at that time. Whether the long-term adverse effects of radiotherapy are reduced with INRT/ISRT is currently a matter of conjecture. In this context, patients with early-stage Hodgkin lymphoma may be considered for treatment with combined modality therapy or with chemotherapy alone. Patients should be made aware of the potential trade-offs involved with either treatment approach.

A new approach to omission of radiotherapy has incorporated early positron emission tomography as a tool to identify patients with favourable prognosis for whom radiotherapy may be safely omitted without worsening outcome. Two recently reported trials have directly addressed this strategy. The EORTC H10 trial [66] performed PET imaging after two cycles of ABVD. Patients with a negative PET scan omitted INRT and continued chemotherapy alone. Patients with a positive PET scan received additional chemotherapy followed by INRT. The primary endpoint was PFS. The trial was terminated early after a planned interim analysis for futility concluded that the trial would not be able to demonstrate noninferiority for omission of radiotherapy. The RAPID trial [9] performed PET imaging after three cycles of ABVD. Patients with a negative PET scan were randomized to either receive or omit IFRT. Patients with a positive PET scan received additional chemotherapy followed by IFRT. The primary endpoint was again PFS. The 95% confidence interval for the difference in PFS exceeded the noninferiority margin of 7%. In each of these trials, the analysis using the primary endpoint and the specified noninferiority margin was obliged to conclude that the experimental strategy that used PET imaging as a guide to omission of radiotherapy did not demonstrate non-inferiority when compared with standard combined modality therapy. Much of the commentary on the RAPID trial has focused on the excellent results of treatment in the experimental arm with a 90.8% progression-free survival at three years, while not highlighting the primary analysis that failed to demonstrate noninferiority. In keeping with the design of these two trials, the members of the Working Group feel that PET imaging may not be used to identify patients for whom radiotherapy may be omitted without compromising PFS. This is not intended to negate the results of the H.6 trial [7]. Prolonged follow-up and use of an OS endpoint rather than a PFS endpoint was required in the H.6 trial [7] to appreciate the competing risks of treatment failure and long-term adverse effects of therapy.

With the establishment of IFRT (in combination with chemotherapy) as a standard treatment approach, several trials have further refined the dose of IFRT to be used in combined modality therapy. The GHSG HD11 trial [16] found equivalent outcomes with 20 Gy and with 30 Gy, administered after ABVD chemotherapy for patients with a favourable risk profile. Twenty Gy is the current recommended dose for patients with a favourable risk profile. Patients with an unfavourable risk profile require a higher dose of radiotherapy when administered after chemotherapy. When administered in combination with ABVD, the GHSG HD11 trial [16] found 20 Gy to be inferior to 30 Gy. The GOELAMS H97E trial [18] found 36 Gy to be equivalent to 40 Gy when administered after ABVD in patients with an unfavourable risk profile. The current recommended dose for patients with an unfavourable risk profile is between 30 and 36 Gy.

With the acceptance of chemotherapy as an integral component of combined modality therapy, it has been necessary to define the optimal number of cycles of chemotherapy prior to radiotherapy. The GHSG HD10 trial [17] demonstrated that two cycles of ABVD was equivalent to four cycles for patients with a favourable risk profile. Patients with a favourable risk profile should receive two cycles of chemotherapy. The EORTC GELA H8U study [11] demonstrated that four cycles of MOPP-ABV was equivalent to six cycles with regard to OS and EFS for patients with an unfavourable risk profile. Adverse effect were more common with more cycles of chemotherapy. Patients with an unfavourable risk profile should receive four cycles of chemotherapy.

Different chemotherapy regimens have been employed prior to radiotherapy when used in combined modality therapy. Many of these regimens represent modifications of the ABVD regimen. In general, none of these alternative regimens has been shown to be more efficacious than ABVD or to maintain efficacy with fewer adverse effects [20-22,24]. Elimination of individual drugs from the ABVD regimen has been associated with a loss of efficacy [23]. The Working Group members therefore believes that ABVD should be considered the chemotherapy regimen of choice when administered prior to radiotherapy. An important exception may exist to this general conclusion. The GHSG HD 14 trial [26] compared four cycles of ABVD with two cycles of escalated BEACOPP followed by two cycles of ABVD before radiotherapy in patients with unfavourable risk profile. The intensified chemotherapy approach was associated with superior FFTF and PFS but no difference in OS at 91 months follow-up. Adverse effects increased. Current follow-up is insufficient for appreciation of late adverse effects and long term outcomes. Patients with an unfavourable risk profile may therefore be considered for either four cycles of ABVD or two cycles escalated BEACOPP followed by two cycles ABVD before radiotherapy.

The management of early-stage Hodgkin lymphoma has evolved substantially over the last 25 years and has been informed by the results of many high-quality clinical trials. Individual trials have provided definitive answers that have allowed clinicians to refine specific aspects of treatment with both radiotherapy and chemotherapy. Careful consideration of these trials has highlighted two important general principles. Firstly, **only** long-term follow-up can truly provide information regarding long term results of treatment and the emergence of late adverse effects. Secondly, where competing risks exist with regard to disease recurrence and toxicity of therapy, selection of appropriate endpoints that measure all relevant risks becomes necessary to interpret the results of ongoing clinical trials and to further optimize therapy.

Management of Early-Stage Hodgkin Lymphoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the Guideline Development Group (GDG) Expert Panel and the Program in Evidence-Based Care (PEBC) Report Approval Panel (RAP) (Appendix 7). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 27 members of the Hematology Disease Site Group, 21 members cast votes and six abstained, for a total of 77.777% response. Of those that cast votes, all approved the document (77.777%). The main comments from the Expert Panel and the Working Group's modifications/actions/responses are summarized in Table 1.

Table 1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
On page 5 I find this. I think it needs to be reviewed. My guess is that the word "no" should be removed. *The GHSG HD7 study [4] found, at seven years follow-up, no statistically significant difference in overall survival, and better freedom from treatment failure in favour of the combination treatment when compared with radiotherapy alone (67% in the radiotherapy alone arm versus 88% in the combination chemotherapy plus radiotherapy arm, p<0.0001).* It is confusing for me. What level of significance is used? *p<0.0001) suggests a highly significant difference was reported. The statement says there was no significant difference, so I would expect p>.05. But there is a 21% difference in freedom from treatment - (or possibly overall survival notice there are outcomes but one set of stats).*	We have added data to clarify the sentence.
Minor syntax modifications are needed.	We have made changes.

Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in July 2015. The RAP approved the document. Table 2 shows the main comments from the RAP and the Working Group's responses.

Table 2. Summary of the Working Group's responses to comments from RAP.

Comment	Responses
Recommendation 1: Make the qualifying statement about nodular lymphocyte predominant HL as part of the recommendation	We have made the change: the recommendation was articulated in A) and B) parts, and what was the qualifying statement now constitutes part B).
Recommendation 2: Could the Working Group consider reframing this message so that language is framed as a more explicit action statement.	We have changed the recommendation from: "Patients with early-stage nonbulky HL may be considered for treatment with combined chemotherapy and radiotherapy or with chemotherapy alone" to: "Chemotherapy plus radiotherapy or chemotherapy alone are recommended treatment options for patients with early-stage nonbulky Hodgkin lymphoma"
Qualifying statement of Recommendation 2:	The conventional treatment, against which others should be compared, is IFRT. ISRT and INRT are newer treatments.

If no evidence of noninferiority, why does the recommendation strongly support IFRT? Why could not any of the three approaches be used – unless there are resource implications with no evidence of superiority. This could be introduced here and expanded on later.	Giving all three equal footing implies a demonstrated equivalence, which really hasn't yet been established. We prefer the wording that we had settled on.
Recommendations 6, 7, and 8: combine them into a two-part recommendation: A) Patients with early-stage, favourable risk Hodgkin lymphoma who are being treated with combined modality therapy should receive two cycles of ABVD chemotherapy before radiotherapy. B) Patients with early-stage, unfavourable risk Hodgkin lymphoma, who are being treated with combined modality therapy, should receive four cycles of ABVD chemotherapy, or two cycles of escalated BEACOPP followed by two cycles of ABVD chemotherapy before radiotherapy.	We decided not to make this change. The current structure (three separate recommendations) clearly separates different issues and scenarios in management and leads the reader to assemble all of the components in a complex, multi-modality treatment. Creating one mega-recommendation makes it much more difficult for a reader who doesn't have detailed familiarity with the evidentiary base to understand where this is coming from.
Spell acronyms the first time.	Change made throughout the document.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Ten targeted peer reviewers from Ontario, British Columbia, Nova Scotia, and United Kingdom who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. An invitation was sent on May 14, 2015. Three experts agreed to be the reviewers (Appendix 2). Four responses were received in October 2015. Results of the feedback survey are summarized in Table 3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 4.

Table 3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=4)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. **Rate the guideline development methods.**				2	2
2. **Rate the guideline presentation.**			1	2	1
3. **Rate the guideline recommendations.**		1	2	1	
4. Rate the completeness of reporting.			2	2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			2	1	1
6. Rate the overall quality of the guideline report.		1		1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			2	1	1
8. I would recommend this guideline for use in practice.		1	2	1	
9. What are the barriers or enablers to the implementation of this guideline report?	No responses were received.				

Table 4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. Working Group includes an appropriate blend of hematologists and radiation oncologists.	No changes required.
2. The methodology seems sound. Most of the relevant sources of which I am aware were identified and the key studies cited. However, one particular study, the RAPID trial, has been fully published and needs to be incorporated.	The RAPID trial was incorporated in its full publication. An update search was conducted in June 19 2015, and it caught the RAPID full publication which appeared in April 2015. This is specified on page 20.
3. The guideline is not well organized. Recommendations overlap (Recommendation 2 overlaps and conflicts with Recommendation 5). Recommendations 6 and 8 overlap and should be combined into one so that the unfavourable limited stage patients are comprehensively addressed.	Each recommendation tried to answer a unique question and was based upon its own evidence base. For example, Recommendation 6 focuses on number of cycles of treatment, whereas Recommendation 8 speaks to the actual chemotherapy combinations that have been studied/used. Recommendation 2 is permissive for the use of either a CMT approach or chemotherapy alone, contingent on a careful discussion between physicians and patients. Recommendation 5 speaks to the utility of interim PET imaging to change therapy. The focus of each recommendation corresponds to each of the comparisons considered, and this is explained before the recommendation text in Section 2, Guideline.
4. Presentation of tables separately from the text makes this somewhat difficult to follow (in my opinion these should be embedded in the text).	The tables are actually embedded in the text.
5. The recommendations around patient-centered considerations about (i) exclusion of radiotherapy and (ii) escalation to BEACOPP, are controversial. The guideline recommendations do a good job of addressing this controversy, but the wording of Recommendations 2 and 8 seem to provide insufficient guidance.	The wording of Recommendation 2 has been changed.
6. Regarding Recommendation #5: The authors quote the EROTC H10 and RAPID trial and make the recommendation that for patients with early stage HL a negative interim PET should not be used to omit radiotherapy. However the authors fail to acknowledge and quantify the risk (toxicity and secondary malignancies) that arise from adding radiotherapy to more than 90% of patients who would not benefit from it. Although there was a modest improvement in the three-year PFS with the addition of radiotherapy, this effect is bought at the expense of exposing all patients to radiation, most of whom will not benefit and some of whom will be harmed. In fact, for patients cured with chemotherapy, the addition of radiotherapy can only contribute additional toxic effects. Among the 46 patients requiring second-line therapy, 32% of those in the group with no further therapy, 50% in the radiotherapy group, and 57% in the group with positive PET findings underwent transplantation; this	We did recommend that pros and cons are to be considered and discussed in a patient-centered discussion. In the RAPID trial the authors changed the noninferiority margin (established in 2003) when the study was already ongoing as a result of experts' opinion ("delegate survey at the 7th International Symposium on Hodgkin Lymphoma in 2007"). As the results stand now, the new (more conservative) margin was crossed, while the previous margin was not.

