Positron Emission Tomography (PET) scans for lymphoma: re-review

Final evidence report: appendices

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Positron Emission Tomography for Lymphoma: Re-Review

Aggregate Analytics, Inc.

Final Evidence Report
APPENDICES

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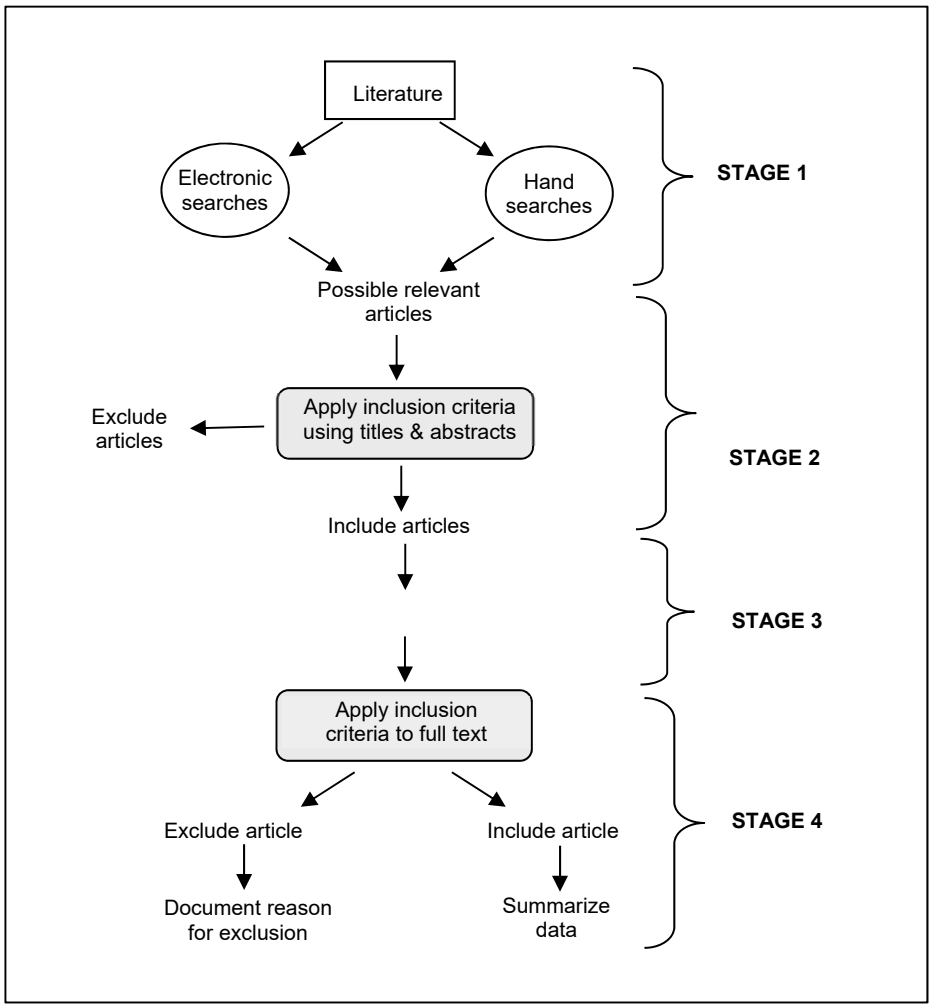
APPENDIX A. Algorithm for Article Selection



APPENDIX B. Search Strategies

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources.

Search strategy (PubMed)
Search date: March 2011 through 05/26/2018
Filters: Abstract available, English, Human

Limits 2011-01-01 to 2018-05-26; Abstracts only

1	Positron-Emission Tomography [MeSH] OR "positron emission tomography" [TIAB] OR "positron-emission tomography" [TIAB] OR Fluorodeoxyglucose [TIAB] OR 2-fluoro-2-deoxy-D-glucose [TIAB] OR fluorine-18-fluorodeoxyglucose [TIAB] OR fluorine-18-fluoro-deoxyglucose [TIAB] OR 18-fluorodeoxyglucose [TIAB] OR 18-fluoro-deoxyglucose [TIAB] OR 18F-fluoro-2-deoxy-D-glucose [TIAB] OR 18F-FDG [TIAB] OR FDG [TIAB] OR FDG-PET [TIAB] OR PET-CT [TIAB] OR PET/CT [TIAB] OR "PET" [TIAB]	57,552
2	Lymphoma [MeSH] OR Hodgkin [TIAB]	32,429
3	#1 AND #2	2356
4	Sensitivity and Specificity [MeSH] OR "diagnostic accuracy" [TIAB] OR Sensitiv* [TIAB] OR Specific* [TIAB] OR "positive predictive value" [TIAB] OR PPV [TIAB] OR "negative predictive value" [TIAB] OR NPV [TIAB] OR "true positive" [TIAB] OR "false positive" [TIAB] OR "true negative" [TIAB] OR "false negative" [TIAB]	
5	#3 AND #4	822
6	Early Detection of Cancer [MeSH] OR Screen* [TIAB] OR Staging [TIAB] OR Stage [TIAB] OR Restaging [TIAB] OR Restage [TIAB] OR Re-staging [TIAB] OR Re-stage [TIAB] OR Follow-up [TIAB] OR Response [TIAB] OR Remission [TIAB] OR Relapse [TIAB] OR Recur* [TIAB] OR Refractory [TIAB] OR Progress* [TIAB] OR Prognosis [MeSH] OR Prognos* [TIAB] OR Predict [TIAB] OR Adapted [TIAB] OR PET-adapt* [TIAB] OR PET adapt* [TIAB]	
7	#5 AND 6	2441

Search strategy (EMBASE)
Search date: March 2010 through 11/10/2016
Filters: age (young adult through elderly), study type (human, controlled study, clinical trial, randomized controlled trial, controlled clinical trial, systematic review), publication type (article)

Parallel strategies were used to search the Cochrane Library, EMBASE, and others listed below. Keyword searches were conducted in the other listed resources. In addition, hand-searching of included studies was performed.

Electronic Database Searches

The following databases have been searched for relevant information:

Agency for Healthcare Research and Quality (AHRQ)
Cochrane Database of Systematic Reviews
Cochrane Registry of Clinical Trials (CENTRAL)
Cochrane Review Methodology Database
Database of Reviews of Effectiveness (Cochrane Library)

EMBASE
PubMed
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database

Additional Economics, Clinical Guideline and Gray Literature Databases

AHRQ - Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

APPENDIX C. Excluded Articles

Articles excluded as primary studies after full text review, with reason for exclusion.

Appendix Table C1. List of Excluded Articles

	Citation	Reason for exclusion after full-text review
1.	Papajik T, Myslivecek M, Sedova Z, et al. Synchronous second primary neoplasms detected by initial staging F-18 FDG PET/CT examination in patients with non-Hodgkin lymphoma. Clinical nuclear medicine 2011;36:509-12.	Case reports
2.	Nasser QJ, Pfeiffer ML, Romaguera J, et al. Clinical value of magnetic resonance imaging and other baseline testing for conjunctival mucosa-associated lymphoid tissue lymphoma. Leuk Lymphoma 2014;55:1013-7.	Focus is on MRI; no relevant clinical data for PET or PET/CT
3.	Hagtvedt T, Seierstad T, Lund KV, et al. Diffusion-weighted MRI compared to FDG PET/CT for assessment of early treatment response in lymphoma. Acta radiologica (Stockholm, Sweden : 1987) 2015;56:152-8.	PET vs. DWMRI for association between ΔSUVmax and ΔADC
4.	Le Roux PY, Gastinne T, Le Gouill S, et al. Prognostic value of interim FDG PET/CT in Hodgkin's lymphoma patients treated with interim response-adapted strategy: comparison of International Harmonization Project (IHP), Gallamini and London criteria. European journal of nuclear medicine and molecular imaging 2011;38:1064-71.	Published online Feb 10 2011; previous HTA search went through May 2011
5.	Tai WM, Quah D, Yap SP, et al. Primary mediastinal large B-cell lymphoma: optimal therapy and prognostic factors in 41 consecutive Asian patients. Leuk Lymphoma 2011;52:604-12.	Primarily a treatment study; PET/CT results provided for a subset of 19 patients (exclude based on sample size <20)
6.	Simontacchi G, Filippi AR, Ciammella P, et al. Interim PET After Two ABVD Cycles in Early-Stage Hodgkin Lymphoma: Outcomes Following the Continuation of Chemotherapy Plus Radiotherapy. Int J Radiat Oncol Biol Phys 2015;92:1077-83. doi: 10.16/j.ijrobp.2015.04.021. Epub Apr 17.	Not PET-adapted; prognostic (PET+ and PET-)
7.	Kobe C, Kuhnert G, Kahraman D, et al. Assessment of tumor size reduction improves outcome prediction of positron emission tomography/computed tomography after chemotherapy in advanced-stage Hodgkin lymphoma. J Clin Oncol 2014;32:1776-81.	subanalysis of GHSG HD15 trial, does not provide relevant data on PET/CT (risk stratification and focus on how CT can improve positive predictive value of PET)
8.	Terezakis SA, Hunt MA, Kowalski A, et al. [(1)(8)F]FDG-positron emission tomography coregistration with computed tomography scans for radiation treatment planning of lymphoma and hematologic malignancies. International journal of radiation oncology, biology, physics 2011;81:615-22.	Earlier study to Terezakis 2014 which is included
9.	Stieglitz E, Dinh T, Phelps AS, Pampaloni MH, Olshen AB, Robbins E. ABVD Without Radiation for Newly Diagnosed Pediatric and Young Adult Patients With Hodgkin Lymphoma: A Single Center Retrospective Analysis of 28 Consecutive Patients. J Pediatr Hematol Oncol 2018;40:290-4. doi: 10.1097/MPH.0000000000001094.	Outcome data for PET-adapted strategies not provided

	Citation	Reason for exclusion after full-text review
10.	Simontacchi G, Filippi AR, Ciammella P, et al. Interim PET After Two ABVD Cycles in Early-Stage Hodgkin Lymphoma: Outcomes Following the Continuation of Chemotherapy Plus Radiotherapy. Int J Radiat Oncol Biol Phys 2015;92:1077-83. doi: 10.16/j.ijrobp.2015.04.021. Epub Apr 17.	Not PET-adapted; prognostic (PET+ and PET-)
11.	Kamran SC, Jacene HA, Chen YH, Mauch PM, Ng AK. Clinical outcome of patients with early stage favorable Hodgkin lymphoma treated with ABVD x two cycles followed by FDG-PET/CT restaging and 20 Gy of involved-site radiotherapy. Leuk Lymphoma 2018;59:1384-90.	Not PET-adapted and no relevant clinical data provided (do not provide details about up or downstaging and/or treatment modification)
12.	Picardi M, Soricelli A, Grimaldi F, Nicolai E, Gallamini A, Pane F. Fused FDG-PET/contrast-enhanced CT detects occult subdiaphragmatic involvement of Hodgkin's lymphoma thereby identifying patients requiring six cycles of anthracycline-containing chemotherapy and consolidation radiation of spleen. Annals of oncology : official journal of the European Society for Medical Oncology 2011;22:671-80.	Compares fused PET/CT vs. PET and CT done separately
13.	Zabrocka E, Sierko E, Wojtukiewicz MZ. Positron Emission Tomography Scanning in the Management of Hodgkin Lymphoma Patients: A Single-Institution Experience. Adv Clin Exp Med 2016;25:1185-92.	comparative data available for only about one-third of population following end of treatment
14.	Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: A report from the Children's Oncology Group. Cancer 2018;124:3210-9.	No data specific to PET-adapted treatment; prognostic
15.	Puchalski AL and Magill C. Imaging Gently. Emerg Med Clin North Am 2018;36:349-368.	Review article
16.	Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med. 2013;368(15):1408-1416.	Earlier population included in the Melani 2018 study which was exclude
17.	Melani C, Advani R, Roschewski M, et al. End-of-treatment and serial PET imaging in primary mediastinal B-cell lymphoma following dose-adjusted-EPOCH-R: A paradigm shift in clinical decision making. Haematologica 2018.	Not comparative; prognostic only
18.	Torok JA, Wu Y, Chino J, et al. Chemotherapy or Combined Modality Therapy for Early-stage Hodgkin Lymphoma. Anticancer Res 2018;38:2875-81. doi: 10.21873/anticanres.12533.	Primarily a treatment study; no relevant data pertaintin specifically to PET/CT
19.	Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. J Clin Oncol 2014;32:3651-8.	<80% of patients received PET
20.	Taghipour M, Marcus C, Sheikhbahaei S, et al. Clinical Indications and Impact on Management: Fourth and Subsequent Posttherapy Follow-up (18)F-FDG PET/CT Scans in Oncology Patients. J Nucl Med 2017;58:737-43. doi: 10.2967/jnumed.116.183111. Epub 2016 Nov 3.	Data in a variety of cancers, not just lymphoma; have data from Taghipour 2016/2016b included.

*These studies were included in the previous report but no longer meet the inclusion criteria for this updated report.

APPENDIX D. Risk of Bias, Class of Evidence, Strength of Evidence, and QHES Determination

Each included study is rated against pre-set criteria that resulted in a Risk of Bias (RoB) assessment and presented in a table. Criteria for RoB assessment are listed in the Tables below.

Definition of the risk of bias categories

Risk of Bias	Definition
Low risk of bias	Study adheres to commonly held tenets of high quality design, execution and avoidance of bias
Moderately low risk of bias	Study has potential for some bias; does not meet all criteria for low risk of bias but deficiencies not likely to invalidate results or introduce significant bias
Moderately high risk of bias	Study has flaws in design and/or execution that increase potential for bias that may invalidate study results
High risk of bias	Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group

PET in lymphoma Risk of Bias Assessment

Appendix Table D1. Definition of the risk of bias for studies on therapy

Risk of Bias	Studies of Therapy*	
	Study design	**Criteria***
Low risk: Study adheres to commonly held tenets of high quality design, execution and avoidance of bias	Good quality RCT	• Random sequence generation • Statement of allocation concealment • Intent-to-treat analysis • Blind or independent assessment of PET/CT (interpreter blinded to clinical assessment/status) • Blind or independent assessment for subjective outcome(s) • Pre-specified threshold for definition of a positive test. • Attrition (≤ 20% overall) • Comparable f/u time or accounting for time at risk • Controlling for possible confounding‡ • Full reporting of specified outcomes

Risk of Bias	Studies of Therapy*	
	Study design	**Criteria***
Moderately low risk: Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias	Moderate quality RCT	• Violation of one or two of the criteria for good quality RCT
	Good quality cohort	• Blind or independent assessment of PET/CT (interpreter blinded to clinical assessment/status) • Blind or independent assessment for subjective outcome(s) • Pre-specified threshold for definition of a positive test. • Attrition (≤ 20% overall) • Comparable f/u time or accounting for time at risk • Controlling for possible confounding‡ • Full reporting of specified outcomes
Moderately High risk: Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results	Poor quality RCT	• Violation of three or more of the criteria for good quality RCT
	Moderate quality cohort	• Violation of any of the criteria for good quality cohort
	Case-control	• Any case-control design
High risk: Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes	Poor quality cohort Case series	• Violation of two or more criteria for a good quality cohort • Any case series design

* Additional domains evaluated in studies performing a formal test of interaction for subgroup modification (i.e., HTE) based on recommendations from Oxman and Guyatt[4]:

- Is the subgroup variable a characteristic specified at baseline or after randomization? (subgroup hypotheses should be developed a priori)
- Did the hypothesis precede rather than follow the analysis and include a hypothesized direction that was subsequently confirmed?
- Was the subgroup hypothesis one of a smaller number tested?

† Outcome assessment is independent of healthcare personnel judgment. Reliable data are data such as mortality or re-operation.

‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods) at time of randomization or allocation to treatment based on PET results. Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Determination of Overall Strength (Quality) of Evidence

The strength of evidence for the overall body of evidence for all critical health outcomes was assessed by one researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ).[6] The strength of evidence was based on the highest quality evidence available for a given outcome. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- Risk of bias: the extent to which the included studies have protection against bias
- Consistency: the degree to which the included studies report results are similar in terms of range and variability.
- Directness: describes whether the evidence is directly related to patient health outcomes.
- Precision: describes the level of certainty surrounding the effect estimates.
- Publication bias: is considered when there is concern of selective publishing.

Bodies of evidence consisting of RCTs were initially considered as High strength of evidence (SoE), while those that comprised nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There could also be situations where the nonrandomized studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association). Publication and reporting bias are difficult to assess. Publication bias is particularly difficult to assess with fewer than 10 RCTs (AHRQ methods guide). When publication bias was unknown in all studies and this domain is often eliminated from the strength of evidence tables for our reports. The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are probably stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; important or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

All AHRQ “required” and “additional” domains (risk of bias, consistency, directness, precision, and if possible, publication bias) are assessed. Bodies of evidence consisting of RCTs were initially considered as High strength of evidence, while those comprised of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There are also situations where the *nonrandomized* studies

could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association).

Appendix Table D2. Example methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table below.

Baseline strength: HIGH = RCTs. LOW = observational, cohort studies, administrative data studies.

DOWNGRADE: Risk of bias for the individual article evaluations (1 or 2); Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2)

UPGRADE (non-randomized studies): Large magnitude of effect (1 or 2); Dose response gradient (1) done for observational studies ***if no downgrade for domains above***

Outcome	Strength of Evidence	Conclusions & Comments	Baseline SOE	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** RCTs	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Cohort studies	**NO** consistent, direct, and precise estimates; high quality (moderately low ROB)	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** RCTs	**YES (2)** Inconsistent Indirect	**NO**

*Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation. Additional domains: dose-response, strength of association, publication bias.

**Single study = "consistency unknown", may or may not be downgraded

ROB for Contextual Questions: Formal, detailed risk of bias assessment was not done for systematic reviews or studies included for the contextual question, however notes on key critical appraisal elements for systematic reviews adapted from the AMSTAR tool and QUADAS tool for diagnostic accuracy studies and pertinent epidemiologic principles were made to provide *a general* context for evidence quality.

Systematic review quality: Was assessed using a modification of the AMSTAR tool seen below in Appendix Table D3.

Appendix Table D3. Modified AMSTAR tool for systematic review quality.

AMSTAR Checklist (please assign each criteria 1 point)		Yes	No	Not Applicable
1	**Was an 'a priori' design provided?** ***The research question and inclusion criteria should be established before the conduct of the review.***			
2	**Was there duplicate study selection and data extraction?** ***Were there at least two independent data extractors and a consensus procedure for disagreements?***			
3	**Was a comprehensive literature search performed?** ***Were at least two electronic sources searched? Were search dates included? Were key words/MeSH terms stated?***			
4	**Was the status of publication (i.e. grey literature) used as an inclusion criterion?** ***Did authors state they searched for reports regardless of publication type? Did they explicitly state what reports were excluded based on publication status, language, etc?***			
5	**Was a list of studies (included and excluded) provided?** ***Is a complete list of both included/excluded studies provided (likely as a table)?***			
6	**Were the characteristics of the included studies provided?** ***Does an aggregated form such as a table exist to provide data from original studies based on participants, interventions and outcomes? Some range of characteristics included might be age, race, sex, etc.***			
7	**Was the scientific quality of the included studies assessed and documented?** ***Did authors state take into account study type and design (e.g. randomization, blinding, placebo controlled studies)?***			
8	**Was the scientific quality of the included studies used appropriately in formulating conclusions?**			
9	**Were the methods used to combine the findings of studies appropriate?** ***Did authors assess homogeneity (i.e. Chi-squared test), and take appropriate meta-analyses based on such?***			

AMSTAR Checklist (please assign each criteria 1 point)		Yes	No	Not Applicable
10	**Was the likelihood of publication bias assessed?** ***Did authors include graphical (e.g. funnel plot) and/or statistical tests (e.g. Egger regression test) to evaluate included study biases?***			
11	**Was the conflict of interest stated?** ***Did authors explicitly state any possible conflicting sources of support from included studies?***			
	Total Score	**0**	**out of**	**11**

Studies of Test Accuracy and Reliability

Appendix Table D4. Assessment of risk of bias for studies of diagnostic test accuracy/validity

	Diagnostic test accuracy/validity studies	
Risk of Bias	**Study type**	**Criteria**
Low risk of bias	Good quality prospective study	Broad spectrum of persons with the expected condition Appropriate reference standard used Adequate description of test and reference for replication Blinded comparison of tests with appropriate reference standard Reference standard performed independently of diagnostic test
Moderately low risk of bias	Moderate quality prospective study	Violation of any one of the criteria for a good quality prospective study (Low RoB)
	Good quality retrospective study	Broad spectrum of persons with the expected condition Appropriate reference standard used Adequate description of test and reference for replication Blinded comparison of tests with appropriate reference standard Reference standard performed independently of diagnostic test
Moderately high risk of bias	Poor quality prospective study	Violation of any two or more of the criteria for a good quality prospective study
	Moderate quality retrospective study	Violation of any one of the criteria for a good quality retrospective study

Risk of Bias	Diagnostic test accuracy/validity studies	
	Study type	**Criteria**
High risk of bias	Poor quality retrospective study	Violation of any two or more of the criteria for a good quality retrospective study
	Case-Control Study	

In instances where the outcomes of interest for diagnostic testing are hard clinical outcomes (e.g. myocardial infarction or death), RoB tools related to RCTs and observational studies for treatment are adapted accordingly. The table below related to our AHRQ-funded report on non-invasive testing for coronary artery disease provides an example of such an adaptation.

Appendix Table D5. Assessment of risk of bias for prognostic studies that evaluate the predictive ability of a diagnostic test

Risk of Bias	Studies of Prognosis	
	Study Design	**Criteria**
Low risk of bias	Good quality cohort*	• Prospective design • Broad spectrum of persons with the expected condition • Patients at similar point in the course of their disease or treatment • Adequate description of test and reference for replication • Blinded comparison of tests with appropriate reference standard • Reference standard performed independently of diagnostic test • F/U rate of ≥ 80%† • Patients followed long enough for outcomes to occur
Moderately low risk of bias	Moderate quality cohort	• Prospective design, with violation of one of the other criteria for good quality cohort study • Retrospective design, meeting all the rest of the criteria in class I
Moderately high risk of bias	Poor quality cohort Good quality case-control or cross-sectional study	• Prospective design with violation of 2 or more criteria for good quality cohort, or • Retrospective design with violation of 1 or more criteria for good quality cohort • A good case-control study‡ • A good cross-sectional study§
High risk of bias	Poor quality case-control or cross-sectional Case series§	• Other than a good case-control study • Other than a good cross-sectional study • Any case series** design

*Cohort studies follow individuals with the exposure of interest over time and monitor for occurrence of the outcome of interest.

†Applies to cohort studies only.

‡A good case-control study must have the all of the following: all incident cases from the defined population over a specified time period, controls that represent the population from which the cases come, exposure that precedes an outcome of interest, and accounting for other prognostic factors.

§A good cross-sectional study must have all of the following: a representative sample of the population of interest, an exposure that precedes an outcome of interest (e.g., sex, genetic factor), an accounting for other prognostic factors, and for surveys, at least a 80% return rate.

**A case-series design for prognosis is one where all the patients in the study have the exposure of interest. Since all the patients have the exposure, risks of an outcome can be calculated only for those with the exposure, but cannot be compared with those who do not have the exposure. For example, a case-series evaluating the effect of smoking on spine fusion that only recruits patients who smoke can simply provide the risk of patients who smoke that result in pseudarthrosis but cannot compare this risk to those that do not smoke.

Appendix Table D6. Assessment of risk of bias for reliability studies

RoB	Study type	Criteria
Low	Good quality study	• Broad spectrum of persons with the expected condition • Adequate description of methods for replication • Blinded performance of tests, measurements or interpretation • Second test/interpretation performed independently of the first
Mod Low	Moderate quality	• Violation of any one of the criteria for a good quality study
Mod High	Poor quality study	• Violation of any two of the criteria
High	Very poor quality study	• Violation of all three of the criteria

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al.[3] QHES embodies the primary components relevant for critical appraisal of economic studies.[1,3] It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (e.g., with respect to age, gender, medical conditions, etc.)? To what extent are the populations for each intervention comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (e.g., complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?
- How were the data and/or patients selected or sampled (e.g., a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?

Economic Studies

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature.

References

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APPENDIX E. Study Quality: RoB evaluation

Appendix Table E1. Risk of Bias Assessment: Early Hodgkin Lymphoma Pet-Adapted Treatment Studies

	RCTs*		OBSERVATIONAL	
Methodological Principle	**Andre 2017/Raemakers 2014 H10 trial**	**Radford 2015 RAPID trial**	**Dann 2017 [Early HL subgroup]**	**Straus 2018**
Study design				
Randomized controlled trial*	■	■		
Prospective cohort study			■	■
Retrospective cohort				
Administrative database				
Registry study				
Case-control				
Case-series				
Methods				
Random sequence generation†	Yes	Yes	NA	NA
Statement of Concealed allocation†	Yes	Yes	NA	NA
Analysis according to random assignment (intention to treat)†	Yes	Yes	NA	NA
Independent or blinded assessment of PET/CT (interpreter blinded to clinical information, clinical status)	Unclear	Yes	Unclear	Unclear
Independent or blinded outcome assessment for subjective clinical outcomes	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)
Prespecified threshold or definition for a positive test	Yes	Yes	Yes	Yes
Attrition (≤ 20% overall);	Yes	Yes	Yes	Yes
Comparable follow-up time or accounting for time at risk	Yes	Yes	Yes	Unclear
Baseline Comparability or Controlling for possible confounding‡	Yes	Yes	Unclear	Yes
Full reporting on pre-specified outcomes	Yes	Yes	Yes	Yes
Overall Risk of Bias	**LOW**	**LOW**	**MODERATELY HIGH**	**MODERATELY HIGH**

NA = not applicable.

* None of the included randomized controlled trials randomized patients to receive PET/CT versus a strategy that did not include use of PET/CT, but rather, patients were randomized to various treatment options based on results of their PET/CT.