Comments	Responses
provides reassurance that recurrence of Hodgkin's lymphoma in the group with no further therapy was not associated with excessive use of intensive treatment approaches. The authors conclude that in stage IA and stage IIA Hodgkin lymphoma with no mediastinal bulk, patients with negative PET findings after three cycles of ABVD have a very good prognosis either with or without consolidation radiotherapy. Although the noninferiority margin was exceeded in this study, the results suggest that radiotherapy can be avoided for patients with negative PET findings. The current recommendations should further clarify why their recommendations/conclusions differ and how the minor added benefit of 3.8 percentage points in the intention-to-treat analysis, justifies adding radiotherapy and toxicity to the entire patient population. At the least, I believe this decision should be left to a multidisciplinary tumour board discussion and discussion with the patient, weighing the benefits and risks of each approach. .	The full publication represents still an ongoing trial. RCTs with longer follow-up to decide on AE related to radiotherapy are not available at this date to decide.
7. Generally complete. The RAPID trial, which is crucial, was incompletely considered and additional perspectives (e.g., consideration of number needed to treat) are missing.	Number needed to treat for time to event data would make sense if we had studies had the same length of follow-up (because NNT varies according to the length of follow-up), were executed at the same time, with same techniques, and for the same time points. What would be important to know is the percentage of people who would get secondary tumours after STNI (worse-case scenario) after 20/25 years follow up.
8. The information is there; however, I find its interpretation lacks balance on some points. Recommendation 2 and its Qualifying Statement are actually the most sound and sensible recommendations in the entire guideline and put forward a flexible position that is most sensitive to this patient population's needs. However, several other recommendations advance much more inflexible interpretations lacking that sensitivity and the need to apply the available data to real-world situations.	Recommendation 5 was changed to: "The Working Group does not recommend the use of a negative interim positron emission tomography (PET) scan **alone** to identify patients with early-stage HL for whom radiotherapy can be omitted without a reduction in progression-free survival (PFS)." This makes it consistent with recommendation 2 and introduces flexibility.
9. Most of the recommendations in this report are sound and would help inform decision making. It would be prudent to identify all recommendations for items that are currently being evaluated prospectively in clinical trials and that should be readdressed when trial results are available (perhaps in a separate table or paragraph).	A section for ongoing trials is presented on page 55, Section 4.
10. (i) Management recommendations for individual patients with limited stage HL requires an essential discussion about the risks and benefits of combined modality treatment versus chemotherapy alone. This discussion can be strongly influenced by the bias of the first practitioner to encounter the patient. Multidisciplinary discussions involving patient, hematologist/oncologist, and radiation oncologist rarely occur simultaneously. (ii) A priori management plans of combined modality treatment can be influenced by negative PET/CT scans after two cycles of chemotherapy, despite the evidence that forms Recommendation 5.	No changes were made.
11. 1. These guidelines are intended to address "early-stage Hodgkin lymphoma" but quite oddly do not define "early stage". This is not a trivial omission. It is clear from the evidence cited in several recommendations, especially Recommendations 6 and 8, that the authors included patients with stage IIB disease and patients	In Appendix 1, page 102, a table presents the definitions of favourable and unfavourable characteristics for early-stage Hodgkin

Comments	Responses
with stage II bulky disease. Many clinicians consider such patients to have advanced stage disease and, therefore, are not appropriately included in guidelines for "early stage" disease. The definition of "early-stage" disease should be clearly stated and the authors should clearly acknowledge that most of the patients addressed in Recommendations 6 and 8, unfavorable subset, have characteristics such as B symptoms or bulky tumors (>10 cm) that many clinicians would consider better managed as advanced stage disease. 2. Recommendation 5. The wording is overly directive. Most readers will interpret this recommendation as firmly recommending against the use of chemotherapy alone for this subset of patients (PET negative after two cycles of ABVD), which directly conflicts with Recommendation 2, which indicates that chemotherapy alone is an acceptable option. Furthermore, the Qualifying Statement for Recommendation 2 indicates that "The decision on which treatment option to use should involve a patient-centered discussion with a hematologist/medical oncologist and a radiation oncologist. Patients should be aware of the trade-offs or risks associated with RT and chemotherapy alone." Certainly the finding of a negative PET scan after two cycles of chemotherapy should be included in any such discussion. Recommendation 5 should simply be dropped from the guideline or replaced with a short statement that the issue is unsettled. Recommendation 2 covers this situation.(Also see comment 6 below.) 3. This review has failed to include the evidence from the RAPID trial, which is relevant to several of the recommendations and should lead to a quite different Recommendation 5 (which, as I mention above should be dropped) and without which the guideline is incomplete. (Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 2015;372(17):1598-607.) Inclusion of the published data from the RAPID trial is also relevant to Recommendation 2 and the Key Evidence section of this recommendation should be revised. 4. Recommendation 8 is too strong. The evidence in favor of using BEACOPP plus ABVD plus radiation is inadequate to justify its known toxicity and, contrary to what is in the qualifying statement, the evidence is sufficiently mature to assess long-term outcomes (overall survival). 5. The study cited in references 7 and 8 (Meyer et al.) is repeatedly referred to as the EORTC H.6 or just H.6 study throughout the review. In fact, this was not an EORTC trial, but rather the NCIC CTG HD.6 trial conducted by the NCIC CTG and ECOG. I would have thought a Canadian guideline would correctly credit such an important Canadian led trial. 6. The discussion in the interpretation of the Evidence for Recommendation 5 omits a very important consideration: number needed to treat. The data from the RAPID trial and the EORTC H10 trial document that treating patients with a negative PET2 scan places them at approximately 4 % higher risk of relapse. This means that at least 25 patients must be given radiation to avoid one relapse. If even one of those 25 patients experiences a negative impact equivalent to the negative impact of having a relapse, which is modest when one remembers that secondary treatment for this type of patient is reliably curative and that overall survivals in the cited trials are the same with and without radiation, the outcomes balance. A more appropriate Recommendation 5 would be to roll it into Recommendation 2 and indicate this decision "should involve a patient-centred discussion with a hematologist/medical oncologist and a radiation oncologist."	lymphoma. This table is referred to on page 4, in Recommendation 4.
My main concern is that Recommendation 2 is for chemotherapy plus radiotherapy or chemotherapy alone for early stage HL but there is no subsequent guidance on how these different philosophies should be implemented in practice i.e., when to use chemotherapy plus RT or chemotherapy alone. This I think will reinforce current practices (which may come down to individual preferences/prejudices) rather than providing countrywide leadership in this important area.	Recommendations 2 (qualifying statement) and Recommendation 5 have been modified.

Comments	Responses
The main issue is that cure is possible in a high proportion of patients with early stage HL but long term survival is dependent on avoiding late treatment toxicity, especially second cancers and cardiovascular disease. This is highly relevant to the HL population most of whom are young at presentation and who will only be in their 50s and 60s after 30 years of follow-up. Data I have reviewed that will be published shortly show that the risk of second cancers in HL survivors is considerable and is linked to exposure to radiotherapy and alkylating agent containing chemotherapy (especially procarbazine). In an editorial accompanying this paper I wrote that every effort must be made to focus these damaging treatments on those at greatest risk (from HL) and avoid them in those at lower risk. In other words individualization of treatment and a move away from a "one size fits all" approach is essential if we are to optimize outcomes. This is where PET directed approaches may be extremely helpful – however I see that in these guidelines the use of PET is not supported (Recommendation 5). I regard this as a major weakness especially when chemotherapy alone is identified as an option for treatment (Recommendation 2). Although results of the UK NCRI RAPID trial (Radford et al NEJM 2015) did not confirm noninferiority of CT alone versus CT plus RT in patients who achieve PET negativity after three cycles ABVD, according to the defined level of noninferiority it is clear that CT alone produces very good outcomes in this population. These results are very similar to those seen in the EORTC/LYSA/FIL H10 trial (Raemaekers et al. J Clin Oncol 2014). In both trials the addition of RT has a marginal benefit on PFS but this is obtained at the expense of irradiating everyone, most of whom don't need it. So my recommendation would be to give three cycles ABVD and then perform a PET scan. If this is "negative" (Deauville score 1 or 2) and the patient is young no further treatment should be considered – patients should be made aware that the risk of relapse is slightly higher but if no relapse there is no subsequent risk of RT induced late toxicity. If the patient is older (say 50 plus) and the PET scan is "negative," RT becomes more appropriate because the threat of relapse and need for salvage treatment then becomes the greater hazard. Those who are PET "positive" after three cycles of ABVD should receive an additional cycle of ABVD followed by RT. The group may like to consider reviewing the second cancer data alluded to above before signing off these guidelines. I understand that their publication is imminent.	

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All medical oncologists, radiation oncologists, hematologists, and nuclear medicine physicians in the PEBC database were contacted by email. In addition, individuals belonging to the Cancer Care Ontario Positron Emission Tomography Committee were contacted and asked to participate in the survey. Practitioners were contacted on September 3, 2015 to inform them of the survey, and the survey period closed on October 16, 2015. Two hundred and thirty-seven professionals from Ontario were asked to participate and 11 (4%) agreed and responded to the survey. Fifty-seven stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 11 people are summarized in Table 5. The main comments from the consultation and the Working Group's responses are summarized in Table 6.

Table 5. Responses to four items on the professional consultation survey.

	Number 11 (4%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1	6	4
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1	3	7
3. I would recommend this guideline for use in practice.			1	3	7
4. What are the barriers or enablers to the implementation of this guideline report?	• No significant barriers. None, this is very practical and addresses real practice issues. • It remains an area where decisions may be complex. Decision aids may be helpful. • Personal beliefs.				

Table 6. Actions taken/Responses regarding main written comments from professional consultants.

Comments	Responses
1. Based on HD 6, many physicians are using chemotherapy alone in early-stage nonbulkyHL if imaging is negative at interim - based on emerging evidence it appears that chemotherapy alone results in still good but not equivalent PFS when compared with combination chemotherapy and radiation - but there is a concern about radiation for young patients because of long term toxicity/second cancer. Therefore, it would be helpful to have a definitive statement as to whether there is any patient population for which you would consider chemotherapy alone if interim PET was negative? (e.g., mediastinal disease in a young woman who does not want to have an increased risk of breast cancer from radiation therapy).	The qualifying statement of Recommendation 2 has been modified.
2. The style of presentation is not very user friendly.	No changes were made.
3. Very comprehensive - more discussion regarding weighing toxicity versus outcome results would be helpful. The discussion is well written.	No changes were made.
4. The last recommendation regarding the use of escalated BEACOPP would be better supported with more detail about off-setting toxicity.	No changes were made.
5. Not earth shaking but reasonable.	No changes were made.
6. Excellent, thorough.	No changes were made.
7. As a non-expert for the treatment of Hodgkin lymphoma, here are a few comments for the guideline: 1) For recommendation 1B - should the phrase starting from "however, no phase III clinical trials....." be a qualifying statement rather than part of the recommendation? 2) Should definitions for nonbulky, favourable, unfavourable Hodgkin lymphoma be discussed in the guideline - as different studies may have used different criteria for patient group selections? Or is this clearly understood by lymphoma-treating physicians? 3) Possible conflict between Recommendations 1B and 2? 4) Consider rearranging the order of the Recommendations - 1, 2, 6,5,3,4,7,8.	No changes were made.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

Glossary of Acronyms

Acronym	Description
Abs	Abstract
ABV	Doxorubicin, bleomycin and vinblastine
ABVD	Doxorubicin, bleomycin, vinblastine and dacarbazine
AE	Adverse events
AMH	Anti-Müllerian hormone
AP-PA	Anteroposterior-posteroanterior
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AV	Doxorubicin and vinblastine
AVD	Doxorubicin, vinblastine and dacarbazine
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone
CARES-SF	Cancer rehabilitation evaluation system-short form
CCO	Cancer Care Ontario
CI	Confidence interval
CMT	Combined modality treatment
COI	Conflict of interest
COPP	Cyclophosphamide, vincristine, procarbazine and prednisone
CR	Complete remission (complete response)
CS	Clinical stage
d(s)	day(s)
DSG	Disease Site Group
EBVM	Epirubicin, bleomycin, vinblastine and methotrexate
EBVP	Epirubicin, bleomycin, vinblastine and prednisone
ECOG	Eastern Cooperative Oncology Group
EF	Extended field
EFRT	Extended field radiation therapy
EFS	Event-free survival
EORTC	European Organization for Research and Treatment of Cancer
EPBV	Epirubicin, prednisone, bleomycin and vinblastine
ESR	Erythrocyte sedimentation rate
EVE	Epirubicin, vinblastine and etoposide
F	Favourable
FDG	Fluorodeoxyglucose
FDP	Freedom from disease progression
FFP	Freedom from progression
FFS	Failure-free survival
FFTF	Freedom from treatment failure
FSH	Follicle-stimulating hormone
GDG	Guideline Development Group