†Applies only to randomized controlled trials

‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods) at time of randomization or allocation to treatment based on PET results

Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix Table E2. Risk of Bias Assessment: Advanced Hodgkin Lymphoma Pet-Adapted Treatment RCTs*

Methodological Principle	Gallamini 2018 GITILFIL HD 0607 trial	Borchmann 2017 (a, b) HD18 trial	Johnson 2016	Engert 2012/2017* HD15 trial
Study design				
Randomized controlled trial*	■	■	■	
Prospective cohort study				
Retrospective cohort				■
Administrative database				
Registry study				
Case-control				
Case-series				
Methods				
Random sequence generation†	NR			NA
Statement of Concealed allocation†	Unclear	Yes		NA
Analysis according to random assignment (intention to treat)†				NA
Independent or blinded assessment of PET/CT (interpreter blinded to clinical information, clinical status)	Yes	Yes	Yes	No
Independent or blinded outcome assessment for subjective clinical outcomes	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)
Prespecified threshold or definition for a positive test	Yes	Yes	Yes	YES
Attrition (≤ 20% overall)	Yes	Yes	Yes	No
Comparable follow-up time or accounting for time at risk	Unclear	Yes	Unclear	Yes
Baseline Comparability or Controlling for possible confounding‡	Unclear	Yes	Yes	Unclear
Full reporting on pre-specified outcomes	Yes	Yes	Yes	Yes

Overall Risk of Bias	MODERATELY HIGH	LOW	MODERATELY LOW	HIGH

NA = not applicable.

* None of the included randomized controlled trials randomized patients to receive PET/CT versus a strategy that did not include use of PET/CT, but rather, patients were randomized to various treatment options based on results of their PET/CT. Although the Engert study was technically a RCT, it did not randomize patients based on PET results and included only a subset of patients with PET scans after initial treatment and who had12 months follow-up; thus, it was considered an observational study for purposes of this HTA

†Applies only to randomized controlled trials

‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods) at time of randomization or allocation to treatment based on PET results

Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix Table E3. Risk of Bias Assessment: Advanced Hodgkin Lymphoma Pet-Adapted Treatment *Observational Studies*

Methodological Principle	Carras 2018	Dann 2017 [Advanced HL subgroup]	Deau 2015	Ganensan 2015	Kedmi 2016	Press 2016	Romano 2018	Zinzani 2016
Study design								
Randomized controlled trial								
Prospective cohort study	■	■		■		■		■
Retrospective cohort			■		■		■	
Administrative database								
Registry study								
Case-control								
Case-series								
Methods								
Random sequence generation†	NA	NA	NA	NA	NA	NA	NA	NA
Statement of Concealed allocation†	NA	NA	NA	NA	NA	NA	NA	NA
Analysis according to random assignment (intention to treat)†	NA	NA	NA	NA	NA	NA	NA	NA
Independent or blinded assessment of PET/CT (interpreter blinded to clinical information, clinical status)	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Unclear	No
Independent or blinded outcome assessment for subjective clinical outcomes	NA (OS, EFS)	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)	NA (PFS)	NA (OS, PFS)

Methodological Principle	Carras 2018	Dann 2017 [Advanced HL subgroup]	Deau 2015	Ganensan 2015	Kedmi 2016	Press 2016	Romano 2018	Zinzani 2016
Prespecified threshold or definition for a positive test	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Attrition (≤ 20% overall);	Yes	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes
Comparable follow-up time or accounting for time at risk	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Baseline Comparability or Controlling for possible confounding‡	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Full reporting on pre-specified outcomes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Overall Risk of Bias	**MODERATELY HIGH**	**MODERATELY HIGH**	**HIGH**	**MODERATELY HIGH**	**MODERATELY HIGH**	**MODERATELY LOW**	**MODERATELY HIGH**	**MODERATELY LOW**

NA = not applicable.
†Applies only to randomized controlled trials
‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods) at time of randomization or allocation to treatment based on PET results
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix Table E4. Risk of Bias Assessment: Relapsed/Refractory Hodgkin Lymphoma Pet-Adapted Treatment *Observational Studies (No RCTs)*

Methodological Principle	Moskowitz 2017	Moskowitz 2015	Moskowitz 2012
Study design			
Randomized controlled trial			
Prospective cohort study	■	■	■
Retrospective cohort			
Administrative database			
Registry study			
Case-control			
Case-series			
Methods			
Random sequence generation†	NA	NA	NA
Statement of Concealed allocation†	NA	NA	NA
Analysis according to random assignment (intention to treat)†	NA	NA	NA
Independent or blinded assessment of PET/CT (interpreter blinded to clinical information, clinical status)	Unclear	Unclear	Unclear
Independent or blinded outcome assessment for subjective clinical outcomes	NA (EFS, OS)	NA (EFS, OS)	NA (EFS, OS)
Prespecified threshold or definition for a positive test	Yes	Yes	Yes
Attrition (≤ 20% overall);	Yes	Yes	Yes
Comparable follow-up time or accounting for time at risk	No	No	Yes
Baseline Comparability or Controlling for possible confounding‡	Yes	Yes	No
Full reporting on pre-specified outcomes	Yes	Yes	Yes
Overall Risk of Bias	**MODERATELY HIGH**	**MODERATELY HIGH**	**MODERATELY HIGH**

NA = not applicable.
†Applies only to randomized controlled trials
‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods) at time of randomization or allocation to treatment based on PET results
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

Appendix Table E5. Risk of Bias Assessment: Aggressive Non-Hodgkin Lymphoma Pet-Adapted Treatment Studies

	RCTs*			OBSERVATIONAL			
Methodological Principle	**Casasnovas 2017 LNH-3B trial**	**Duhrsen 2018 PETAL trial**	**Lamy 2018 LYSA/GOELAMS trial**	**Pardal 2014**	**Stewart 2014**	**Swinnen 2015**	**Zinzani 2015**
Study design							
Randomized controlled trial*	■	■	■				
Prospective cohort study				■	■	■	
Retrospective cohort							■
Administrative database							
Registry study							
Case-control							
Case-series							
Methods							
Random sequence generation†	No	Yes	Yes	NA	NA	NA	NA
Statement of Concealed allocation†	No	Yes	Yes	NA	NA	NA	NA
Analysis according to random assignment (intention to treat)†	Yes	Yes	Yes	NA	NA	NA	NA
Independent or blinded assessment of PET/CT (interpreter blinded to clinical information, clinical status)	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear
Independent or blinded outcome assessment for subjective clinical outcomes	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)	NA (OS, PFS)
Prespecified threshold or definition for a positive test	Yes	Yes	Yes	No	Yes	Yes	Yes
Attrition (≤ 20% overall);	Yes	Unclear§	Yes	Yes	Yes	Yes	Yes
Comparable follow-up time or accounting for time at risk	Unclear	Unclear§	Unclear	Yes	Yes	Yes	Yes
Baseline Comparability or Controlling for possible confounding‡	Yes	Yes	Yes	Yes	No	Unclear	Unclear
Full reporting on pre-specified outcomes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall Risk of Bias	**MODERATELY HIGH**	**MODERATELY LOW**	**MODERATELY LOW**	**MODERATELY LOW**	**MODERATELY HIGH**	**MODERATELY HIGH**	**MODERATELY HIGH**

NA = not applicable.
* None of the included randomized controlled trials randomized patients to receive PET/CT versus a strategy that did not include use of PET/CT, but rather, patients were randomized to various treatment options based on results of their PET/CT.
†Applies only to randomized controlled trials
‡Groups must be comparable on baseline characteristics or evidence of control for confounding presented (e.g. by restriction, matching, statistical methods) at time of randomization or allocation to treatment based on PET results
Unclear indicates that it could not be determined from the information provided whether or not the criterion was met.

APPENDIX F. Hodgkin's Lymphoma (Early, Advanced, Pediatric, and Relapsed/ Refractory)

Appendix Table F1. Study Characteristics and data abstraction: clinical studies of Hodgkin's Lymphoma

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
Early Stage HL				
Initial Staging				
Figura 2017	Retrospective cohort Population N = 37 Mixed adults (81%) and pediatric (19%) M(%)/F(%): 13(35)/24(65) Stage I: 14% (5/37) II: 86% (32/37) B symptoms: 27% (10/37) Bulky Disease: 54% (20/37) Comparator Pre-treatment PET for therapy planning (n=31) vs. No pre-treatment PET for therapy planning (n=6) Median follow-up: 46 months.	**4-year Relapse Free Survival (RFS)** No Pre-treatment PET vs. Pre-treatment PET: 67% vs 97%; p= 0.001 Among the 6 patients who did not receive a baseline PET/CT scan, all 3 recurrences occurred in lymph node regions outside of, but immediately adjacent to, the radiation field.	NR	NR
Interim				
Pommier 2011	Prospective cohort Population N=123 (patients receiving curative radiotherapy, n=118) Adults: 108/124 (87%) (median age 33 years, range 19 to 80)	NR	Proportion with modifications of initial treatment strategy *pre-treatment PET vs. no pre-treatment PET*: 78.7% (95% CI, 66.3% to 88.1%) (3 cancellations, 10 modifications*) vs. 85.5% (95% CI, 74.2% to 93.1%) (3 cancellations	NR

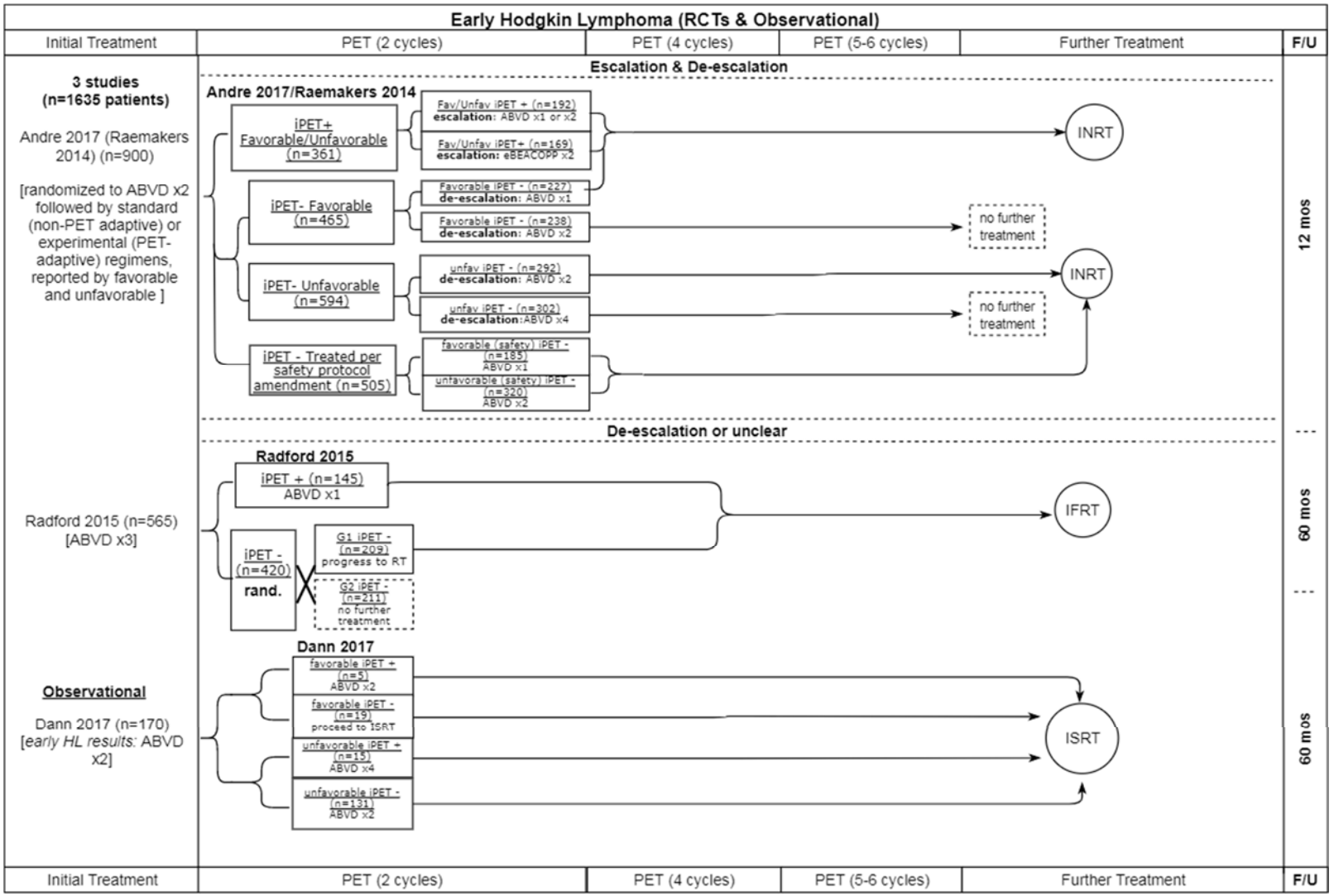
Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	AND Pediatric: 16/124 (13%) (median age 16 years, range 10 to 18) Adults: M(%)/F(%): 61(56.6)/47(43.5) Pediatric M(%)/F(%): 7(43.5)/9(56.3) Stage Adults: I: 16.7% (18/108) II: 83.3% (90/108) Pediatric: II: 100% (16/16) Comparator PET/CT prior to radio therapy (n=61) vs. Conventional therapy including enhanced CT (n=62) Median follow-up: 16 months.		and 6 modifications)	
Advanced Stage HL				
Surveillance				
Picardi 2014	RCT Population N = 300 **PET/CT:** Adults (median 29, range 18-70 years) M(%)/F(%): 91(61)/59(39) Stage	NR	Proportion of patients undergoing unnecessary surgical biopsies (mediastinotomy) due to false positives in the deep compartments of the mediastinum, (PET/CT vs. US/chest radiography: 50% (20/40) vs. 15% (6/40) p=0.04 (For PET, 11/20 were FP; for US 1/6 was FN) Exposure to ionizing radiation:	Likelihood Ratio PET/CT vs. US/Chest Radiography: Positive: 7.3 (96% CI, 4.5 to 11.7) vs. 26.8 (95% CI, 10.2 to 70.2) Negative: 0.00 vs. 0.02 (95% CI, 0.04 to 0.18) Sensitivity PET/CT vs. US/Chest Radiography: 100% (95% CI, 91.2 to 100) vs. 97.5% (95% CI, 87.1 to 99.5)

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	IIB: 25/150 (17) IIIA: 40/150 (27) IIIB: 45/150 (30) IVA: 10/150 (7) IVB: 30/150 (20) **US/Chest Radiography:** Adults (median 29, range 18-70 years) M(%)/F(%): 90(60)/60(40) <u>Stage</u> IIB: 20% (30/150) IIIA: 23% (35/150) IIIB: 27% (40/150) IVA: 7% (10/150) IVB: 23%(35/150) <u>Comparator</u> PET/CT (n=150) vs. US/Chest radiography (n=150) <u>Median follow-up:</u> 60 month <u>Reference standard for diagnostic accuracy</u>: histological examination		PET/CT vs. US/chest radiography: 14.5 mSv vs. 0.1 mSv Secondary malignancies: PET/CT 5.3% (8/150) vs. US radiography 5.3% (8/150)	<u>Specificity</u> PET/CT vs. US/Chest Radiography: 86.3% (95% CI, 78.7% to 91.5%) vs. 96.3% (95% CI, 91.0 to 98.5) <u>False-negatives</u> PET/CT vs. US/Chest Radiography: 0 (0%) vs. 1 (2.5%) <u>False-positives</u> PET/CT vs. US/Chest Radiography: 15 (13.7%) vs. 4 (3.7%) <u>PPV</u> PET/CT vs. US/Chest Radiography: 72.7% (95% CI, 59.0% to 83.8%) vs. 90.7% (95% CI, 77.8% to 97.4%) <u>NPV</u> PET/CT vs. US/Chest Radiography: 100% (95% CI, 96.2% to 100%) vs. 99.1% (95% CI, 94.9% to 99.9%)

CI = Confidence interval; CT = Computed Tomography; F = Female; HL = Hodgkin's Lymphoma; IFRT = In Field Radiation Therapy; M = Male; NPV = Negative Predictive Value; NR = Not reported; PET/CT = Combined Positron Emission Tomography and Computed Tomography; PET = Positron Emission Tomography; PPV = Positive Predictive Value; US = Ultra Sound

*Modification in both groups included panned dose, CTV1, number of beam incidences, and number of CTVs.

Appendix Figure F1. Flowchart of Treatment Adaptations: PET-adapted therapy in Early Hodgkin Lymphoma



ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; eBEACOPP = escalated bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; F/U = follow-up; G1/G2 = group 1, group 2; HL = Hodgkin Lymphoma; iPET = interim positron emission tomography; IFRT = involved field radiation therapy; INRT = involved node radiation therapy; ISRT = involve site radiation therapy; PET = positron emission tomography; mos. = months; RCTs = randomized controlled trials; RT = radiation therapy; unfav. = unfavorable;

Appendix Table F2. Study characteristics and patient demographics: PET-adapted therapy for early-stage Hodgkin Lymphoma, escalation, interim PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)
RCTS					
André 2017 *EORTC/LYSA/FIL H10 Trial* **Raemakers 2014** *Interim Analysis of EORTC/LYSA/FIL H10 Trial* **RCT w/ Observational Cohort** RoB Low *Funding:* *Supported by European Organisation for Research and Treatment of Cancer (Belgium),* *Lymphoma Study Association (France),* *Fondazione Italiana Limfomi (Italy),* *Fondation Belge contre le Cancer (Belgium),* *Dutch Cancer Society (the Netherlands),* *Institut National du Cancer (France),* *Assistance Publique des Hopitaux de Paris (France),* *Societe Française de Medecine Nucleaire et Imagerie Moleculaire (France),* *Associazone Angela Serra (Italy),* *van Vlissingen Lymfoom Fonds (the Netherlands), and Chugai Pharmaceutical (Japan).*	Early stage classic HL (stage I-II) **Randomized Cohort (n=1900)** Ann Arbor, % (n/N): I: 23.5% (334/1420) B symptoms, % (n/N): 28.0% (391/1420) Bulky mediastinum, % (n/N): 26.9% (382/1420) **Treated per Safety Amendment (Observational) (n=505)** Ann Arbor, % (n/N): I: 18.6% (94/505) B symptoms, % (n/N): 29.3% (148/505) Bulky mediastinum, % (n/N): 26.7% -(135/505)	N=1925, n=1900 actually treated, n=1420 randomized to treatment per-initial protocol, n=505 treated in safety amendment Adults and children (range 15-70 years) M: 50.1% (451/900) F: 49.9% (449/900)	ABVD chemo Previously treated: No	Deauville 5PS + scans: 3, 4, & 5	**Number of cycles**: 2 **Groups** **PET + Favorable and Unfavorable (n=361) (Escalation)** 1. 1 or 2 cycles ABVD + INRT (n=192) 2. 2 eBEACOPP + INRT (n=169) **PET- Favorable (n=465) (De-escalation)** 1. 1 ABVD + INRT (n=227) 2. 2 ABVD (n=238) **PET- Unfavorable (n=594) (De-escalation)** 1. 2 ABVD + INRT (n=292) 2. 4 ABVD (n=302) **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 1. 1 ABVD + INRT [favorable] (n=185) 2. 2 ABVD + INRT [unfavorable] (n=320) **Median F/U** PET+ favorable and unfavorable patients: 54 months (4.5 years)

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)
COI: *1 or more authors received the following: Honoraria, Consulting or Advisory Role, Travel/Accommodations/Expenses, Speakers' Beaureau, Research Funding. Several authors reported that they had no relationship to disclose.* Also provides data for a de-escalation strategy (see Table F3)					PET- favorable patients: 60 months (5 years) PET- unfavorable patients: 61.2 months (5.1 years) PET- favorable patients treated per safety amendment: 39.6 months (3.3 years) PET- unfavorable patients treated per safety amendment: 42 months (3.5 years)

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; CI = Confidence Interval; COI = Conflicts of interest; F/U = Follow-up; F = Female; HL = Hodgkin's lymphoma; HR = Hazard ratio; INRT = Involved node radiotherapy; iPET = interim PET; ITT = Intention to Treat; M = Male; NR = Not reported; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial; RoB = Risk of Bias; RR = Risk Ratio

*All early PET-negative patients who were included after the August, 2010 safety amendment received treatment with ABVD + INRT, as the independent data monitoring committee recommended to close the ABVD only arm. Thus, randomization no longer occurred in this proportion of patients and are therefore reported separately from the randomized patients.

Appendix Table F3. Study characteristics and patient demographics: PET-adapted therapy for early-stage Hodgkin lymphoma, de-escalation, interim PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
RCTs						
André 2017 *EORTC/LYSA/FIL H10 Trial* Raemakers 2014 *Interim Analysis of EORTC/LYSA/FIL H10 Trial* **RCT w/ Observational Cohort** RoB Low *Funding:* *Supported by European Organisation for Research and Treatment of Cancer (Belgium), LYmphoma Study Association (France), Fondazione Italiana Limfomi (Italy), Fondation Belge contre le Cancer (Belgium), Dutch Cancer Society (the Netherlands), Institut National du Cancer (France), Assistance Publique des Hopitaux de Paris (France), Societe Française de Medecine Nucleaire et Imagerie Moleculaire (France), Associazone Angela Serra (Italy), van Vlissingen Lymfoom Fonds (the Netherlands), and Chugai Pharmaceutical (Japan).*	Early stage classic HL (stage I-II) **Randomized Cohort (n=1900)** Ann Arbor, % (n/N): I: 23.5% (334/1420) B symptoms, % (n/N): 28.0% (391/1420) Bulky mediastinum, % (n/N): 26.9% (382/1420) **Treated per Safety Amendment* (Observational) (n=505)** Ann Arbor, % (n/N): I: 18.6% (94/505)	N=1925, n=1900 actually treated, n=1420 randomized to treatment per-initial protocol, n=505 treated in safety amendment Adults and children (range 15-70 years) M: 50.1% (451/900) F: 49.9% (449/900)	ABVD chemo Previously **treated**: No	Deauville 5PS + scans: 3, 4, & 5	**Number of cycles**: 2 **Groups** **PET + Favorable and Unfavorable (n=361) (Escalation)** 3. 1 or 2 cycles ABVD + INRT (n=192) 4. 2 eBEACOPP + INRT (n=169) **PET- Favorable (n=465) (De-escalation)** 3. 1 ABVD + INRT (n=227) 2 ABVD (n=238) **PET- Unfavorable (n=594) (De-escalation)** 3. 2 ABVD + INRT (n=292) 4. 4 ABVD (n=302) **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 3. 1 ABVD + INRT [favorable] (n=185) 4. 2 ABVD + INRT [unfavorable] (n=320)	**Clinical** PFS **Safety** Toxic Effects

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
COI: *1 or more authors received the following: Honoraria, Consulting or Advisory Role, Travel/Accommodations/Expenses, Speakers' Beaureau, Research Funding. Several authors reported that they had no relationship to disclose.* Also provides data for an escalation strategy (see Table F2)	B symptoms, % (n/N): 29.3% (148/505) Bulky mediastinum, % (n/N): 26.7% -(135/505)				**Median F/U** PET+ favorable and unfavorable patients: 54 months (4.5 years) PET- favorable patients: 60 months (5 years) PET- unfavorable patients: 61.2 months (5.1 years) PET- favorable patients treated per safety amendment: 39.6 months (3.3 years) PET- unfavorable patients treated per safety amendment: 42 months (3.5 years)	
Radford 2015 RAPID trial **RCT** RoB Low *Funding:* *Supported by Leukaemia and Lymphoma Research, the Lymphoma Research Trust, Teenage Cancer Trust, and the U.K. Department of Health. No commercial support was provided. No one who is not an author contributed to the writing of the manuscript.* *COI:* None reported	Early stage classic HL (stage (IA or IIA) **PET-** **Radiotherapy Tx** Ann Arbor, % (n/N): IA: 33.0% (69/209) IIA: 67.0% (140/209) No. Nodal Sites, % (n/N): 1: 37.0% (77/208) 2: 32.2% (67/208)	N=602 Mixed (median 35, range 16-75 years) **Radiotherapy Tx**: M: 103 (49.3%) F: 106 (50.7%) **No Further Tx**: M: 107 (50.7%)	ABVD chemo Previously treated: No	Deauville 5PS + scans: 3, 4, & 5	**Number of cycles**: 3 **Groups** **PET + (n=145)** 1. Additional cycle ABVD (4 total) + RT **PET – (randomized) (n=426, n=420 actually randomized)** 1. Involved-field RT (n=209) [ITT] 2. No further treatment (n=211) [ITT] **Median F/U: 60 months (5 years)**	**Clinical** OS, PFS, disease progression **Safety**

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
	≥3: 30.8% (64/208) **No Further Tx**: Ann Arbor, % (n/N): IA: 33.2% (70/211) IIA: 66.8% (141/211) No. Nodal Sites, % (n/N): 1: 33.8% (7/210) 2: 37.1% (78/210) ≥3: 29.0% (61/210) **PET+** Ann Arbor Stage, % (n/N): IA: 33.1% (48/145) IIA: 66.9% (97/145) No. Nodal Sites, % (n/N): 1: 35.2% (51/145) 2: 30.3% (78/145)	F: 104 (49.3%) **PET+:** M: 96 (66.2%) F: 49 (33.8%)				

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
	≥3: 34.5% (50/145)					

5PS = 5 point scale; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; CI = Confidence Interval; COI = Conflicts of interest; F/U = Follow-up; F = Female; HL =Hodgkin's lymphoma; INRT = Involved node radiotherapy; iPET = interim PET; ITT = Intention to Treat; M = Male; NR = Not reported; OS = Overall Survival; PFS = Progression Free Survival; RCT = Randomized controlled trial; RoB = Risk of Bias; RT = Radiation therapy; Tx = treatment

*All early PET-negative patients who were included after the August, 2010 safety amendment received treatment with ABVD + INRT, as the independent data monitoring committee recommended to close the ABVD only arm. Thus, randomization no longer occurred in this proportion of patients and are therefore reported separately from the randomized patients.