GELA	Group d'Études des Lymphomes de l'Adulte
GHSG	German Hodgkin Study Group
GOELAMS	Groupe Ouest-Est d'étude des Leucémies et Autres Maladies du Sang
HL	Hodgkin lymphoma
HR	Hazard ratio
IF	Involved field
IFRT	Involved field radiation therapy
IN	Involved node
INRT	Involved node radiation therapy
ISRT	Involved site radiation therapy
iv	Intravenous
med mass	Mediastinal mass
MFRT	Mantle field radiotherapy
mg	Milligram
MIC	Mitomycin, ifosfamide and cisplatin
MOPP-ABV	Sequential mechlorethamine, vincristine, procarbazine and prednisone and doxorubicin, bleomycin, and vinblastine
MOS	Medical outcomes study
N	Sample size
NCCN	National Comprehensive Cancer Network
NCIC	National Cancer Institute of Canada
NCRI	National Cancer Research Institute
NLPHL	Nodular lymphocyte predominant Hodgkin Lymphoma
nr	Not reported
NS	Not statistically significant
OMHLTC	Ontario Ministry of Health and Long-Term Care
OS	Overall survival
PEBC	Program in Evidence-based Care
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial remission (partial response)
PS	Pathological stage
Pts	Patients
QOL	Quality of life
RAP	Report Approval Panel
RCT	Randomized controlled trial
ref	Reference
RFS	Relapse-free survival
RR	Relative risk
RT	Radiotherapy
SDS	Symptom distress scale
SN	Second neoplasms

SR	Systematic review
STLI	Subtotal lymphoid irradiation
STNI	Subtotal nodal irradiation
SWOG	Southwest Oncology Group
Sx	Symptoms
T	Thoracic
TRM	Treatment-related mortality
U	Unfavourable
uCR	Unconfirmed complete response
UK	United Kingdom
VAPEC-B	Doxorubicin, cyclophosphamide, etoposide, vincristine, and bleomycin with prednisolone and prophylactic cotrimoxazole or ketoconazole
vs	Versus
wk	Week
x	Times
yr	Year

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APPENDICES

Appendix 1. Definition of favourable and unfavourable characteristics by different groups

Unfavourable Risk Factors in Early-stage HL: Risk stratification

Risk factor	EORTC	GHSG	NCIC/ECOG	NCCN 2010
Med Mass	>0.35 at T/6	>1/3	<1/3 or 10 cm	> 1/3 or >10 cm
Histology			MC or LD	
Age	≥50 years old		≥40 years old	-
EN disease	-	Any		>1
ESR and B Sx	≥50 or ≥30 and B Sx	≥50 or ≥30 and B Sx	≥50	≥50 or any B Sx
Number of nodal sites	>3	>2	>3	>3

EORTC = European Organization for Research and Treatment of Cancer; ESR = erythrocyte sedimentation rate; GHSG = German Hodgkin Study Group; med mass = mediastinal mass; NCIC/ECOG = National Cancer Institute of Canada/Eastern Cooperative Oncology Group; NCCN 2010 = National Comprehensive Cancer Network 2010; Sx = symptoms; T = thoracic.

Note: for all the scoring systems, if any one risk factor is present, than the patient is considered unfavourable.

Appendix 2. Members of the Working Group, Disease Site Group, Report Approval Panel, Target Peer Reviewers, their affiliation, and their conflict-of-interest declarations

Name	Affiliation	Declarations of interest
Working Group		
Michael Crump Working Group co-chair	Princess Margaret Hospital, Toronto, Ontario	Received $5000 as Eli Lilly consultant in 2013; has been the principal investigator in a trial involving one of the objects of study
Jordan Herst Working Group co-chair	Northeastern Ontario Regional Cancer Centre at Sudbury Regional Hospital, Sudbury, Ontario	No conflict of interest declared
Fulvia Baldassarre Health Research Methodologist	Program in Evidence-Based Care, McMaster University, Hamilton, Ontario	No conflict of interest declared
Janet MacEachern Hematologist/oncologist	Grand River Regional Cancer Centre, Kitchener, Ontario	No conflict of interest declared
Jonathan Sussman Radiation Oncologist	Juravinski Cancer Centre, Hamilton, Ontario	Received grants, research support as a principal investigator in a trial involving one of the objects of study
David Hodgson Radiation Oncologist	Princess Margaret Hospital, Toronto, Ontario	No conflict of interest declared
Matthew Cheung Hematologist /oncologist Disease Site Group co-chair	Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto, Ontario	No conflict of interest declared
Hematology Disease Site Group		
Patricia Disperati Hematologist/oncologist	Toronto East General Hospital, Toronto, Ontario	No conflict of interest declared
Graeme Fraser Hematologist / internist	Juravinski Cancer Centre, Hamilton, Ontario	No conflict of interest declared
David Robinson Patient Representative	Sudbury	No conflict of interest declared
Robert Stevens Hematologist/oncologist	Grand River Regional Cancer Centre, Kitchener	No conflict of interest declared
Nicole Laferriere Hematologist/ internist	Northwestern Ontario Regional Cancer Centre at Thunder Bay Regional Health Sciences Centre, Thunder Bay, Ontario	No conflict of interest declared

Yael Zaretski Hematologist / internist	Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto, Ontario	No conflict of interest declared
Jason Tay Hematologist	Ottawa Hospital-General Campus, Ottawa, Ontario	No conflict of interest declared
Leonard Minuk Hematologist	London Health Sciences, London Cancer Centre, London, Ontario	No conflict of interest declared
Mitchell Sabloff	Ottawa General Hospital, Ottawa	No conflict of interest declared
Irwin Walker Hematologist / internist	McMaster University Medical Centre, Hamilton, Ontario	No conflict of interest declared
Sindu Kanjeekal Hematologist/oncologist	Windsor Regional Cancer Centre at Windsor Regional Hospital, Windsor, Ontario	No conflict of interest declared
Andrea Lee Hematologist	1060 Speers Road, Suite 118, Oakville, Ontario	No conflict of interest declared
Ivan Tyono Pharmacist	Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto, Ontario	No conflict of interest declared
Lisa Hicks Hematologist/internist	St. Michael's Hospital, Toronto, Ontario	No conflict of interest declared
Tom Kouroukis Hematologist/internist	Juravinski Cancer Centre, Hamilton, Ontario	No conflict of interest declared
André Schuh Hematologist/internist	Princess Margaret Hospital, Toronto, Ontario	No conflict of interest declared
Chris Bredeson Hematologist/internist	The Ottawa Hospital General Campus, Ottawa, Ontario	No conflict of interest declared
Report Approval Panel		
Melissa Brouwers	McMaster University, Hamilton, Ontario	No conflict of interest declared
Shailendra Verma	The Ottawa Hospital Cancer Centre, Ottawa, Ontario	No conflict of interest declared
Marko Simunovic	Juravinsky Cancer Centre, Hamilton, Ontario	No conflict of interest declared
Targeted Peer Reviewers		
David McDonald	Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia	Has been a principal investigator in a trial involving one of the interventions object of study. Has published an opinion paper regarding the object of study.

Joseph Connors	BC Cancer Agency, Vancouver, British Columbia	Has supervised research sponsored by Seattle Genetics, Roche Canada, and Millennium Takeda. Has been the principal investigator in a trial involving one of the interventions under study. Has published several opinion papers on the topic of study.
Ur Metser	University Health Network, Toronto, Ontario	No conflict of interest declared

Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, the members of the Hematology Disease Site Group, and internal and external reviewers were asked to disclose potential conflicts of interest. Their responses in this regard are reported in the table above. The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.

Appendix 3. Search strategies

Database: Ovid MEDLINE(R) Daily Update <June 07, 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 (favo?rable or unfavo?rable).tw,kf,ot.
2 (I-II or I-III).tw,kf,ot.
3 ((earl$ or low$ or limit$) adj3 (stag$ or grad$)).tw,kf,ot.
4 Intermediate$.tw,kf,ot.
5 or/1-4
6 exp Lymphoma/
7 exp Hodgkin Disease/
8 germinoblastom$.tw,kf,ot.
9 reticulolymphosarcom$.tw,kf,ot.
10 Hodgkin$.tw,kf,ot.
11 (malignan$ adj2 (lymphogranulom$ or granulom$)).tw,kf,ot.
12 or/6-11
13 exp Antineoplastic Agents/
14 Remission induction/
15 exp Antineoplastic Protocols/
16 ((consolidat$ or induct$ or maintenance or conditioning$) and (therap$ or treat$ or regimen$ or patient$)).tw,kf,ot.
17 ((therap$ or induc$) adj3 remission$).tw,kf,ot.
18 (Antineoplast$ or anti-neoplast$).tw,kf,ot.
19 ((cytosta$ or cytotox$) adj2 (therap$ or treat$ or regimen$)).tw,kf,ot.
20 (chemotherap$ or chemo-therap$).tw,kf,ot.
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 exp Radiotherapy/
23 (radiotherap$ or radio-therap$).tw,kf,ot.
24 exp Lymphatic Irradiation/
25 22 or 23 or 24
26 (chemoradiotherap$ or chemo-radio-therap$).tw,kf,ot.
27 exp Combined Modality Therapy/
28 ((multimodal$ or multi-modal$) adj3 (treat$ or therap$)).tw,kf,ot.
29 (combi$ adj3 modalit$).tw,kf,ot.
30 26 or 27 or 28 or 29
31 Tomography, Emission-Computed/
32 (positron adj2 emission adj2 tomography).tw,kf,ot.
33 Fluorodeoxyglucose F18/
34 18f fluorodeoxyglucose.tw,kf,ot.
35 PET.tw,kf,ot.
36 (PET adj2 FDG).tw,kf,ot.
37 18f-fdg.tw,kf,ot.
38 2-fluoro-2deoxy-d-glucose.tw,kf,ot.
39 2-fluoro-2-deoxyglucose.tw,kf,ot.
40 18f-fdg.tw,kf,ot.
41 Positron-Emission Tomography/
42 Fluorodeoxyglucose F18/

43 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44 randomized controlled trial.pt.
45 controlled clinical trial.pt.
46 controlled clinical trials/
47 (clinical trials, phase II or clinical trials, phase III or clinical trials, phase IV or multicenter studies)/
48 random allocation/
49 double blind method/
50 cross-over studies/
51 single-blind method/
52 clinical trial.pt.
53 (clin: adj25 trial:).ti,ab.
54 ((singl: or doubl: or trebl: or tripl:) adj25 (blind: or mask:)).ti,ab.
55 placebos/
56 placebo:.ti,ab.
57 random:.ti,ab.
58 or/44-57
59 meta-analysis.sh,pt. or meta-analy:.tw. or metaanaly:.tw.
60 ((systematic: or quantitativ:) adj (review: or overview:)).tw.
61 (cochrane or medline or cinahl or embase or scisearch or psychinfo or psycinfo or psychlit or psyclit or (national and library)).tw.
62 ((handsearch: or search:) and (cochrane or medline or cinahl or embase or scisearch or psychifo or psycinfo or psychlit or psyclit or (national and library) or (hand: or manual: or electronic: or bibliograph: or database:))).tw.
63 ((review or guideline).pt. or consensus.ti. or guideline:.ti. or literature.ti. or overview.ti. or review.ti.) and (61 and 62)
64 ((synthesis or overview or review or survey) and (systematic or critical or methodologic or quantitative or qualitative or literature or evidence or evidence-based)).ti.
65 59 or 60 or 62 or 63 or 64
66 5 and 12
67 21 or 25 or 30 or 43
68 66 and 67
69 58 and 68
70 65 and 68
71 69 or 70
72 limit 71 to english language
73 animal/ not (human/ and animal/)
74 72 not 73
75 limit 74 to yr="2003 -Current"