Appendix Table F4. Study characteristics and patient demographics: PET-adapted therapy for early-stage Hodgkin Lymphoma, unclear escalation/de-escalation, interim PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)§	Outcomes
Observational cohorts						
Dann 2017 **Pro Cohort** [includes results for advanced HL] RoB Moderately High *Support:* *In part by the Israel Cancer*	Classic HL (stage I-IV), *categorized into*: **Early HL (IA-IIA) (n=170):** Ann Arbor, % (n/N) Stage IA: 13/170 (7.6%) Stage IIA: 157/170 (92.4%) *Further categorized into*: **EF-HL**: 14.1% (24/170)	N=355 Adults (median 30, range 18-60 years) M: 46% (162/355) F: 54% (193/355)	**EF-HL, EUF-HL, and advanced HL with IPS 0-2**: ABVD chemo	Dynamic visual scoring system for PET-2 evaluation* & Deauville 5ps	**Number of cycles**: 2 **Groups** **EF-HL (n=24) [De-escalation]** **PET+ (n=5)** Two additional ABVD courses (4 total) followed by ISRT **PET– (n=19)** ISRT **OR** two additional cycles (4 total) of ABVD† **EUF-HL (n = 146) [De-escalation]** **PET+ (n=15)**	**Clinical** PFS, OS **Safety** Toxic effects, dose intensity, secondary malignancies, restoration of menstrual function, pregnancy rate

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)§	Outcomes
Association, with generous assistance of the Neta Buksenbaum Fund, and the Israel Society of Haematology and Blood Transfusion *COI:* *The authors declare no conflicts of interest.*	**EUF-HL**: 85.9% (146/170) ***A**dvanced Disease (B symptoms or stages III/IV) (n=185) reported separately in Table F7*				Four additional ABVD courses (6 total) then ISRT **PET– (n=131)** Two additional ABVD courses (4 total) then ISRT **OR** four additional ABVD courses (6 total)† **<u>All Early HL (n=170) [De-escalation]</u>** **PET+ (n=20)** Two or four additional courses of ABVD **PET- (n=150)** ISRT (n=87) Two additional courses of ABVD (n=83) **Median F/U: 60 months (5 years)**	

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; COI = Conflicts of interest; EF = Early favorable; EUF = Early unfavorable; HL = Hodgkin's lymphoma; iPET = interim PET; IPS = International Prognostic Score; ISRT = Involved Site Radiation Therapy; OS = Overall Survival; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial

*Study does not provide further detail describing the dynamic visual scoring system, but does reference Dann et al., 2010.

†PET- patients with multiple or extensive disease sites or fields overlapping breast tissue (women), could forego radiotherapy and receive two further courses of ABVD instead.

‡Patients progressing during the study were withdrawn and received salvage therapy.

§ This study reports on a mixture of early and advanced HL patients. Data is reported here and with advanced HL data for convenience.

Appendix Table F5. Study characteristics and patient demographics: PET-adapted therapy for advanced-stage Hodgkin lymphoma, escalation, interim PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
RCTs						
Gallamini 2018 *GITIL/FIL HD 0607 Trial* **RCT** RoB Moderately High Also provides data for end-of-treatment PET PET scan administered twice in this study; after 2 cycles of ABVD treatment (denoted as PET2 in study), after subsequent assigned treatment (denoted as PET in study). *Funding:* *Supported by Associazione Italiana per la Ricerca sul Cancro IG n.2013 (A.G.), by Associazione Italiana Lotta alla Leucemia Sezione di Bergamo, and by a research grant of Cassa di Risparmio di Cuneo.* *COI:* *1 or more authors received the following: Honoraria, Consulting or Advisory Role, Travel/Accomodations/Expenses, Speakers' Beaureau, Research Funding. Several authors reported that they had no relationship to disclose.*	Advanced classic HL (stage IIB-IVB) Ann Arbor, % (n/N) II: 35.7% (279/782) III: 32.2% (252/782) IV: 32.1% (251/782) B symptoms: 81.1% (634/782) IPS, % (n/N) 0-1: 36.6% (286/782) 2-3: 50.9% (398/782) >3: 12.5% (98/782) Large Nodal Mass (cm), % (n/N) <5: 41.9% (328/782) 5-7: 17.9% (140/782) 8-10: 20.3% (159/782) >10: 19.8% (155/782)	N=783 enrolled, n=782* received ABVD treatment, n=780 received iPET scan [ITT] Adults (14-60 years) M: 48.9% (382/782) F: 51.1% (400/782)	ABVD chemo Previously treated: No	Deauville 5PS + scans: 4 & 5	**Number of cycles**: 2 **Interim PET** **Groups** **PET +** (randomized) (n=150) n=148† actually randomized to treatment: 1. BEACOPP + IV rituximab given on day 1 of each course, 8 cycles (n=72) 2. BEACOPP, 8 cycles (n = 76) In both groups, BEACOPP given as 4 cycles of escalated + 4 cycles of baseline **PET –** (n=630) n=629‡ actually randomized to treatment: Standard ABVD for 4 additional cycles (6 cycles total) **Median F/U: 43.2 months (3.6 years)**	**Clinical** OS , PFS, Mortality **Safety** % Under treated, Toxic effects

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
Borchmann 2017b HD18 trial **RCT** RoB Low *Funding: Deutsche Krebshilfe (review trial protocol); Roche Pharma AG provided rituximab and financial support. Played no role in design, data collection, analysis and interpretation, or writing of report.* *COI: None declared.*	Advanced classic HL (stage IIB-IV) Proportion with Ann Arbor Stage (n=1945): -II: 14.5% -III: 49.1% -IV: 36.4% Proportion with ECOG Status (n=1945): -0: 59.2% -1: 38.3% -2: 2.5% Proportion with Subtypes (n=1945): -classic HL: 94.7% -NLPHL: 5.3% Extranodal Involvement: 19.5% (379/1945) B Symptoms: 100% (see inclusion criteria) Large Mediastinal Mass (≥ 1/3 of transverse diameter of	N = 2101 recruited, 1964 randomized, 1945 analyzed (ITT), 115 subgroup (nonrandomized) Median Age (IQR): 32 years (24-43) Male: 61%	escalated BEACOPP Previously treated: No	PET + (≥3 on 5-PS) PET -	**PET Timing:** Interim (2 cycles) **<u>PET + (randomized) (n=951)</u>** Randomized to standard therapy or rituximab escalation: 1a. Standard therapy escalated BEACOPP x8 (n=220) OR 2. escalated BEACOPP + rituximab x8 (n=220) **<u>PET + subgroup (allocated after protocol change)</u>** A protocol change occurred after which standard therapy was reduced from x8 to x6 eBEACOPP. Randomization ceased at this point: 1b. Reduced Standard Therapy (escalated BEACOPP x6) (n=511) **<u>PET - (randomized) (n=1013)</u>** Randomized to standard therapy/reduced therapy (after protocol change) or de-escalation therapy: 1.Standard therapy escalated BEACOPP x8 (n=220) or x6 reduced standard (n=218) OR 2. de-escalation: escalated BEACOPP x4 (n=505) **Median F/U 67.5 mos. (PET +)**	**Clinical** OS (3-year, 5-year) PFS (3-year, 5-year) Mortality **Safety** PET-related: NR Treatment-Related: Toxicities Grade 3-4 (CTCAE), death

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
	thorax): 28.8% (561/1944)				**Median F/U 56.5 mos. (PET -)**	
Observational studies (prospective)						
Carras 2018 *GOELAMS LH 2007 trial* **Prospective Cohort** RoB Moderately High *Funding:* *This study was supported by the GOELAMS group and AMGEN.* *COI:* *The authors have stated that they have no conflicts of interest.*	Advanced HL (GOELAMS Prognostic Score System ≥ 4) Ann Arbor Stage, % (n/N) II: 2% (1/51) III: 20% (10/51) IV: 78% (40/51) ECOG performance status, % (n/N) 0-1: 88% (45/51) Num. Involved Sites, % (n/N) 1-2: (10% (5/51) 3-4: 17% (9/51) ≥5: 69% (35/51) Presence of bulky disease, % (n/N): 43% (22/51)	N=51 Adults (18-65 years) M: 57% (29/51) F: 43% (22/51)	VABEM chemo Previously treated: No	Deauville 5PS + scans: 4 & 5	**Number of cycles**: 2 **Groups** **PET+ (n=12)** n=11§ actually treated with salvage therapy: 2 courses of PDG (cisplatin, gemcitabine, and dexamethasone) After 2 courses of PDG: • PET+ (n=1) patients received 2 courses of a MINE-R • PET- (n=10) patients received 1 course of PDG chemo All n=11 patients received HDT and ASCT following the above treatments • n=3 received Radiotherapy, 30Gy, IFRT for initial bulky lesions **PET- (i.e., complete remission) (n = 37)** Additional (3rd) course of VABEM chemo	**Clinical** EFS, OS, mortality **Safety** Toxic effects, secondary malignancies, death related to adverse events

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
					• n=15 received Radiotherapy, 30Gy, IFRT for initial bulky lesions **Median F/U: 63.6 months (5.3 years)**	
Press 2016 *The Southwest Oncology Group S0816 study* **Prospective Cohort** RoB Moderately Low *Support:* *Supported in part by Grants No. CA180888, CA180819, CA180821, CA180820, CA180799, CA180816, CA180801, CA180835, CA180858, CA180801, CA180846, CA180835, CA180818, CA180828, CA180826, and CA180834 from the Public Health Service, Department of Health and Human Services, National Cancer Institute (NCI), National Clinical Trials Network; by Grants No. CA189830, CA189971, CA189808, CA189854, CA189821, CA189848, CA189858, CA189860, CA189872, and CA189856 from the NCI Community Oncology Research Program; by Grant No. CA31946 from the National Institutes of Health (NIH)-NCI; by Grant No. 3U10CA032102-30S1 from the NIH American Recovery and Reinvestment*	High-risk stage II or stage III to IV HL Ann Arbor Stage, % (n/N) III: 52% (175/336) IV: 48% (161/336) IPS, % (n/N) 0-2: 49% (165/336) 3-7: 51% (177/336) B symptoms, % (n/N): 62% (208/336) Bulk>10 cm: 18% (60/336)	N=358 enrolled, n=336 eligible, n=331 treated [ITT] Adults (range, 18-60 years) M: 56% (188/336) F: 44% (175/336)	ABVD chemo Previously treated: No	Deauville 5PS + scans: 4 & 5	**Number of cycles**: 2 **Groups** **PET+ (n=60)** n=49** actually treated per protocol: Escalated BEACOPP for 6 cycles **PET- (n = 271)** n=270 actually treated: Additional 4 cycles (6 cycles total) of AVBD **Median F/U: 39.7 months (3.3 years)**	**Clinical** PFS, OS **Safety** Toxic effects, dose intensity, secondary malignancy

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
Act of 2009 for the interim FDG-PET imaging; by Grant No. CA121947 from the NCI AIDS Malignancy Clinical Trials Consortium; and by the David and Patricia Giuliani Family Foundation (O.W.P.), The Lymphoma Foundation (D.J.S.), the Adam Spector Fund for Hodgkin's Research (D.J.S.), and the Ernest and Jeanette Dicker Charitable Foundation (D.J.S.). *COI:* *1 or more authors received the following: Stock or Ownership, Honoraria, Consulting or Advisory Role, Travel/Accommodations/Expenses, Speakers' Bureau, Research Funding. Several authors reported that they had no relationship to disclose.*						
Zinzani 2016 *HD0801 study* **Prospective Cohort** RoB Moderately Low *Support:* *Italian Lymphoma Foundation* *COI:* *1 or more authors received the following: Stock or Ownership, Honoraria, Consulting or Advisory Role,*	Advanced HL (stage IIB-IV) Ann Arbor, % (n/N): II: 19% (99/512) II: 35% (179/512) IV: 46% (234/512) IPS, % (n/N): 0-2: 56% (261/512) ≥3: 44% (206/512)	N = 512 [ITT] Adults (median 22 years, range 18-68 years) M: 54% (275/512) F: 46% (237/512)	ABVD chemo Previously treated: No	Deauville 5PS + scans: 3, 4, & 5	**Number of cycles:** 2 **Groups** **PET+ (n=103)** n=81†† received treatment per protocol: Four cycles IGEV salvage • PET+ after salvage treatment (n=38): 1. High-dose melphlan BEAM-conditioned ABMT (n=24)	**Clinical** PFS, OS **Safety** Toxic effects

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
Travel/Accommodations/Expenses, Speakers' Bureau, Research Funding. Several authors reported that they had no relationship to disclose.	B symptoms, % (n/N): 64% (326/512) Performance Status, % (n/N): 0: 66% (339/512) 1: 28% (142/512) 2: 6% (30/512) 3: 0% (1/512) Bulky Disease, % (n/N): 35% (181/512) Extranodal Involvement, % (n/N): 46% (236/512) Bone Morrow Involvement, % (n/N): 10% (49/512)				2. High-dose melphanlan reduced-intensity alloBMT (n=14) • PET- after salvage treatment (n=43): 1. BEAM-conditioned ABMT (n=43) **PET- (n = 409)** Additional 4 cycles of ABVD (6 cycles total) **Median F/U from enrollment: 27 months (2.3 years)** **Median F/U from iPET scan: 25 months (2.1 years)**	
Ganesan 2015 **Prospective Cohort** RoB Moderately High *Support:* Cancer Institute (WIA) funds. No grant number is applicable.	Advanced stage HL (stages IIB–IVB) Ann Arbor, % (n/N) IIB: 6% (3/50) III: 58% (29/50) IV: 36% (18/50) High Risk Disease, % (n/N)	N=50, n=47‡‡ for EFS analysis Mixed adults and pediatric (median 28 years, range 12-60 years) M: 39/50 (78%) F: 11/50 (22%)	ABVD chemo Previously treated: No	Deauville 5PS + scans: 4 & 5	**Number of cycles: 2** **Groups** **PET+ (n=8)** Four cycles of escalated BEACOPP **PET- (n=41)** n= Four additional ABVD cycles (6 total)	**Clinical** PFS, OS, Mortality **Safety** Toxic effects, Negative predictive value of PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
COI: *The authors have declared no conflicts of interests.*	(IPS of 4-7): 32% (16/50) B symptoms, % (n/N): 64% (32/50) Bulky Disease, % (n/N): 24% (12/50) ECOG performance status, % (n/N): 0-1: 94% (47/50) 2-4: 6% (3/50) IPS, % (n/N): 0-3: 68% (34/50) 4-7: 32% (16/50)				**Median F/U: 24.7 months (2.1 years)**	
Observational studies (retrospective)						
Romano 2018 **Retrospective Cohort** RoB Moderately High *Support:* *A grant from Ministero della Salute (Ricerca Finalizzata, 10/PE-2011-02350147, F.D.R and N.L.P.) and Fondazione Veronesi (A.R.).* *COI:* *The authors declare that they have no competing interests.*	Advanced stage HL (stage IIB, III-IV) Ann Arbor, % (n/N) Early (Stage I–IIA): 34% (61/180) Advanced (Stage ≥ IIB): 66% (119/180) Bulky disease, % (n/N): 30% (54/180) B-symptoms, % (n/N): 58.9% (106/180)	N=180, n=119§§ advanced stage patients Mixed adults and pediatric (age range 14.8-6.9 years, median 31.7 years) M: 90 (50%) F: 90 (50%)	ABVD chemo (6 cycles), followed by involved field RT if clinically indicated. **Early-stage patients** ABVD 2 cycles + IFRT: 9 (5%) ABVD 4 cycles + IFRT: 20 (11%) ABVD 6 cycles + IFRT: 28 (16%)	Deauville 5PS + scans: 4 & 5	**Number of cycles: 2** **Groups** **PET+ (n=21)** n=16, actually treated: BEACOPP for 8 cycles (and in case of persistent disease, bone marrow autologous transplant) **PET- (n=98)** Continued ABVD for 4 additional cycles, followed by consolidation RT on initial bulky nodal site of disease in a subset	**Clinical** PFS, HR **Safety** Treatment failure

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
	IPS (for advanced stage only): 0–1: 29% (35/180) 2–7: 41% (84/180)		ABVD 6 cycles: 4 (2%) **Advanced-stage patients** ABVD 6 cycles (%) + IFRT: 24 (22%) ABVD 6 cycles: 59 (33%) ABVD 2 cycles + 8 BEACOPP ± IFRT: 16 (9%) Previously treated: No		**Median F/U: 68 months (5.7 years)**	

5PS = 5 point scale; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT = autologous stem cell transplant; BEACOPP= bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BEAM = carmustine, etoposide, cytarabine, and melphalan; CTCAE = Common Terminology Criteria for Adverse Events; COI = Conflicts of interest; EB = Escalated BEACOPP; ECOG = Eastern Cooperative Oncology Group; EFS = Event Free Survival; F/U = Follow-up; F = Female; G = Grade; GOELAMS = Groupe d'étude des Leucémies Aigues et des Maladies du Sang; HDT = High-dose therapy; HL = Hodgkin's lymphoma; IFRT = Involved field radiation therapy; iPET = interim PET; IPS = International Prognostic Score; ITT = Intention to Treat; M =Male; MINE-R = mesna, ifosfamide, mitoxantrone, etoposide, and rituximab; mos. = months; OS = Overall Survival; PDG = cisplatin, gemcitabine, and dexamethasone; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial; RoB = Risk of Bias; RT = Radiation therapy; VABEM = vindesine, doxorubicin, carmustine, etoposide, and methylprednisolone

* 1 patient eliminated due to presenting with composite lymphoma. 2 patients died before receiving first two cycles of ABVD.

†Death due to progressive disease (n=1). No random assignment on basis of medical decision (n = 1).

‡1 consent withdrawal.

§1 Exclusion owing to a local investigator decision.

**3 were treated with ABVD and 3 denied any protocol treatment.

††2 patients had diagnostic failure, 15 patients received four more cycles of ABVD, and 5 patients shifted to a different salvage treatment.

‡‡3 patients defaulted after two, four and five cycles of chemotherapy (one did not undergo PET-2 and the other two were PET-2-negative). These 3 patients are excluded from EFS analysis (as their final disease status is unknown), but included in the OS analysis.

§§The PET-adapted treatment strategy was only applied to advanced staged patients, thus results are only reported for the advanced stage patients. However, population characteristics are for all 180 patients included in the study.

Appendix Table F6. Study characteristics and patient demographics: PET-adapted therapy for advanced Hodgkin Lymphoma, de-escalation, interim PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
RCTs						
Johnson 2016 **RCT** RoB Moderately Low *Funding:* *No commercial support was provided, and no commercial entity had any role in the study. Supported by Cancer Research UK (reference CRUK/07/033), Leukaemia and Blood Cancer New Zealand, and Cancer Australia.* *COI:* *Not reported*	Advanced classic HL (stage II-IV) Ann Arbor, % n/N II: 41.6% (500/1203) III: 30.2% (363/1203) IV: 28.3% (340/1203) B symptoms, % n/N: 61.35%(738/1203) Bulky disease, % n/N: 32.1%(386/1203) ECOG Performance Status, % n/N: 0: 73.9% (889/1203) 1: 22.5% (271/1203) 2: 22.3% (8/1203) 3: 1.2% (14/1203) Missing: 0.1% (1/1203) IPS, % n/N: 0-1: 33.6% (404/1203) 2-3: 48.1% (579/1203) 4: 17.4% (209/1203) Missing: 0.9% (11/1203)	N=1214 enrolled, n=1203 eligible, n=1135 underwent iPET scan, n=1119* [per-protocol] Adults (median 33, range 18-79 years) M: 54.5% (656/1203) F: 45.5% (547/1203)	ABVD chemotherapy Previously treated: No	Deauville 5PS + scans: 4 & 5	**Number of cycles**: 2 **Groups** **PET+** (n=182) n=172† actually received treatment: Either BEACOPP-14 (n=94) or escalated BEACOPP (n=78) **PET -** (randomized) (n= 937) n=935 actually randomized to treatment: additional cycles (cycles 3-6) 1. Continue ABVD for 4 cycles (n=470 [ITT]/468 [per-protocol]) 2. Omit bleomycin (AVD) for 4 cycles (n=465 [ITT]/456 [per-protocol]) **Median F/U: 41 months (3.4 years)**	**Clinical** PFS, OS, HR, Mortality **Safety** Toxic effects, Secondary malignancies

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
Borchmann 2017b HD18 trial **RCT** RoB Low Funding: Deutsche Krebshilfe (review trial protocol); Roche Pharma AG provided rituximab and financial support. Played no role in design, data collection, analysis and interpretation, or writing of report. COI: None declared.	Advanced classic HL (stage IIB-IV) Proportion with Ann Arbor Stage (n=1945): -II: 14.5% -III: 49.1% -IV: 36.4% Proportion with ECOG Status (n=1945): -0: 59.2% -1: 38.3% -2: 2.5% Proportion with Subtypes (n=1945): -classic HL: 94.7% -NLPHL: 5.3% Extranodal Involvement: 19.5% (379/1945) B Symptoms: 100% (see inclusion criteria) Large Mediastinal Mass (≥ 1/3 of transverse	N = 2101 recruited, 1964 randomized, 1945 analyzed (ITT), 115 subgroup (nonrandomized) Median Age (IQR): 32 years (24-43) Male: 61%	escalated BEACOPP Previously treated: No	PET + (≥3 on 5-PS) PET -	**PET Timing:** Interim (2 cycles) **<u>PET + (randomized) (n=951)</u>** Randomized to standard therapy or rituximab escalation: 1a. Standard therapy escalated BEACOPP x8 (n=220) OR 2. escalated BEACOPP + rituximab x8 (n=220) **<u>PET + subgroup (allocated after protocol change)</u>** A protocol change occurred after which standard therapy was reduced from x8 to x6 eBEACOPP. Randomization ceased at this point: 1b. Reduced Standard Therapy (escalated BEACOPP x6) (n=511) **<u>PET - (randomized) (n=1013)</u>**	**Clinical** OS (3-year, 5-year) PFS (3-year, 5-year) Mortality **Safety** PET-related: NR Treatment- Related: Toxicities Grade 3-4 (CTCAE), death

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
	diameter of thorax): 28.8% (561/1944)				Randomized to standard therapy/reduced therapy (after protocol change) or de-escalation therapy: 1.Standard therapy escalated BEACOPP x8 (n=220) or x6 reduced standard (n=218) OR 2. de-escalation: escalated BEACOPP x4 (n=505) **Median F/U 67.5 mos. (PET +)** **Median F/U 56.5 mos. (PET -)**	
Observational studies (retrospective)						
Deau 2015 **Retrospective Cohort** RoB High *Funding:* This work was undertaken at UCLH/UCL who received a proportion	Classic HL (stage high risk IIB-IV) Ann Arbor, % n/N IIB: 17.2% (11/64) III: 14.0% (9/64) IV: 68.8% (44/64) Bulky mediastinal mass, % n/N: 56% (36/64)	N = 64 Mixed adults and adolescents (median 25, range 15-57 years) M: 42% (27/64) F: 58% (37/64)	Escalated BEACOPP Previously treated: No	Deauville 5PS + scans: 4 & 5	**Number of cycles**: 2 **Groups** **PET +** (n = 9) Escalated BEACOPP for 2 additional rounds (4 cycles total) • **PET +** (n=5) Salvage therapy • **PET –** (n=4)	**Clinical** OS , PFS, Mortality **Safety** Infection related toxicity Acute toxicity

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
of funding from the NIHR Biomedical Research Centres funding scheme of the UK Department of Health. ST was supported by a UCL Biomedicine Grand Challenge Studentship and CS by the Kay Kendall Leukaemia Fund. *COI:* All authors report no conflict of interest					ABVD for 2 cycles **PET –** (n = 55) Standard ABVD for 4 cycles **Median F/U: 30 months (2.5 years)**	
Kedmi 2016 **Retrospective Cohort** RoB Moderately High Funding: NR COI: NR	Advanced HL (IIB - IV) Staging: -unfavorable IIB: 6% -III: 17% -IV: 77% IPS: <3: 13% ≥3: 87% Subtypes: -Nodular Sclerosis: 78.3%	N = 69 recruited Median Age (range): 30 (18.8 to 58.7) Male: 65%	escalated BEACOPP x2 Previously treated: No	PET+(defined as ≥1 residual lesions at previously involved sites and >50% size reduction of majority of large nodal masses) PET - (CR with or without residual mass)	**PET Timing:** Interim (2 cycles) **iPET + (n=17)** Patients in Partial Response (PR): De-escalation to ABVD x4 **iPET - (n=52)** Patients in Complete Response (CR): De-escalation to ABVD x4	**Clinical** 5-Year OS, PFS Mortality **Safety** Treatment- Related: Toxicities Grade 3-4 (CTCAE), Secondary Malignancies

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
	-Mixed Cellularity: 11.6% -Lymphoctye-Rich: 1.5% -Not Documented: 8.6% B symptoms: 77% Extranodal Sites: 74% Bulky Mediastinal Mass (≥10cm): 29%				**Median F/U (range): 67.2 (4.8 to 132) mos**	

5PS = 5 point scale; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AVD = doxorubicin, vinblastine, dacarbazine; COI = Conflicts of interest; ECOG = Eastern Cooperative Oncology Group; CTCAE = Common Terminology Criteria for Adverse Events; F/U = Follow-up; F = Female; HL = Hodgkin's lymphoma; iPET = interim PET; IPS = International Prognostic Score; IQR = interquartile range; ITT = Intention to Treat; M = Male; mos. = months; NR= Not reported; OS = Overall Survival; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial; RoB = Risk of Bias

*10 patients stopped the trial prior to treatment.

†16 patients were excluded owing to deviations from the PET-CT protocol.