Database: Embase <1996 to 2013 Week 24>
Search Strategy: Executed on June 18, 2013
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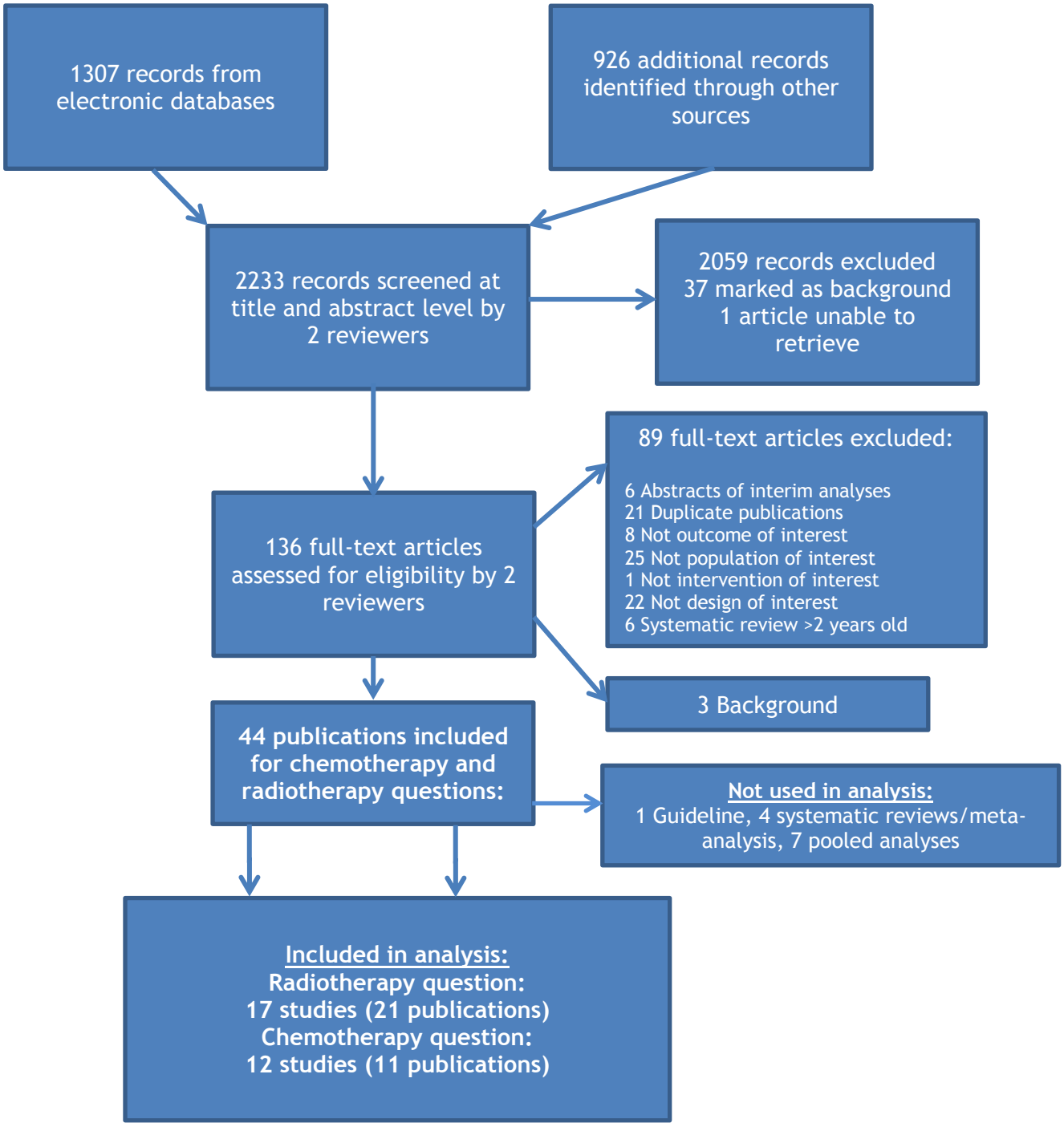
1 (favo?rable or unfavo?rable).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2 ((earl$ or low# or limit$) adj3 (stag$ or grad$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3 intermediate$.mp.
4 bulky.mp.
5 1 or 2 or 3 or 4
6 *lymphoma/
7 exp Hodgkin disease/
8 Hodgkin$.mp.
9 (malingnan$ adj2 (lymphogranulom$ or granulom$)).mp.
10 6 or 7 or 8 or 9
11 5 and 10
12 exp antineoplastic agent/
13 remission/
14 exp clinical protocol/
15 ((consolidat$ or induct$ or maintenance or conditioning$) and (therap$ or treat$ or regimen$ or patient$)).tw.
16 ((therap$ or induc$) adj3 remission$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
17 (chemotherap$ or chemo-therap$).mp.
18 (antineoplast$ or anti-neoplast$).mp.
19 ((cytosta$ or cytotox$) adj2 (therap$ or treat$ or regimen$)).mp.
20 exp radiotherapy/
21 (radiotherap$ or radio-therap$).mp.
22 (chemoradiotherap$ or chemo-radio-therap$).tw.
23 exp multimodality cancer therapy/
24 ((multimodal$ or multi-modal$) adj3 (treat$ or therap$)).tw.
25 exp lymph node irradiation/
26 (combi$ adj3 modalit$).mp.
27 positron emission tomography/
28 (positron adj2 emission adj2 tomography).mp.
29 fluorodeoxyglucose f 18/
30 (18f fluorodeoxyglucose or PET orFDG or 18f-fdg or 2-fluoro-2deoxy-d-glucose or 2-fluoro-2-deoxyglucose).mp.
31 computer assisted tomography/ or tomography/
32 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33 11 and 32
34 clinical trial/
35 "randomized controlled trial (topic)"/
36 randomization/
37 single blind procedure/
38 double blind procedure/

39 crossover procedure/
40 placebo/
41 randomi?ed controlled trial$.tw.
42 RCT.tw.
43 random allocation.tw.
44 randomly allocated.tw.
45 allocated randomly.tw.
46 (allocated adj2 randomly).tw.
47 single blind$.tw.
48 double blind.tw.
49 ((treble or triple) adj blind$).tw.
50 Placebo$.tw.
51 prospective study/
52 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53 33 and 52
54 limit 53 to (english language and yr="2003 -Current")
55 animal/ not (human/ and animal/)
56 54 not 55

Appendix 4. Study flow chart



Appendix 5. Dose and schedule of chemotherapy and radiotherapy treatments

Table 1. Management of early-stage Hodgkin lymphoma, Radiotherapy question: dose and schedule of chemotherapy and radiotherapy in studies included.

Study	Comparison	Chemotherapy dose and schedule	Radiotherapy dose and schedule
A. Radiotherapy in combination with chemotherapy compared with chemotherapy alone			
NCIC CTG/ECOG H.6 Meyer, 2012 [7]	Arm A: ABVD only Arm B: STNI with or without chemotherapy.	ABVD: 4 to 6 cycles doxorubicin 25 mg/m^2 ds 1 and 15 bleomycin 10 mg/m^2 ds 1 and 15, vinblastine 6 mg/m^2 ds 1 and 15, dacarbazine 375 mg/m^2 ds 1 and 15 + repetition on d 29.	Pts with a favourable risk profile received only STNI (35 Gy) in 20 daily fractions; patients with an unfavourable risk profile received 2 cycles of ABVD and STNI.
RAPID Radford, 2015 [9]	All pts: 3xABVD[A]. If PET negative: Arm A: IFRT Arm B: no further intervention (If PET positive: 1 more cycle of ABVD and IFRT)	NA	30 Gy IFRT
EORTC-GELA H9F Thomas, 2007 [abs] [10]	Arm A: 36 Gy IFRT + 6xEBVP Arm B: 20 Gy IFRT + 6xEBVP Arm C: No RT + 6 cycles EBVP + 30 Gy IFRT (arm stopped early)	*nr*	*nr*
B. Low dose compared with high-dose radiotherapy			
GHSG HD10 Engert, 2010 [17]	Arm A 4 x ABVD + IFRT 30 Gy vs. Arm B 4 x ABVD + IFRT 20 Gy vs. Arm C 2 x ABVD + IFRT 30 Gy vs. Arm D 2 x ABVD + IFRT 20 Gy	ABVD: 4 to 6 cycles doxorubicin 25 mg/m^2 ds 1 and 15 bleomycin 10 mg/m^2 ds 1 and 15, vinblastine 6 mg/m^2 ds 1 and 15, dacarbazine 375 mg/m^2 ds 1 and 15 + repetition on d 29.	Started 4-6 wks after the end of chemotherapy. 30 Gy or 20 Gy IFRT in single fractions of 1.8 to 2.0 Gy administered five times weekly.
GHSG HD11 Eich, 2010 [16]	4 x ABVD + IFRT 30 Gy vs. 4 x ABVD + IFRT 20 Gy vs. 4 x BEACOPP standard + 30 Gy IF-RT vs. 4 x BEACOPP standard + 20 Gy IF-RT	ABVD: 4 to 6 cycles doxorubicin 25 mg/m^2 ds 1 and 15 bleomycin 10 mg/m^2 ds 1 and 15, vinblastine 6 mg/m^2 ds 1 and 15, dacarbazine 375 mg/m^2 ds 1 and 15 + repetition on d 29. BEACOPP: doxorubicin 25 mg/m^2 d 1, etoposide 100 mg/m^2 ds 1 through 3, cyclophosphamide 650 mg/m^2 d 1 procarbazine 100 mg/m^2 ds 1 through 7 prednisone 40 mg/m^2 ds 1 through 14, vincristine 1.4 mg/m^2 d 8, bleomycin 10 mg/m^2 d 8, repeated on d 22.	30 Gy or 20Gyof IFRT in single fractions of 1.8 to 2.0 Gy administered 5 times weekly.

Study	Comparison	Chemotherapy dose and schedule	Radiotherapy dose and schedule
EORTC GELA H9U Thomas, 2007 [abs] [10]	H9F: Arm A: 36 Gy IFRT + 6xEBVP Arm B: 20 Gy IFRT + 6xEBVP Arm C: No RT + 6xEBVP + 30 Gy IFRT (arm stopped early)	H9F: EBVP (1 cyle = 21 ds): Epirubicin 70 mg/m^2 d 1 Bleomycin 10 mg/m^2 d 1 Vinblastine 6 mg/m^2 d 1 Prednisone 40 mg/m^2 ds 1 through 5	*nr*
GOELAMS H97-E Arakelyan, 2010 [18]	Arm A (reduced dose arm): 3xABVD + irradiation at 36 Gy to initially involved sites and 24 Gy to adjacent sites, the upper infradiaphragmatic area, and the spleen. Arm B: same chemotherapy regimen and the same irradiation as Arm A given at doses of 40 Gy and 30 Gy, respectively. Arm C: historical control: 202 pts from 2 previous trials who had received Arm B treatment before.	ABVD: 4 to 6 cycles doxorubicin 25 mg/m^2 ds 1 and 15 bleomycin 10 mg/m^2 ds 1 and 15, vinblastine 6 mg/m^2 ds 1 and 15, dacarbazine 375 mg/m^2 ds 1 and 15 + repetition on d 29.	The irradiation of chemotherapy-responding patients in both arms was started 4 to 5 weeks after the last ABVD infusion. Arm B: pts in CR after chemotherapy received full-dose irradiation, i.e., 40 Gy to initially involved sites (10 Gy per week) and 30 Gy to adjacent lymph node areas, the spleen, and the upper infradiaphragmatic area. Arm A (experimental arm) pts in CR after chemotherapy received reduced doses of irradiation, i.e., 36 Gy to initially involved sites (10 Gy per week) and 24 Gy to adjacent uninvolved lymph nodes, the upper infradiaphragmatic area, and the spleen. Arm A and B: Pts in PR after chemotherapy received the same irradiation dose as patients in arm B (40/30 Gy). Pts with progressive disease after chemotherapy received salvage therapies.
C. Smaller field compared with larger radiotherapy field			
GHSG HD8 Engert, 2003 [14]	Arm A: 30 Gy EFRT (10 Gy to bulky disease) Arm B: 30 Gy IFRt (10 Gy to bulky disease)	2 cycles of COPP/ABVD COPP: cyclophosphamide 650 mg/m^2 ds 1 through 8, vincristine 1.4 mg/m^2 ds 1 through 8, procarbazine 100 mg/m^2 ds 1 through 14, prednisone 40 mg/m^2 d 1 through 14; ABVD: 4 to 6 cycles doxorubicin 25 mg/m^2 ds 1 and 15 bleomycin 10 mg/m^2 ds 1 and 15, vinblastine 6 mg/m^2 ds 1 and 15, dacarbazine 375 mg/m^2 ds 1 and 15 + repetition on d 29.	Pts received 30 Gy in either the EFRT technique (arm A) or IFRT technique (arm B) over a period of 3 to 3.5 wks. Additional 10 Gy were given during the 4th week to areas of initial bulky disease. Single-fraction size was 1.8 to 2.0 Gy given 5 times/wk.
Italian study (Istituto Tumori Milano) Bonadonna, 2004 [13]	Arm A: ABVD +STNI Arm B: ABVD + IFRT	ABVD: doxorubicin 25 mg/m^2, bleomycin 10 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2.	Started 4 wks after last chemotherapy cycle. Pts in CR received 36 Gy and pts in uCR or PR received 40 Gy to previously involved sites. Pts allocated to receive STNI 30.6 Gy to uninvolved sites. Radiotherapy was given in daily fractions was 0.90 + 0.90 Gy 5 ds per wk.
D. Smaller radiotherapy field plus chemotherapy compared with larger radiotherapy field			