Appendix Table F7. Study characteristics and patient demographics: PET-adapted therapy for advanced Hodgkin Lymphoma, unclear escalation/de-escalation, interim PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after iPET Follow-up (post allocation)	Outcomes
Observational studies						
Dann 2017 **Prospective Cohort** RoB Moderately High *Support:* *In part by the Israel Cancer Association, with generous assistance of the Neta Buksenbaum Fund, and the Israel Society of Haematology and Blood Transfusion* *COI:* *The authors declare no conflicts of interest.*	Classic HL (stage I-IV), *categorized into*: **Advanced Disease (B symptoms or stages III/IV) (n=185):** Ann Arbor, % (n/N) Stage IB and IIB: 62/185 (33.5%) Stage III: 58/185 (31.4%) Stage IV: 65/185 (35.1%) *Further categorized into*: **IPS 0-2**: 108/185 (58.4%) **IPS ≥3**: 77/185 (41.6%) B symptoms, % (n/N): 68.6% (127/185) *Early-stage HL (IA-IIA) (n=170) reported separately in Table F4*	N=355 Adults (median 30, range 18-60 years) M: 46% (162/355) F: 54% (193/355)	**Advanced HL with IPS 3-7**: Escalated BEACOPP	Dynamic visual scoring system for PET-2 evaluation* & Deauville 5ps	**Number of cycles**: 2 **Groups** **Advanced HL, IPS 0-2 (n=111) [Escalation]** **PET+ [without evidence of disease progression] (n=13)‡** Four additional escalated BEACOPP courses (6 total) with ISRT to residual masses **PET– (n=98)** Four additional ABVD courses (6 total) **Advanced HL, IPS ≥3 (n=74) [De-escalation]** **PET+ [without evidence of disease progression]‡ (n=14)** Four additional escalated BEACOPP courses (6 total) with ISRT to residual masses **PET– (n=60)** Four ABVD courses **All Advanced HL Patients (n=185) [Escalation/De-escalation]** **PET+ (n=27)** Four additional escalated BEACOPP courses (6 total) with ISRT to residual masses **PET- (n=158)** Four ABVD courses **Median F/U: 60 months (5 years)**	**Clinical** PFS, OS **Safety** Toxic effects, dose intensity, secondary malignancies, restoration of menstrual function, pregnancy rate

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; COI = Conflicts of interest; EF = Early favorable; EUF = Early unfavorable; HL = Hodgkin's lymphoma; iPET = interim PET; IPS = International Prognostic Score; ISRT = Involved Site Radiation Therapy; OS = Overall Survival; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial

*Study does not provide further detail describing the dynamic visual scoring system, but does reference Dann et al., 2010.

†PET- patients with multiple or extensive disease sites or fields overlapping breast tissue (women), could forego radiotherapy and receive two further courses of ABVD instead.

‡Patients progressing during the study were withdrawn and received salvage therapy.

Appendix Table F8. Study characteristics and patient demographics: PET-adapted therapy for Advanced Hodgkin Lymphoma, escalation, end-of-treatment PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after PET Follow-up (post allocation)	Outcomes
RCTs						
Gallamini 2018 *GITIL/FIL HD 0607 Trial* **RCT** RoB Moderately High Also provides data for interim PET PET scan administered twice in this study; after 2 cycles of ABVD treatment (denoted as PET2 in study), after subsequent assigned treatment (denoted as PET in study). *Funding:* *Supported by Associazione Italiana per la Ricerca sul Cancro IG n.2013 (A.G.), by Associazione Italiana Lotta alla Leucemia Sezione di Bergamo, and by a research grant of Cassa di Risparmio di Cuneo.* *COI:* *1 or more authors received the following: Honoraria, Consulting or Advisory Role, Travel/Accomodations/Expenses, Speakers' Beaureau, Research Funding. Several*	Advanced classic HL (stage IIB-IVB) Ann Arbor, % (n/N) II: 35.7% (279/782) III: 32.2% (252/782) IV: 32.1% (251/782) B symptoms: 81.1% (634/782) IPS, % (n/N) 0-1: 36.6% (286/782) 2-3: 50.9% (398/782) >3: 12.5% (98/782) Large Nodal Mass (cm), % (n/N) <5: 41.9% (328/782) 5-7: 17.9% (140/782) 8-10: 20.3% (159/782) >10: 19.8% (155/782)	N=783 enrolled, n=782* received ABVD treatment, n=780 received iPET scan [ITT] Adults (14-60 years) M: 48.9% (382/782) F: 51.1% (400/782)	ABVD chemo Previously treated: No	Deauville 5PS + scans: 4 & 5	**Number of cycles**: 2 <u>**End-of-treatment PET**</u> Patients in CR after six ABVD cycles w/ large nodal mass (n=320) were randomized n=296† actually randomized to treatment: **Groups** 1. Radiotherapy (n=148) 2. No Radiotherapy (n=148) **Median F/U: 43.2 months (3.6 years)**	**Clinical** OS , PFS, Mortality **Safety** % Under treated, Toxic effects

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after PET Follow-up (post allocation)	Outcomes
authors reported that they had no relationship to disclose.						
Observational studies						
Engert 2012/Engert 2017 *HD15 trial* **Prospective Observational**: though technically a RCT, this trial did not randomize patients based on PET results and included only a subset of patients with PET scans after initial treatment and who had 12 months follow-up; thus, it was considered an observational study for purposes of this HTA **Criteria for PET assessment objective:** Inclusion: partial response after six to eight cycles of BEACOPP and at least one involved nodal site of 2.5 cm or larger in the transverse or longitudinal diameter as measured by CT. Exclusion: Diabetes mellitus, elevated fasting blood sugar level of more than 130 mg/dL, and skeletal; involvement with risk of instability. RoB High *Funding:* Deutsche Krebshilfe and the Swiss Federal Government	Advanced classic HL (stage IIB-IV) Note: Information regarding the diagnosis and stage for the subset of 711 is not available. Only information for the larger population of 2126 is reported.	N=711‡ Adults (18-60 years) Note: Demographic information for the subset of 711 patients is not available. Only information for the larger population of 2126 is reported.		Deauville 5PS + scans: 4 & 5	**Treatment prior to iPET:** eBEACOPP or BEACOPP14 or BEACOPP, 6 or 8 cycles **Groups** **PET +** (n = 182) Radiotherapy **PET –** (n = 529) No radiotherapy **F/U: 12 months (1 year)**	**Clinical** PFS, HR, Progression/early relapse **Safety** Negative Predictive Value of PET **F/U: 12 months (1 year)**

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	Treatment prior to iPET Previously treated?	Interpretation Criteria	Number treatment cycles before iPET Treatment groups after PET Follow-up (post allocation)	Outcomes
COI: *Not reported.*						

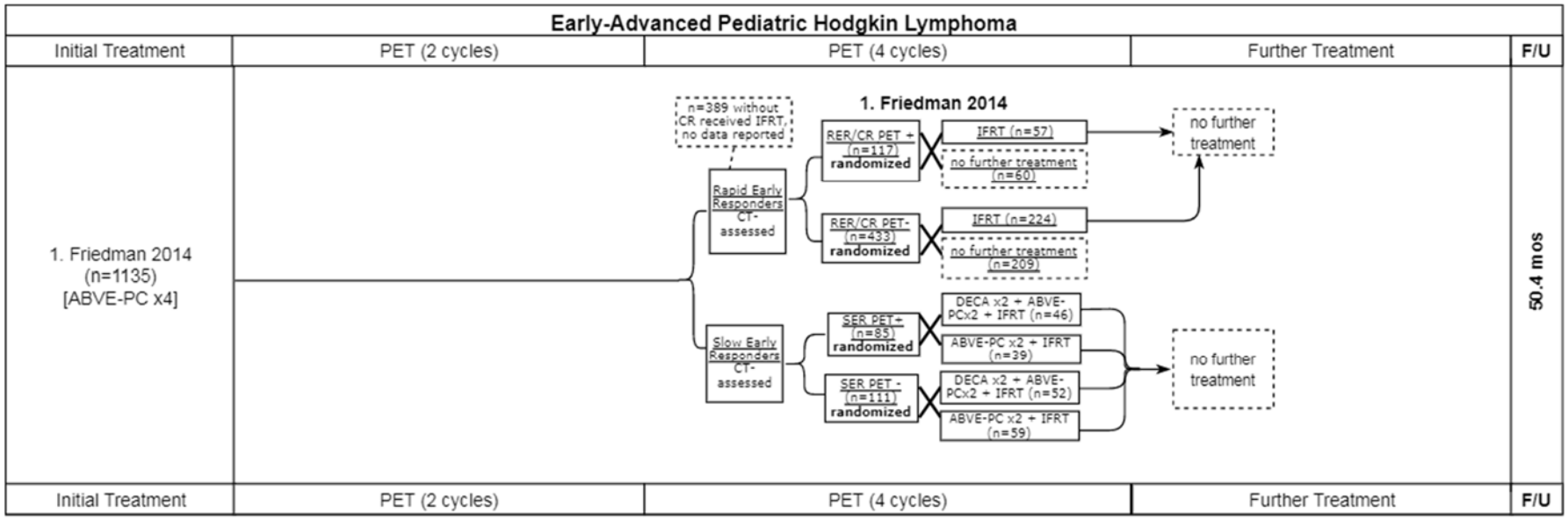
ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; 5PS = 5 point scale; CI = Confidence Interval; COI = Conflicts of interest; CR = Complete Response; CT = Computed tomography; EOT = End of treatment; F/U = Follow-up; F = Female; HR = Hazard ratio; iPET = interim PET; IPS = International Prognostic Score; ITT = Intention to Treat; M = Male; OS = Overall Survival; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial; RoB = Risk of Bias; RR = Risk Ratio

*1 patient eliminated due to presenting with composite lymphoma. 2 patients died before receiving first two cycles of ABVD.

†24 patients had no assignment based on patient or medical decision.

‡The central PET review panel assessed 822 (39%) of 2126 patients in the intention-to-treat set of whom 739 were qualified. 28 of these patients had no documented follow-up of at least 12 months. Thus, 711 patients qualified for the assessment of the negative predictive value of PET.

Appendix Figure F2. Flowchart of Treatment Adaptations: PET-adapted therapy in Pediatric Hodgkin Lymphoma



ABVE-PC = Doxorubicin Hydrochloride (Adriamycin) + Bleomycin + Vincristine Sulfate + Etoposide Phosphate + Prednisone + Cyclophosphamide; CR = complete response; CT = computerized tomography ; DECA = dexamethasone + etoposide + cisplatin + cytarabine ; F/U = follow-up; ; IFRT = involved field radiation therapy; mos. = months; PET = positron emission tomography; RER = rapid early responders; SER = slow early responders;

Appendix Table F9. Study characteristics and patient demographics: PET-adapted therapy in pediatric Hodgkin Lymphoma, escalation, interim PET (reference only, not included in main body of report)

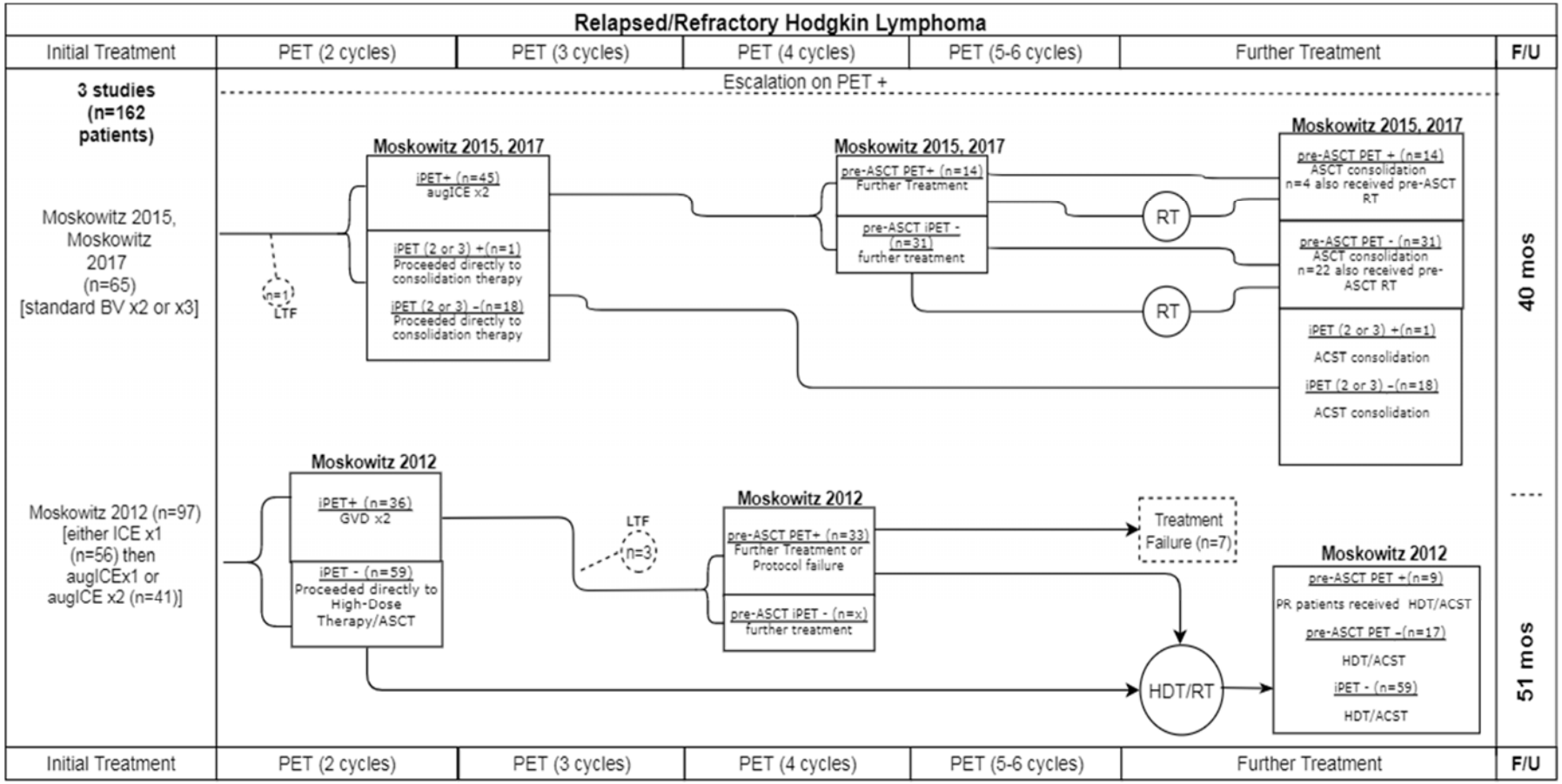
Author, Study Design RoB, Funding & COI	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
RCTS						
Friedman 2014* COG Study (AHOD0031) **RCT (non-PET randomized)** Risk of bias not assessed* Funding: Supported by National Cancer Institute Grant No. U10 CA98543 to the Children's Oncology Group Chair COI: None reported	Early-Advanced HL Ann Arbor Stage: -I or II: 64.5% -III or IV: 35.5% Subtype: -nodular sclerosis: 80.8% -Mixed Cellularity: 9.1% -Lymphocyte predominant: 5.7% -lymphocyte depleted: 0.2% -unknown/unreported: 4.2% B Symptoms: 22.2% Bulky Disease: 73.4%	N= 1601 treated, 1,135 PET recipients, 746 randomized and evaluated Median Age at diagnosis (range): 15.2 (1.9 to 21.9) years Age ranges, years: -0 to 4: 1.7% -5 to 9: 8.6% -10 to 14: 37.4% -15 to 21: 52.3% Male: 53%	ABVE-PC x4	PET+ (NR) PET -	**PET Timing:** Interim PET (4 cycles) **Allocated first according to ER (early responder status) as determined by CT.** **After 1 or 2 additional cycles (4 total), CR status was assessed by CT-gallium or PET-CT. Only groups with PET recipients are detailed below** **Randomized PET recipients (n=746)** RER (Rapid Early Responders): **PET+ RER/CR (n=117)** **randomly** assigned to: • IFRT (n=57) • No IFRT (n=60) **PET- RER/CR (n=433)** **Randomly** assigned to • IFRT (n=224) • No IFRT (n=209) SER (Slow Early Responders): **PET+ SER (n=85)** **randomly** assigned to:	**Clinical** EFS **Safety** NR for PET