Study	Comparison	Chemotherapy dose and schedule	Radiotherapy dose and schedule
EORTC GELA H7F Noordijk, 2006 [12]	H7F: Arm A: STNI Arm B: 6 cycles EBVP +IFRT	EBPV: epirubicin 70 mg/m^2 d 1 bleomycin 10 mg/m^2 d 1 vinblastine 6 mg/m^2 d 1 prednisone 40 mg/m^2 d 1 through 5 MOPP/ABV hybrid: mechlorethamine 6 mg/m^2 d 1 vincristine 1.4 mg/m^2 d 1 procarbazine 100 mg/m^2 d 1 through 7 prednisone 40 mg/m^2 d 1 through 14 doxorubicin 35 mg/m^2 d 8 bleomycin 10 mg/m^2 d 8 vinblastine 6 mg/m^2 d 8	In all groups radiation was administered in fractions of 1.5 to 2.0 Gy, 5 fractions per week, with both fields treated each day. STNI: involved areas, 40 Gy; uninvolved areas and spleen, 36 Gy IFRT: 36 to 40 Gy;
EORTC GELA H8 Ferme, 2007 [11]	H8F: Arm A: STNI Arm B: a combination of 3 cycles of MOPP-ABV + IFRT H8U: Arm A: 6 cycles of MOPP-ABV + IFRT Arm B: 4 cycles of MOPP-ABV + IFRT Arm C: 4 cycles of MOPP-ABV + STNI	MOPP: mecholrethamine (6 mg/m^2 d 1) vincristine 1.4 mg/m^2 (max 2 mg, d 1) procarbazine (100 mg/m^2 ds 1 through 7) prednisone (40 mg/m^2 ds 1 through 14) ABV: doxorubicin (35 mg/m^2 d 8) bleomycin (10 mg/m^2 d 8) vinblastine (6 mg/m^2 d 8)	1 cycle = 28 days IFRT: target volumes included involved nodal regions. Pts in CR after chemotherapy had 36 Gy, and those in PR had 40 Gy (+ 4 Gy if needed) in fractions of 2 Gy. STNI: mantle field, spleen and para-aortic nodes. Pts had 36 Gy of radiation to nodal regions + 4 Gy in initially involved nodal regions
NCRI LY07 Thistlethwaite, 2007 [abs] [15]	Arm A: MFRT Arm B: minimal initial chemotherapy (i.e., 4 wks of VAPEC-B) + IFRT	VAPEC-B chemotherapy: doxorubicin 35 mg/m^2 iv at wks 1 and 3, cyclophosphamide 350 mg/m^2 iv at wk 1, etoposide 100 mg/m^2 po days 1-5 at wk 3, vincristine 1.4 mg/m^2 iv at wks 2 and 4 and bleomycin 10,000 IU/m^2 iv at wks 2 and 4 with prednisolone 50 mg daily for 4 wks and prophylactic cotrimoxazole/ketoconazole	In both arms RT dose was: 30-40 Gy in daily fractions of 1.8 to 2 Gy.
E. PET used for tailoring the therapeutic strategy			
EORTC /Lysa/Fil H10F Raemaekers, 2014 [1]	Arm A: 2 ABVD + 30 Gy INRT (PET only for comparison) (control arm) Arm B: 2x ABVD +PET. If PET negative, 2x ABVD and no radiotherapy. If PET positive 2x BEACOPP +30 Gy INRT	*nr*	*nr*
EORTC /Lysa/Fil H10U Raemaekers, 2014 [1]	Arm A (control): 4xABVD + 30 Gy INRT. PET performed to all pts after cycle 2 with no change in treatment	*nr*	*nr*

Study	Comparison	Chemotherapy dose and schedule	Radiotherapy dose and schedule
	Arm B (intervention): 2 x ABVD +PET. If PET positive, 2 x BEACOPP + 30 Gy INRT.		
RAPID Radford 2015 [9]	All pts: 3xABVD. If PET negative: Arm A: IFRT Arm B: no further intervention (If PET positive: One more cycle of ABVD and IFRT)	NA	30 Gy IFRT
F. Chemotherapy + radiotherapy compared with radiotherapy alone			
GHSG HD7 Engert, 2007 [4]	Arm A: 30 Gy EFRT + 10 Gy IFRT Arm B: 2 x ABVD + 30 Gy EFRT+ 10 Gy IFRT	2xABVD before Rt. ABVD: doxorubicin 25 mg/m^2 ds 1 and 14, bleomycin 10 mg/m^2 ds 1 and 14, vinblastine 6mg/m^2 ds 1 and 14 dacarbazine 375 mg/m^2 ds 1 and 14.	30 Gy EF-RT (spleen, 36 Gy) + 10 Gy to the IF. Single fraction size was 1.8 to 2.0 Gy administered 5 times a week.
SWOG 9284A[A] Ganz, 2003 [5]	Arm A: STLI Arm B: 3 cycles of doxorubicin and vinblastine + STLI	3x: doxorubicin 25 mg/m^2 iv and vinblastine 6 mg/m^2 iv on ds 1 and 15 of each 28-d course. At the completion of the third cycle of chemotherapy, staging studies were repeated, and a period of 6 weeks after the last doses of doxorubicin and vinblastine was allowed to elapse before the initiation of RT.	STLI: sequential mantle and periaortic/spleen fields, to a dose of 36 to 40 Gy for 4 wks each (1.8 or 2 Gy administered in 20 fractions), using megavoltage Rt in the 4- to 10-MeV range.
G. Less intensive chemotherapy regimens plus radiotherapy compared with more intensive regimens plus radiotherapy			
GHSG HD14 Von Tresckow, 2012 [26]	Arm A: 4xABVD + 30 Gy IFRT Arm B: 2xBEACOPP increased + 2xABVD + 30 Gy IFRT	doxorubicin 25 mg/m^2 ds 1 and 15 bleomycin 10 mg/m^2 ds 1 and 15 vinblastine 6 mg/m^2 ds 1 and 15 dacarbazine 375 mg/m^2 ds 1 and 15, repeated on d 29.	30 Gy IFRT in single fractions of 1.8 to 2.0 Gy administered 5 times per wk.
EORTC-GELA H7U Noordijk, 2006 [12]	Arm C: 6xEPBV +IFRT Arm D: 6xMOPP-ABV hybrid + IFRT	6xEBVP or MOPP-ABV hybrid (mechlorethamine 6 mg/m^2 iv on d 1 vincristine 1.4 mg/m^2 [max dose, 2 mg] iv d 1 procarbazine 100 mg/m^2 orally ds 1 through 7 prednisone 40 mg/m^2 orally ds 1 through 14 doxorubicin 35 mg/m^2 iv d 8 bleomycin 10mg/m^2 im or iv d 8 vinblastine 6 mg/m^2 iv d 8)	Patients in the H7-U group were randomly assigned to either 6xEBVP or 6xMOPP-ABV hybrid; both regimens were followed by IFRT (36 to 40 Gy). In all groups, radiation was administered in fractions of 1.5 Gy to 2.0 Gy, 5 fractions per week, with both fields treated each day.
H. More intensive chemotherapy plus radiotherapy compared with less intensive regimens plus radiotherapy			
Pavone, 2008 [20]	Arm A: 4 x ABVD + IFRT Arm B: 4 x EVE + IFRT	4xABVD: doxorubicin iv 25 mg/m^2 bleomycin iv 10 U/m^2 vinblastine iv 6 mg/m^2 dacarbazine iv 375 mg/m^2 4xEVE: epirubicin iv 70 mg/m^2 d 1	IF-RT on all sites of disease documented before the start of treatment. Rt was started 4 wks after the last cycle of chemotherapy and after complete restaging was achieved. Total dose to previously involved areas was 36 Gy, administered in 20 daily fractions, 5 ds/wk, using 6 to 18 MV linear accelerator; X-rays energy, dose prescription and technique of

Study	Comparison	Chemotherapy dose and schedule	Radiotherapy dose and schedule
		vinblastine i.v. 6 mg/m^2 d 1 etoposide iv 100 mg/m^2 d 1 followed by etoposide orally 150 mg/m^2 ds 2 and 3. Each course was repeated every 21 ds. All drugs were delivered on ds 1 and 15 every 4 wks.	irradiation (parallel opposed fields and direct field) varied according to disease's presentation.
E2496 Advani, 2010, 2011 [abs] [21,24]	Arm A: ABVDx6 to 8 cycles (every 28 days) + modified IFRT 36 Gy Arm B 12 weeks of Stanford V, (weekly) + RT	6 to 8xABVD every 28 ds or 12 wks of Stanford V, administered weekly	Modified involved field Rt was delivered at 36 Gy to the mediastinum to all pts
H90-NM Le Maignan, 2004 [22]	Arm A: 3xABVDm + tailored, high-dose RT Arm B: 3xEBVMm + tailored, high-dose RT	ds 1 and 14: Arm A: adriamycin 25 mg/m^2 bleomycin 10 mg/m^2 vinblastine 6 mg/m^2 dacarbazine 375 mg/m^2 methylprednisolone 120 mg/m^2. Arm B: epirubicin 30 mg/m^2 bleomycin 10 mg/m^2 vinblastine 6 mg/m^2 methotrexate 30 mg/m^2 methypredenisolone 120 mg/m^2.	Pts in CR or PR after chemotherapy were irradiated. Rt started 4 to 5 wks after the last infusion of CT. All patients were treated with megavoltage beam energy of 15 MV to 25 MV. Rt of initially involved nodes was administered at a daily dose of 1.8 Gy per day (by equally weighted parallel opposed anteroposterior-posteroanterior [AP-PA] fields), 9 Gy per week up to 40 Gy. Noninvolved sites received prophylactic RT (30 Gy).
GHSG HD11 Eich, 2010 [16]	Arm A: 4xABVD + 30 Gy IFRT (standard treatment); Arm C: 4xBEACOPP + 30 Gy IFRT; Arm D: 4xBEACOPP + 20 Gy IFRT Arm B: 4xABVD + 20 Gy IFRT	ABVD: doxorubicin 25 mg/m^2 ds 1 and 15 bleomycin 10 mg/m^2 ds 1 and 15 vinblastine 6 mg/m^2 ds 1 and 15 dacarbazine 375 mg/m^2 ds 1 and 15 repeated on d 29. BEACOPP: cyclophosphamide 650 mg/m^2 (d 1), doxorubicin 25 mg/m^2 (d 1), etoposide 100 mg/m^2 (ds 1 through 3), procarbazine 100 mg/m^2 (ds 1 through 7), prednisone 40 mg/m^2 (ds 1 through 14), vincristine 1.4 mg/m^2 (d 8), bleomycin 10 mg/m^2 (d 8), repeated on d 22.	Either 30 or 20Gyof IFRT in single fractions of 1.8 to 2.0 Gy administered five times weekly.
GHSG HD13 Behringer, 2015 [25]; Behringer, 2013 [subgroup] [23]	30 Gy IF-RT 2xABVD + 30 Gy IFRT vs. 2xABV + 30 Gy IFRT vs. 2xAVD + 30 Gy IFRT vs. 2xAV + 30 Gy IFRT	All chemotherapy regimens were administered on ds 1 and 15 in 4-wk cycles at the standard doses: doxorubicin, 25 mg/m^2 bleomycin 10 mg/m^2 vinblastine, 6 mg/m^2 dacarbazine (if applicable), 375 mg/m^2.	The interval between completion of chemotherapy and the start of radiotherapy was 4 to 6 wks. The total dose of 30 Gy was given in fractions of 1.8–2.0 Gy 5 times per week.

Study	Comparison	Chemotherapy dose and schedule	Radiotherapy dose and schedule
I. More cycles of a specific chemotherapy plus radiotherapy compared with fewer cycles of the same chemotherapy plus radiotherapy			
Hamed, 2012 [19]	Arm A: 4 x ABVD + 30 Gy IFRT Arm B: 2 x ABVD + 20 Gy IFRT	ABVD ds 1 and 15 in monthly cycles at the following dose: doxorubicin, 25 mg/m^2 bleomycin: 10 mg/m^2 vinblastine 6 mg/m^2 dacarbazine 375 mg/m^2.	External beam irradiation by a 6 MV linear accelerator planned as IF radiation according to the sites of disease 4 to 6 wks after the end of ABVD. Pts received either 30 or 20 Gy of IFRT in single fraction of 1.8 to 2.0 Gy administered 5 times weekly.
GHSG HD10 Engert, 2010 [17] EORTC GELA H8U Ferme, 2007 [11]	Arm A 4xABVD + IFRT 30 Gy vs. Arm B 4xABVD + IFRT 20 Gy vs. Arm C 2xABVD + IFRT 30 Gy vs. Arm D 2xABVD + IFRT 20 Gy	ABVD ds 1 and 15 in monthly cycles at the following dose: doxorubicin, 25 mg/m^2 bleomycin: 10 mg/m^2 vinblastine 6 mg/m^2 dacarbazine 375 mg/m^2.	Pts received either 30 Gy or 20 Gy of IFRT in single fractions of 1.8 to 2.0 Gy administered 5 times weekly. 4 to 6 wks after the end of ABVD.
EORTC-GELA H8U Ferme, 2007 [11] **also in RT section**	Arm A: 6xMOPP-ABV + IFRT Arm B: 4xMOPP-ABV + IFRT	MOPP: mecholrethamine (6 mg/m^2 d1) vincristine 1.4 mg/m^2 (max 2 mg d 1) procarbazine (100 mg/m^2 ds 1through 7) prednisone (40 mg/m^2 ds 1 through 14) ABV: doxorubicin (35 mg/m^2 d 8) bleomycin (10 mg/m^2 d 8) vinblastine (6 mg/m^2 d 8)	1 cycle=28 days IFRT: target volumes included involved nodal regions. Pts in CR after chemotherapy had 36 Gy, and those in PR had 40 Gy (+ 4 Gy if needed) in fractions of 2 Gy. STNI: mantlefield, spleen, and para-aortic nodes. Pts had 36 Gy of radiation to nodal regions + 4 Gy in initially involved nodal regions.

[A]A PET scan was then performed during the 2 weeks after day 15 of ABVD cycle 3

Abs = abstract; ABVD = Doxorubicin, bleomycin, vinblastine, and dacarbazine; ABVDm = ABVD and methylprednisolone; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; COPP = cyclophosphamide, oncovin, procarbazine and prednisone; CR = complete remission; d =day; EBVP = epirubicin, bleomycin, vinblastine and prednisone; ECOG = Eastern Cooperative Oncology Group; EBVMm = epirubicin, bleomycin, vinblastine, methotrexate, and methylprednisolone; EVE = etoposide, vincristine, epirubicin; F = favourable; GHSG = German Hodgkin Study Group; IFRT = involved-field radiation therapy; INRT = involved node radiotherapy; iv = intravenous; MFRT = mantle field radiotherapy; MOPP-ABV = sequential mechlorethamine, oncovin, procarbazine, prednisone and doxorubicin, bleomycin, vinblastine; PET = positron emission tomography; PFS = progression free survival; PR = partial remission; Pts = patients; RT = radiotherapy; STNI = subtotal nodal irradiation; U = unfavourable; CRu =unconfirmed complete response; VAPEC-B = doxorubicin, cyclophosphamide, etoposide, vincristine, and bleomycin with prednisolone and prophylactic cotrimoxazole or ketoconazole; vs = versus; wk = week; yrs = years.

Appendix 6. Classification of important outcomes.

GRADE SURVEY – Please rate the following outcomes according to importance:
7, 8, 9 represent CRITICAL
4, 5, 6 represent IMPORTANT
1, 2, 3 represent NOT IMPORTANT

COMPARISON A Radiotherapy in combination with chemotherapy versus chemotherapy alone

Outcomes	Average	Dr. Matt Cheung	Dr. Michael Crump	Dr. Jordan Herst	Ms. Fulvia Baldassarre
OS	8.5	9	8	9	8
EFS / FFS	7	8	7	7	6
FDP /PFS	6.5	7	7	6	6
AE	6.25	6	6	6	7

AE = adverse events; EFS = event free survival; FDP = freedom from disease progression; FFS = failure free survival; OS = overall survival; PFS = progression free survival; RFS = relapse free survival;

COMPARISON B – Low-dose radiotherapy versus high-dose radiotherapy

Outcomes	Average	Dr. Matt Cheung	Dr. Michael Crump	Dr. Jordan Herst	Ms. Fulvia Baldassarre
OS	8.5	9	8	9	8
Death	8	8	8	8	8
FFTF	7.5	8	8	7	7
PFS	7	8	7	6	7
EFS / FFS	7	8	7	6	7
FDP	7	7	=FFTF	6	7
late AE	6.5	7	7	6	6
Early AE	6	6	6	6	6
Response	5.75	6	5	7	5
CR	5.25	6	6	4	5
PR	4.5	5	4	4	5

AE = adverse events; CR = complete response; EFS = event free survival; FDP = freedom from disease progression; FFS = failure free survival; FFTF = freedom from treatment failure; OS = overall survival; PFS = progression free survival; PR = partial response; RFS = relapse free survival.

COMPARISON C: Narrow versus large field radiotherapy

Outcomes	Average	Dr. Matt Cheung	Dr. Michael Crump	Dr. Jordan Herst	Ms. Fulvia Baldassarre
OS	8.5	9	8	9	8
Death	8	8	8	8	8
FFTF	7.5	8	8	7	7
PFS	7.5	8	8	7	7
FDP	7.25	7	=FFTF	7	7
AE	6.25	6	7	6	6
late AE	6.75	7	7	6	7
AE from radiotherapy	6.5	6	7	6	7
Early AE	5.75	6	6	6	5
Secondary malignancies	5.75	7	3	6	7
Response	5.5	6	4	7	5
AE from chemotherapy	5	6	7	6	1
CR	5	6	5	4	5
PR	4.5	5	4	4	5

AE = adverse events; CR = complete response; EFS = event free survival; FDP = freedom from disease progression; FFS = failure free survival; FFTF = freedom from treatment failure; OS = overall survival; PFS = progression free survival; PR = partial response; RFS = relapse free survival.

COMPARISON D: Narrow field radiotherapy with chemotherapy versus large field radiotherapy.

Outcomes	Average	Dr. Matt Cheung	Dr. Michael Crump	Dr. Jordan Herst	Ms. Fulvia Baldassarre
OS	8.5	9	8	9	8
Death	8	8	8	8	8
late AE	6.75	7	7	6	7

AE = adverse events; OS = overall survival

COMPARISON E: Standard therapy versus tailored therapy using PET.

Outcomes	Average	Dr. Matt Cheung	Dr. Michael Crump	Dr. Jordan Herst	Ms. Fulvia Baldassarre
PFS	7.5	8	8	7	7

PET = positron emission tomography; PFS= progression-free survival.

For the other comparisons, the members of the Working Group agreed unanimously that survival (e.g., overall survival) disease control (e.g., progression-free survival, event-free survival, freedom from treatment failure etc.) and late adverse events are outcomes that clinicians and patients alike would value highly.

Appendix 7. Recommendations submitted for external review.

DRAFT RECOMMENDATIONS (approved for external review on September 3, 2015)

Recommendation 1A
Patients with early-stage classical Hodgkin lymphoma (HL) should not be treated with radiotherapy alone.

Recommendation 1B
In patients with early-stage Nodular Lymphocyte Predominant HL (NLPHL), it is reasonable to use involved-field radiation therapy alone. However, no phase III clinical trials have focused exclusively on NLPHL, therefore, no strong evidence base for such treatment, or for relative dosage, is currently available, and this recommendation is based on the expert opinion of the guideline authors.

Recommendation 2
Chemotherapy plus radiotherapy or chemotherapy alone are recommended treatment options for patients with early-stage non bulky Hodgkin Lymphoma.

Qualifying Statements for Recommendation 2
The decision on which treatment option to use should involve a patient-centred discussion with a hematologist/medical oncologist and a radiation oncologist. Patients should be aware of the trade-offs or risks associated with RT and chemotherapy alone.

Recommendation 3
When delivered as part of a planned combined modality treatment approach, involved field radiation therapy (IFRT) should be used for patients with early stage HL.

Qualifying Statements for Recommendation 3
The evidence at the present time is insufficient to support or refute the comparative superiority of involved nodal radiation therapy (INRT) or involved site radiation therapy (ISRT) over IFRT. It is recognized that the EORTC H10 study [1] demonstrated the statistically superior event-free survival (EFS) associated with INRT compared with chemotherapy alone in patients with two-cycle positron emission tomography (PET-2)-negative early-stage HL, and content experts have published guidelines describing ISRT treatment planning [2].

Recommendation 4
The dose of involved field radiation should be 20 Gy for patients with favourable characteristics and between 30 to 36 Gy for patients with unfavourable characteristics (see Appendix 1 for definitions of favourable and unfavourable characteristics).

Recommendation 5
The Working Group does not recommend the use of a negative interim positron emission tomography (PET) scan to identify patients with early-stage HL for whom radiotherapy can be omitted without a reduction in progression-free survival (PFS).

Recommendation 6
A) Patients with early-stage, favourable risk Hodgkin lymphoma who are being treated with combined modality therapy should receive two cycles of chemotherapy before radiotherapy.

B) Patients with early-stage, unfavourable risk Hodgkin lymphoma, who are being treated with combined modality therapy, should receive four cycles of chemotherapy before radiotherapy.

Recommendation 7
Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) should be the regimen of choice when administered before radiotherapy, except under the circumstances that follow in Recommendation 8.

Recommendation 8
Patients with early-stage, unfavourable-risk Hodgkin lymphoma may be considered for treatment with either four cycles of ABVD, or two cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) followed by two cycles of ABVD before radiotherapy.

Qualifying Statement for Recommendation 8
The BEACOPP approach improves freedom from treatment failure (FFTF) and PFS but is associated with more adverse events. Overall survival at 91 months follow-up did not differ, but available data are not sufficiently mature to assess late adverse effects and long-term outcomes.

Ontario Health
Cancer Care Ontario

Evidence-Based Series 6-20 Version 2: Section 6

Management of Early-Stage Hodgkin Lymphoma

Section 6: Document Assessment and Review

J. Herst, C. Arinze, and Members of the the Hematology Disease Site Group

May 26, 2023

The 2015 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2015.

In November 2021, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (CA) conducted an updated search of the literature. A clinical expert (JH) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. An expert panel from the Hematology Disease Site Group (DSG) (Appendix 1) endorsed the recommendations found in Section 1 (Clinical Practice Guideline) in February 2023.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

5. What are the optimum radiation dose and schedule and what are the best chemotherapy regimens for the treatment of patients with early-stage Hodgkin lymphoma (HL)?
6. What are the best strategies for the prevention of early and late adverse events in patients with early-stage HL?
7. What is the role of PET in guiding therapeutic decisions in the management of early-stage HL?
8. What are the best strategies for the treatment of subgroups of patients with early-stage HL, such as those with very favourable or unfavourable disease?

Literature Search and New Evidence
The new search (June 2015 to April 2022) yielded one pooled analysis and 11 publications covering nine studies investigating the management modalities in early-stage Hodgkin lymphoma. One of the included articles (1) is a full publication of a study that was included as an abstract in the original guideline. An additional search for ongoing studies on clinicaltrials.gov yielded 10 potentially relevant ongoing trials. Brief results of these publications are shown in the Document Review Tool.

Impact on the Guideline and Its Recommendations
The new data support all existing recommendations except for Recommendation 1B:
In patients with early-stage nodular lymphocyte predominant HL (NLPHL), it is reasonable to use involved-field radiation therapy alone. However, no phase III clinical trials have focused exclusively on NLPHL, therefore, no strong evidence base for such treatment, or for relative dosage, is currently available, and this recommendation is based on the expert opinion of the guideline authors.

The Hematology DSG decided to remove this recommendation from the guideline. NLPHL is a rare disease, with an incidence of 0.1 to 0.2/100,000/y, presenting with distinct clinical and pathological features (2). Treatment modalities for NLPHL are different than for classical Hodgkin lymphoma, and the type of literature on this topic rarely involves randomized controlled trials. Treatment of NLPHL sometimes includes immunotherapy (e.g., rituximab) along with ABVD and radiotherapy. Sometimes other agents (e.g., cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] and cyclophosphamide, vinblastine, and prednisone [CVP]) that are not typically prescribed for classical Hodgkin lymphoma are used for NLPHL. The DSG elected to remove recommendations regarding NLPHL from the guideline as it was felt that evidence-based recommendations would require a fulsome evidence update outside of the scope of the original guideline.

The Hematology DSG ENDORSED the 2015 recommendations (with removal of Recommendation 1B) on the Management of Early-Stage Hodgkin Lymphoma.

Document Review Tool

Number and Title of Document under Review	6-20 Management of Early-Stage Hodgkin Lymphoma
Original Report Date	December 8, 2015
Date Assessed (by DSG or Clinical Program Chairs)	November 19, 2021
Health Research Methodologist	Chika Arinze
Clinical Expert	Dr. Jordan Herst
Approval Date and Review Outcome (once completed)	May 26, 2023 ENDORSE

Original Question(s):

9. What are the optimum radiation dose and schedule and what are the best chemotherapy regimens for the treatment of patients with early-stage Hodgkin lymphoma (HL)?
10. What are the best strategies for the prevention of early and late adverse events in patients with early-stage HL?
11. What is the role of PET in guiding therapeutic decisions in the management of early-stage HL?
12. What are the best strategies for the treatment of subgroups of patients with early-stage HL, such as those with very favourable or unfavourable disease?

Target Population:
Patients with early-stage Hodgkin Lymphoma.

Study Selection Criteria:
Studies were selected for inclusion in this systematic review if they were:

- Studies of patients treated for early-stage HL who were of age >15 years.
- Studies of systemic treatment for early-stage HL, including chemotherapy, biological agents, field, and dose of radiation therapy (e.g., involved field or involved nodes radio therapy [IFRT or INRT]), or a combination of the above.
- Study designs including systematic reviews (SR) published from 2011 to current, and randomized controlled trials (RCTs) published from 2003 to current.
- Studies that reported on the following outcomes:
    - Overall survival (OS)
    - Disease control (e.g., progression free survival)
    - Response
    - Quality of life
    - Adverse events (early and late)
- Published in English.

Studies were excluded if they were:

- Systematic reviews published in abstract format only.
- Studies including patients receiving treatment for advanced stage HL

- Studies including early and advanced stage HL, and with no separate data for the early-stage population.
- Abstract publication of interim analyses (although these will be discussed in the section on ongoing trials).
- Narrative reviews.
- Nonrandomized trials.
- Studies of PET used for staging.
- RCTs with sample size < 30 patients.
- Studies including age groups other than 15 years and over, and with no separate results for the age group of interest.

Search Details:
- 2019 to April 2022 Cochrane Database of Systematic Reviews
- June 2015 to April 2022 (Medline and Embase)
- January 2017 to April 2022 (Clinicaltrials.org for ongoing trials)

Summary of new evidence:
Of 1568 hits from searches of Medline, Embase, and the Cochrane Database for Systematic Reviews, the full texts of 160 publications were reviewed and 12 articles were retained for inclusion. The articles meeting inclusion criteria were one pooled analysis and 11 publications covering nine studies investigating management modalities in early-stage Hodgkin lymphoma. One of the included studies (Thomas 2017) is a full publication of a study that was included as an abstract in the original guideline.

Clinical Expert Interest Declaration:
J. Herst and C. Arinze declared no conflict of interest.

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No.
2. Does the newly identified evidence support the existing recommendations?	Yes.
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes, with the exception of Recommendation 1B. With respect to Recommendation 1B: ***In patients with early-stage nodular lymphocyte predominant HL (NLPHL), it is reasonable to use involved-field radiation therapy alone. However, no phase III clinical trials have focused exclusively on NLPHL, therefore, no strong evidence base for such treatment, or for relative dosage, is currently available, and this recommendation is based on the expert***

	opinion of the guideline authors, the recommendation should be removed. Since this recommendation was made, clinical practice has changed and the use of radiation therapy alone in NLPHL is not considered best practice.
Review Outcome as recommended by the Clinical Expert	ENDORSE
If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	
DSG/Expert Panel Commentary	Future considerations include We now have evidence from HD17 that if giving 2BEACOPP + 2ABVD and PET neg at the end, radiotherapy can be omitted, I see the study is described in the evidence table, but not used for this recommendation, only HD14 is described, and in another section, it's described that results are pending. I'm not sure if it was an update, but I think the wording should be changed to reflect that radiotherapy can be safely omitted if using this approach, as this is the first RCT to show you can omit radiotherapy in early stage HL pt without effect on outcomes.

Author [Ref#] (Study Name)	Study Design and Med F/U in Months)	Population and number of patients	Result
A. Chemotherapy plus Radiotherapy compared with chemotherapy alone for early-stage Hodgkin lymphoma			
Thomas 2017 (1) FROA	6x EBVP + RT (20 Gy) vs 6x EBVP + IFRT (36Gy) vs. 6x EBVP + no RT, **NOTE:** Randomization to the no-RT arm was prematurely stopped	Patients with untreated supradiaphragmatic HL who achieved complete remission after EBVP chemotherapy • Med Age 30 n = 578	• 5yrs RFS: The difference of 4.4% (90% CI 1.2% to 9.9%) between 36-Gy and 20-Gy arms was not significant HR = 1.53 (95% CI 0.92 to 2.55). P = 0.102. • 5yrs RFS estimates of the no-RT arm and the IFRT (36Gy) arms were 69.8% and 86.3% respectively with a difference of 16.5% (90% CI 8.0 to 25.0). HR = 2.55 (95% CI 1.44-4.53;) P<0.001
B. Low dose compared with high dose radiotherapy			
Gillessen 2021 (3) Gillessen 2020 (4) (GHSG HD14)	4x ABVD + IFRT (30Gy) vs. 2+2 (BEACOPP + ABVD) + IFRT (30Gy) Med F/U = 112mos	Patients with early, unfavorable HL • Med Age: 32yrs • Performance Status: <2 n = 1550	• 10 yrs PFS was significantly better in the 2+2 group but there was no difference between the groups in the 10 yrs OS • PFS: 85·6% (95% CI 82·6-88·1) vs. 91·2% (95% CI 88·4-93·3). HR 0·5% [95% CI 0·4–0·7; p = 0·0001 • OS: 94·1% (95% CI 92·0–95·7) vs. 94·1% (95% CI 91·8–95·7). HR 1·0 [95% CI 0·6–1·5; p=0·88
Bröckelmann 2020 (5) (GHSG-NIVAHL)	concomitant 4x Nivo-AVD + ISRT (30-Gy) vs. Sequential 4x Nivo + 2x Nivo-AVD + 2x AVD + ISRT (30-Gy) Med F/U = 20mos vs. 21 mos	Treatment naïve early-stage unfavorable cHL patients • Med Age: 27yrs n = 109	• Nivo-based first-line treatment was shown to be highly effective in early-stage unfavorable cHL patient: • CR in the concomitant and sequential groups were reported as 90%; (95% CI, 79% to 97%) and 94% (95% CI, 84% to 99%) after 2 cycles of Nivo-AVD or 4 doses of nivolumab monotherapy • 2-year PFS estimates are 100% for patients receiving concomitant treatment and 98% (95%CI 88-100%) for patients receiving sequential therapy. • 2-year OS is 100% in both groups. • Toxicity: Ttreatment-related AE was 74% in the concomitant group and 56% in sequential group. •

Gac 2019 (6) (GHSG HD10) [ABSTRACT]	3xABVD + INRT or 4xABVD vs. 4x ABVD + INRT or 6xABVD **NOTE**: study protocol was amended to allow all early PET-negative patients to receive CMT	previously untreated Early- PET-negative favorable and unfavorable cHL patients in the H10 trial that relapsed after first line treatment • Age: 15-70 years old, n= 94	• There was no significant difference in the 3yrs OS and PFS between those treated initially with CMT or CT: • OS at 3yrs 89% (95% CI: 69.7-96.3) in the CMT arm vs 93.9% (95% CI: 84.6 to 97.7) in the Ct arm. • PFS: 79.6 (95% CI:57.5 to 91) vs 78% (95% CI:65.7 to 86.3). • More patients received ASCT as first line salvage in the CMT group compared to the CT group (89.3% vs 63.1%, p = 0.012).
Ferme 2017 (7)	6-ABVD + IFRT vs 4-ABVD + IFRT or 4-EACOPP + IFRT.	untreated supradiaphragmatic HL with at least one risk factor stage I-II HL • Med Age: 30.7 n = 808	• The response rate for those treated with ABVD was significantly better than those in the BEACOPP arm: • CR: was 75% in the 6-ABVD, 71% in the 4-ABVD arm, and 59% in the 4-BEACOPP arm (P = 0.002) • There were no significant differences in EFS and OS between 6-ABVD-IFRT and 4-ABVD-IFRT or 4-BEACOPP. • 5yr EFS were 89.9%, 85.9% and 88.8% for 6-ABVD-IFRT, 4-ABVD-IFRT and 4-BEACOPP respectively • 5yr OS were 94%, 93% and 93%6-ABVD-IFRT, 4-ABVD-IFRT and 4-BEACOPP respectively • Toxicity: The incidence of adverse events was almost double in the BEACOPP arm compared to the pooled ABVD arms (P 0.001
C. PET used for tailoring the therapeutic strategy			
Borchmann 2021 (8) (GHSG HD17)	2 + 2 (BEACOPP + BVD) + IFRT (30Gy) vs. PET4-guided treatment + INRT (omitting RT in PET4-negative patients) Med F/U = 46.2mos	Newly diagnosed early-stage (IA, IB, or IIA) unfavourable HL. • Median Age: 31 • ECOG≥ 2 n = 1100	• There was no significant different between the 2+2 and the PET4 guided groups in PFS. • PFS at 5yrs: 97·3% (95% CI 94·5–98·7) vs. 95·1% (92·0–97·0). HR= 0·523 (95% CI 0·226 to 1·211) • 5-year PFS was significantly higher in the PET-negative group than in the PET-positive subgroups (HR 3·03 [95% CI 1·10–8·33], p=0·024

			• PET positivity, defined as a Deauville score of 4 or higher, identified as a significant risk factor for poor progression-free survival. HR 10·47 (95% CI 4·00–27·38]), p<0·0001. • Toxicity: grade 3 or 4 adverse events were: leucopenia 83% vs 84%; thrombocytopenia 26% vs 33%; acute infection 6% vs 8%; nausea or vomiting 7% vs 6%; dysphagia 6% 2%; serious adverse events 29% vs 30%
Baues 2021 (9) Fuchs 2019 (10) (GHSG HD16)	2x ABVD + IFRT (20Gy) vs. 2x ABVD (IFRT was restricted to Pet positive patients only) Med F/U = 47mos	Newly diagnosed patient with early-stage favorable HL and • Stage: IA to IIB • PET- negative (n = 628) • no risk factors • ECOG: 0-2 • Med age= 39yrs n = 628	• PET-negative patients treated on chemotherapy alone had a significantly higher risk of local recurrences than patients on CMT therapy. • The 5-year cumulative incidence of in-field progression in the chemotherapy arm was 10.5% (95% CI, 6.5 to 14.6) vs. 2.4% (95% CI, 0.5 to 4.3) with CMT. P = 0.0008). • There was no significant difference in out-field recurrences. 5-year incidence in the chemotherapy arm was 4.1% (95% CI, 1.7 to 6.6) vs 6.6% (95% CI, 3.0 to 10.3) in the CMT group. P = 0.54. • No grade 4 toxicity was observed during IFRT, and incidence of second primary malignancies was similar in both groups. • 5-year PFS estimates of 93.4% (95% CI, 90.4%-96.5%) in the CMT group and 86.1% (95% CI, 81.4%-90.9%) in the ABVD group. HR = 1.78 (95% CI, 1.02-3.12). P = 0.04 • 5yr OS in the CMT vs ABVD groups were 98.1% (95% CI, 96.5% to 99.8%) and 98.4% (95% CI, 96.5% to 100.0%) respectively.
Barrington 2019 (11) Barrington 2018 (12)	Subsidiary analysis of PET +ve and PET -ve pts ABVD + IFRT (PET +ve) vs	Stage IA/IIA HL pts with no mediastinal bulk treated with 3 cycles of ABVD • Med age-34yr	• PFS @5yrs was not significantly different between PET positive and PET negative pts: • 87.2% (95% CI: 81.6–92.7) vs. 91.2% (95% CI: 88.3–94.1),

(RAPID STUDY)	IFRT or no RT (PET -ve)	n = 602	• HR = 0.71 (95% CI: 0.41–1.24; p = 0.23). • High PET score was significantly associated with an increased risk of progression or HL-related death even after adjusting for baseline risk (p= 0.01)
Pooled Analysis			
Shaikh 2020 (13)	Pooled analysis of 4 RCT RT vs No RT	PET responders in early-stage (stage I/II) HL treated with anthracycline-based chemotherapy. n = 2267	• The use of 2nd line CT was significantly lower in the group that had RT: 3.7% vs. 11.7% in the group with no RT (OR = 3.24; 95% CI 2.37 to 4.44, p<0.00001) • Recurrence was less in the in RT group; 4.7% vs. 11.2% in group without RT. This trend was maintained in the subsets • In those with favorable early-stage HL, recurrence was 3.7% in RT group and 10.8% in group without RT • infield recurrence was significantly lower in the RT; 2.6% compared to 9.6% in the without RT. (OR 3.98; 95% CI 2.51–6.32, p < .00001). • The improvement in infield recurrence was larger in those with favorable early-stage HL; 1.4% in RT group and 9.5% without RT. (OR = 7.24; 95% CI 3.39–15.48, p < .00001) than in those with unfavorable early-stage HL; 4.3% in RT group and 9.7% without RT (OR = 2.40; 95% CI 1.31–4.40, p = .005). • The decrease in infield recurrence due to addition of RT was significantly larger in the favorable subset than the unfavorable subset (p < .00004). • There was not difference in the infield recurrence between the favorable (9.5%) and unfavorable (9.7%) groups in those that did not receive RT • PFS: There was a significant difference in PFS in favor of RT. HR = 2.08 (95% CI 1.27–3.43) p<.004. • PFS in those with favorable early-stage HL was significantly improved • HR = 2.77 (95% CI 1.08–7.11) p = 0.03

			• OS: there was no difference in OS between the groups receiving RT and the group without RT • HR = 0.92 (95% CI 0.37 to 2.30) p = 0.85)

ABVD: Doxorubicin, bleomycin, vinblastine sulfate, and dacarbazine; ASCT: autologous stem cell transplantation; AVD - Doxorubicin, vinblastine sulfate, and dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone: BLT: bleomycin-induced lung toxicity; EBVP: epirubicin, bleomycin, vinblastine, and prednisone; ECOG: IFRT: Involved-field radiotherapy; INRT - Involved-node radiotherapy; N-AVD: nivolumab and doxorubicin, vinblastine, and dacarbazine; RFS: Recurence free survival; STLI: subtotal lymphoid irradiation.

Ongoing Trials

Official Title	Status	Protocol ID	Last Updated
An Open-label, Uncontrolled, Multicenter Phase II Trial of MK-3475 (Pembrolizumab) in Children and Young Adults with Newly Diagnosed Classical Hodgkin Lymphoma with Inadequate (Slow Early) Response to Frontline Chemotherapy (KEYNOTE 667)	Recruiting	NCT03407144	October 13, 2022
A Randomized Phase 3 Study of Brentuximab Vedotin (SGN-35) for Newly Diagnosed High-Risk Classical Hodgkin Lymphoma (chl) in Children and Young Adults	Active, not recruiting	NCT02166463	September 19, 2022
A Randomised Phase III Trial With a PET Response Adapted Design Comparing ABVD +/- ISRT With A2VD +/- ISRT in Patients With Previously Untreated Stage IA/IIA Hodgkin Lymphoma	Recruiting	NCT04685616	September 8, 2022
Nivolumab and AVD in Early-stage Unfavorable Classical Hodgkin Lymphoma	Active, not recruiting	NCT03004833	August 8, 2022
Phase II Trial of Individualized Immunotherapy in Early-Stage Unfavorable Classical Hodgkin Lymphoma	Not yet recruiting	NCT04837859	August 8, 2022
Enhancing Effect on Tumour Apoptosis with the Combined Use of Pentoxifylline Plus Chemotherapeutical Agents in Pediatrics and AYA Patients with Hodgkin´s Lymphoma	Recruiting	NCT05490953	August 8, 2022
Immune Reconstitution and Biomarker Identification in Patients with Newly Diagnosed Low and Intermediate Risk Hodgkins Lymphoma Receiving Chemotherapy with or Without Radiation Therapy: TXCH-HD-12A	Active, not recruiting	NCT01858922	January 20, 2022
A Phase 2 Front-Line PET/CT-2 Response-Adapted Brentuximab Vedotin and Nivolumab Incorporated and Radiation-Free Management of Early-Stage Classical Hodgkin Lymphoma (chl)	Recruiting	NCT03712202	November 26, 2021

Official Title	Status	Protocol ID	Last Updated
The H10 EORTC/GELA/IIL Randomized Intergroup Trial on Early FDG-PET Scan Guided Treatment Adaptation Versus Standard Combined Modality Treatment in Patients with Supradiaphragmatic Stage I/II Hodgkin's Lymphoma	Active, not recruiting	NCT00433433	February 3, 2021
HD16 for Early Stages - Treatment Optimization Trial in the First-line Treatment of Early-Stage Hodgkin Lymphoma; Treatment Stratification by Means of FDG-PET	Active, not recruiting	NCT00736320	November 4, 2020

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Appendix 1. Members of the Expert Panel

Name	Affiliation	Conflict of Interest Declaration
Dr. A. Bhargi	London Health Sciences Centre, London, ON.	No conflict of interest declared
Dr. C. Bredson	The Ottawa Hospital, Ottawa, ON	No conflict of interest declared
Dr. M. Cheung	Odette Cancer Centre, Toronto, ON	No conflict of interest declared
Dr. M. Crump	Princess Margaret Cancer Centre, Toronto, ON	Consultant for Novartis, Kity Gilead and Ipsen.
Dr. J. Dudebout	Cancer Centre of Southeastern Ontario, Kingston, ON	Consultant for Novartis. Principal Investigator for studies on the subject of interest
Dr. R. Gupta	Windsor Regional Cancer Centre, Windsor, ON.	No conflict of interest declared
Dr. L. Hicks	St Michael's Hospital, Toronto, ON	No conflict of interest declared
Dr. R. Kassis	The Ottawa Hospital, Ottawa, ON	No conflict of interest declared
Dr. T. Kouroukis	Juravinski Cancer Centre, Hamilton ON.	No conflict of interest declared
Dr. N. Laferriere	Thunder Bay Regional Health Sciences Centre, Thunder Bay ON.	No conflict of interest declared
Dr. J. Liu	Trillium Health Partners, Mississauga, ON	Advisory board member for Abbvie
Dr. R. McClure	Health Sciences North, Sudbury, ON	No conflict of interest declared
Dr. H. Mian	Juravinski Cancer Centre, Hamilton ON.	Consultant for Pfizer, GSK, Celgene/BMS, Sanofi, Janssen, Amgen, Takeda. Received funding for a study on the subject of interest.
Dr. L. Mozessohn	Sunnybrook Health Sciences Centre, Toronto, ON	No conflict of interest declared
Dr. A. Prica	Sunnybrook Health Sciences Centre, Toronto, ON	Received Honoraria from Astra-zeneca and Kite Gilead.
Dr. D. Rodin	Princess Margaret Cancer Centre, Toronto, ON	Received travel monies from Union for International Cancer Control to attend Board of Directors meetings
Dr. M. Sabloff	The Ottawa Hospital, Ottawa, ON	Consultant for Astellas, Abbvie, Pfizer, BMS, Taiho, Jazz, Celgene, Roche, Novartis. Recived grants from Taiho, AbbVie, Astellas
Dr. R. Stevens	Grand River Regional Cancer Centre, Kitchener, ON	No conflict of interest declared

Appendix 2. Search strategies

Database(s): Ovid MEDLINE(R) 1996 to May 25, 2022, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 2018 to May 25, 2022

1 (favo?rable or unfavo?rable).tw,kf,ot.
2 (I-II or I-III).tw,kf,ot.
3 ((earl$ or low$ or limit$) adj3 (stag$ or grad$)).tw,kf,ot.
4 Intermediate$.tw,kf,ot.
5 or/1-4
6 exp Lymphoma/
7 exp Hodgkin Disease/
8 germinoblastom$.tw,kf,ot.
9 reticulolymphosarcom$.tw,kf,ot.
10 Hodgkin$.tw,kf,ot.
11 (malignan$ adj2 (lymphogranulom$ or granulom$)).tw,kf,ot.
12 or/6-11
13 exp Antineoplastic Agents/
14 Remission induction/
15 exp Antineoplastic Protocols/
16 ((consolidat$ or induct$ or maintenance or conditioning$) and (therap$ or treat$ or regimen$ or patient$)).tw,kf,ot.
17 ((therap$ or induc$) adj3 remission$).tw,kf,ot.
18 (Antineoplast$ or anti-neoplast$).tw,kf,ot.
19 ((cytosta$ or cytotox$) adj2 (therap$ or treat$ or regimen$)).tw,kf,ot.
20 (chemotherap$ or chemo-therap$).tw,kf,ot.
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 exp Radiotherapy/
23 (radiotherap$ or radio-therap$).tw,kf,ot.
24 exp Lymphatic Irradiation/
25 22 or 23 or 24
26 (chemoradiotherap$ or chemo-radio-therap$).tw,kf,ot.
27 exp Combined Modality Therapy/
28 ((multimodal$ or multi-modal$) adj3 (treat$ or therap$)).tw,kf,ot.
29 (combi$ adj3 modalit$).tw,kf,ot.
30 26 or 27 or 28 or 29
31 Tomography, Emission-Computed/
32 (positron adj2 emission adj2 tomography).tw,kf,ot.
33 Fluorodeoxyglucose F18/
34 18f fluorodeoxyglucose.tw,kf,ot.
35 PET.tw,kf,ot.
36 (PET adj2 FDG).tw,kf,ot.
37 18f-fdg.tw,kf,ot.
38 2-fluoro-2deoxy-d-glucose.tw,kf,ot.
39 2-fluoro-2-deoxyglucose.tw,kf,ot.
40 18f-fdg.tw,kf,ot.
41 Positron-Emission Tomography/
42 Fluorodeoxyglucose F18/
43 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44 randomized controlled trial.pt.
45 controlled clinical trial.pt.
46 controlled clinical trials/
47 (clinical trials, phase II or clinical trials, phase III or clinical trials, phase IV or multicenter studies).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-

heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
48 random allocation/
49 double blind method/
50 cross-over studies/
51 single-blind method/
52 clinical trial.pt.
53 (clin: adj25 trial:).ti,ab.
54 ((singl: or doubl: or trebl: or tripl:) adj25 (blind: or mask:)).ti,ab.
55 placebos/
56 placebo:.ti,ab.
57 random:.ti,ab.
58 or/44-57
59 meta-analysis.sh,pt. or meta-analy:.tw. or metaanaly:.tw.
60 ((systematic: or quantitativ:) adj (review: or overview:)).tw.
61 (cochrane or medline or cinahl or embase or scisearch or psychinfo or psycinfo or psychlit or psyclit or (national and library)).tw.
62 ((handsearch: or search:) and (cochrane or medline or cinahl or embase or scisearch or psychifo or psycinfo or psychlit or psyclit or (national and library) or (hand: or manual: or electronic: or bibliograph: or database:))).tw.
63 ((review or guideline).pt. or consensus.ti. or guideline:.ti. or literature.ti. or overview.ti. or review.ti.) and (61 and 62)
64 ((synthesis or overview or review or survey) and (systematic or critical or methodologic or quantitative or qualitative or literature or evidence or evidence-based)).ti.
65 59 or 60 or 62 or 63 or 64
66 5 and 12
67 21 or 25 or 30 or 43
68 66 and 67
69 58 and 68
70 65 and 68
71 69 or 70
72 limit 71 to english language
73 animal/ not (human/ and animal/)
74 72 not 73
75 limit 74 to yr="2015 -Current"

Database(s): Embase **1996 to 2022 May 25**

1 (favo?rable or unfavo?rable).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
2 (favo?rable or unfavo?rable).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
3 intermediate$.mp.
4 bulky.mp.
5 1 or 2 or 3 or 4
6 *lymphoma/
7 exp Hodgkin disease/
8 Hodgkin$.mp.
9 (malingnan$ adj2 (lymphogranulom$ or granulom$)).mp.
10 6 or 7 or 8 or 9
11 5 and 10
12 exp antineoplastic agent/
13 remission/

14 exp clinical protocol/
15 ((consolidat$ or induct$ or maintenance or conditioning$) and (therap$ or treat$ or regimen$ or patient$)).tw.
16 ((therap$ or induc$) adj3 remission$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
17 (chemotherap$ or chemo-therap$).mp.
18 (antineoplast$ or anti-neoplast$).mp.
19 ((cytosta$ or cytotox$) adj2 (therap$ or treat$ or regimen$)).mp.
20 exp radiotherapy/
21 (radiotherap$ or radio-therap$).mp.
22 (chemoradiotherap$ or chemo-radio-therap$).tw.
23 exp multimodality cancer therapy/
24 ((multimodal$ or multi-modal$) adj3 (treat$ or therap$)).tw.
25 exp lymph node irradiation/
26 (combi$ adj3 modalit$).mp.
27 positron emission tomography/
28 (positron adj2 emission adj2 tomography).mp.
29 fluorodeoxyglucose f 18/
30 (18f fluorodeoxyglucose or PET orFDG or 18f-fdg or 2-fluoro-2deoxy-d-glucose or 2-fluoro-2-deoxyglucose).mp.
31 computer assisted tomography/ or tomography/
32 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33 11 and 32
34 clinical trial/
35 "randomized controlled trial (topic)"/
36 randomization/
37 single blind procedure/
38 double blind procedure/
39 crossover procedure/
40 placebo/
41 randomi?ed controlled trial$.tw.
42 RCT.tw.
43 random allocation.tw.
44 randomly allocated.tw.
45 allocated randomly.tw.
46 (allocated adj2 randomly).tw.
47 single blind$.tw.
48 double blind.tw.
49 ((treble or triple) adj blind$).tw.
50 Placebo$.tw.
51 prospective study/
52 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53 33 and 52
54 limit 53 to (english language and yr="2015 -Current")
55 animal/ not (human/ and animal/)
56 54 not 55

DEFINITIONS OF REVIEW OUTCOMES

1. ARCHIVE – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "ARCHIVE."

2. ENDORSE – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. UPDATE – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.