Author, Study Design RoB, Funding & COI	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
					• Escalation with DECAx2 + additional ABVE-PCx2 + IFRT (n=46) • Consolidation with additional ABVE-PCx2 + IFRT (n=39) **PET- SER (n=111)** **Randomly** assigned to • Escalation with DECAx2 + additional ABVE-PCx2 + IFRT (n=52) • Consolidation with additional ABVE-PCx2 + IFRT (n=59) An additional n=389 RER patients were assessed with PET scanning and went on to receive IFRT but were not randomized because of sub-optimal response (< CR) and no data was provided. **Median F/U 50.4 mos.**	

ABVE-PC = Doxorubicin Hydrochloride (Adriamycin) + Bleomycin + Vincristine Sulfate + Etoposide Phosphate + Prednisone + Cyclophosphamide; COI = conflict of interest; CR = complete response; DECA = dexamethasone + etoposide + cisplatin + cytarabine; EFS = event free survival; F/U = follow-up; IFRT = involved field radiation therapy; mos. = months ; NR = not reported; PET = positron emission tomography; RCT = randomized controlled trial; RER = rapid early responders; RoB = Risk of Bias; SER = slow early responders;

* A subset of this population received PET scanning and provided data relevant to our key questions, however, no PET-recipient-specific population characteristics were not available and the demographic information relates to the whole study population. Additionally, the portion of the overall study who received PET was less than 80% of the total population (e.g. threshold for inclusion as per our PICOTS table), therefore data was abstracted here for reference only, and is not considered in the main body of the report.

Appendix Figure F3. Flowchart of Treatment Adaptations: PET-adapted therapy in Relapsed/Refractory Hodgkin Lymphoma



ASCT = autologous stem cell transplant; augICE = augmented Ifosfamide, carboplatin, etoposide; BV = Brentuximab vedotin; F/U = follow-up; GVD = Gemcitabine, Vinorelbine, Doxil; HDT = high dose therapy; ICE = Ifosfamide, carboplatin, etoposide; iPET = interim positron emission tomography; LTF = loss to follow-up; mos. = months; PET = positron emission tomography; RT = radiation therapy;

Appendix Table F10. Study characteristics and patient demographics: PET-adapted therapy in Relapsed/Refractory Hodgkin Lymphoma, escalation, interim PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
Observational Studies						
Moskowitz 2015, Moskowitz 2017 **Prospective cohort** RoB Moderately High *Funding: supported by Seattle Genetics; grant from the National Institutes of Health, National Cancer Institute (P30CA008748); and Adam R. Spector Hodgkin Lymphoma Fund* *COI: One or more authors received research funding, honoraria, and/or consulting fees from Seattle Genetics (funder) and/or Takeda.*	Transplant-eligible, relapsed/refractory classical HL Ann Arbor Stage at Initial Diagnosis: -I or II: 54% -III or IV: 46% Ann Arbor Stage at Relapse: -I or II: 55% -III or IV: 45% Subtypes: Refractory: 52% (34/65) B Symptoms: 15% (10/65) Extranodal Sites: 37% (24/65) Bulky Disease (>5cm): 25% (16/65)	N=65 enrolled, 64 treated Mixed adults and pediatric (age range 13-65 years, median 33 years) Median Age (range): 33 (13 to 65) years Male: 48%	Brentuximab vedotin (BV) (standard dose, 1.2 mg/kg) x2 or 3 Previously treated: Yes	PET +(Deauville ≥3 for pre-ASCT analysis, ≥2 for others) PET -	**PET Timing:** Interim (2 or 3 cycles), pre-ASCT PET (iPET + only) Non-randomized allocation based on PET results: **1. iPET + (n=47)** Two cycles of augmented-ICE before consideration for ACST Pre- PET + (n=14) Proceeded to ASCT consolidation therapy. n=4 received pre-ASCT RT Pre-ASCT PET - (n=31) Proceeded to ASCT consolidation therapy. n=22 received pre-ASCT RT **2. iPET – (n=19)** N=18 iPET - proceeded directly to ACST consolidation therapy, joined by n=1 iPET + patient. **Median F/U (range): 40 mos**	**Clinical** OS (3-year) EFS (3-year) **Safety** PET-Specific: NR Treatment- Related: Toxicities, Tumor-Related

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
Moskowitz 2012 **Prospective cohort** RoB Moderately High *Funding: Supported by the Eli Lilly Company, the Singer Family Lymphoma Research Fund and the Lymphoma Foundation. COI: Authors declare no competing financial interests.*	Transplant-eligible, relapsed/refractory classical HL Ann Arbor: Subtypes: NR Relapse/Refractory Disease: -Primary Refractory Disease: 42% (41/97) -Relapsed HL: 58% (56/97) -early relapse (<12 mos from primary treatment): 36% (35/97) -Relapse >1 year from primary treatment: 21.6% (21/97) Primary Treatment -ABVD: 81% (79/97) -IFRT: 27% (26/97) Extranodal Sites: 38.1% (37/97) B Symptoms: 11.3% (11/97) Bulky Mass (>5cm): 33% (32/97)	N=97 enrolled, 95 treated (chemotherapy), 85 treated (ASCT) Adults (18 to 72 years) Median Age (range): 35 (19 to 72) years Male: 42%	Arm A: ICE x1 followed by augmented ICE x1 Arm B: augmented ICE x2	PET+(based on SUV) PET-	**PET Timing:** Pre-treatment, Interim (2 cycles), Pre-ASCT, Follow-up Non-randomized allocation based on PET results: **1. iPET + (n=36)** Extended Salvage thereapy with Gemcitabine, vinorelbine, and liposomal doxorubicin (GVD), x2 cycles Pre-ASCT PET + (n=21) • Patients with PD were considered protocol failures (n=12) • Patients with PR, proceeded to High-Dose Therapy/ASCT (n=9) Pre-ASCT PET – n=17) • Proceeded to High-Dose Therapy/ASCT **2. iPET – (n=59)** High-Dose Therapy/ASCT; received 1 of 2 ASCT conditioning regimens (involving varying RT and chemotherapy) based on previous RT and presence of noncontiguous extra nodal sites **Median F/U (range): 51 (16 to 86) mos.**	**Clinical** OS (51 mos) EFS (51 mos) **Safety** PET-Specific: NR Treatment- Related: Toxicities, Transplant-Related, Tumor-Related

ASCT =autologous stem cell transplant; CBV = cyclophosphamide, carmustine, etoposide; COI = conflict of interest; CR = complete response; CT = computerized tomography; EFS = event free survival; F/U = follow-up; GVD = Gemcitabine, Vinorelbine, Doxil; HL = Hodgkin lymphoma; ICE = Ifosfamide, carboplatin, etoposide; IFRT = involve field radiation therapy; mos. = months; NMT = nonmyeloablative allogeneic stem cell transplant; NR = not reported; OS = overall survival; PET = positron emission tomography; PET/CT = positron emission tomography / computerized tomography; PD = progressive disease; PR = partial response; RoB = risk of bias; RT = radiation therapy

Detailed Data Abstraction

Appendix Table F11. Detailed data abstraction: PET-adapted therapy in early Hodgkin Lymphoma, escalation, interim PET

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
RCTS			
André 2017 *EORTC/LYSA/FIL H10 Trial* **Raemakers 2014** *Interim Analysis of EORTC/LYSA/FIL H10 Trial* **RCT w/ Observational Cohort** RoB Low	**Treatment prior to iPET**: ABVD chemo, 2 cycles **Groups** **PET + Favorable and Unfavorable (n=361) (Escalation)** 1. 1 or 2 cycles ABVD + INRT (n=192) 2. 2 eBEACOPP + INRT (n=169) **PET- Favorable (n=465) (De-escalation)** 1. 1 ABVD + INRT (n=227) 2. 2 ABVD (n=238) **PET- Unfavorable (n=594) (De-escalation)** 1. 2 ABVD + INRT (n=292) 2. 4 ABVD (n=302) **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 1. 1 ABVD + INRT [favorable] (n=185) 2. 2 ABVD + INRT [unfavorable] (n=320) **Median F/U:** PET+ favorable and unfavorable patients: 54 months (4.5 years) PET- favorable patients: 60 months (5 years) PET- unfavorable patients: 61.2 months (5.1 years) PET- favorable patients treated per safety amendment: 39.6 months (3.3 years) PET- unfavorable patients treated per safety amendment: 42 months (3.5 years)	**5-year OS, (95% CI) [ITT]** **PET+ Favorable and Unfavorable (n=361) (Escalation)** 1 or 2 cycles ABVD + INRT vs. 2 eBEACOPP + INRT: 89.3% (83.4%-93.2%) vs. 96.0 (91.1%-98.2%), HR 0.45 (0.19-1.07), p=0.62 **PET- Favorable (n=465) (De-escalation)** 1 ABVD + INRT vs. 2 ABVD: 100.0% (NR) vs. 99.6% (97.0%-99.9%), HR=NR **PET- Unfavorable (n=594) (De-escalation)** 2 ABVD + INRT vs. 4 ABVD: 96.7% (93.7%-98.3%) vs. 98.3% (96.0%-99.3%), HR=NR **3-year OS, (95% CI)** **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 3 ABVD + INRT [favorable] vs. 4 ABVD + INRT [unfavorable]: 100% (NR) vs. 99.7% (97.7%-100.0%), HR=NR **5-year PFS, (95% CI) [ITT]** **PET+ Favorable and Unfavorable (n=361) (Escalation)**	**PET-specific:** **Treatment-Related:** Grade 3/4 Hematologic Toxicities **PET+ Favorable and Unfavorable (n=361) (Escalation)** 1 or 2 cycles ABVD + INRT vs. 2 eBEACOPP + INRT • Neutropenia: 30.3% vs. 53.5% • Anemia: 0.0% vs. 4.9% • Thrombocytopenia: 0.0% vs. 19.7% • Febrile neutropenia episodes: 1.1% vs. 23.9% • Infection without neutropenia: 1.1% vs. 5.6% Secondary Malignancy **PET+ Favorable and Unfavorable (n=361) (Escalation)** 1 or 2 cycles ABVD + INRT vs. 2 eBEACOPP + INRT: 2.1%(4/192) vs. 2.4% (4/169), RR 0.88, 95% CI 0.22-3.47, p=0.8553 **PET- Favorable (n=465) (De-escalation)** 1 ABVD + INRT vs. 2 ABVD: 1.3% (3/227) vs. 2.9% (7/238), RR 0.45, 95% CI 0.12-1.7, p=0.2293 **PET- Unfavorable (n=594) (De-escalation)** 2 ABVD + INRT vs. 4 ABVD: 3.4% (10/292) vs. 3.0% (9/302), RR 1.14, 95% CI 0.47-2.79, p=0.758 **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 3 ABVD + INRT [favorable] vs. 4 ABVD + INRT [unfavorable]: 0.54% (1/185) vs. 1.25% (4/320), RR 0.43, 95% CI 0.05-3.84, p=0.4383

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
		1 or 2 cycles ABVD + INRT vs. 2 eBEACOPP + INRT: 77.4% (70.4%-82.9%) vs. 90.6 (84.7%-94.3%), HR 0.42 (0.23-0.74), p=0.002 **PET- Favorable (n=465) (De-escalation)** 1 ABVD + INRT vs. 2 ABVD: 99.0% (95.9%-99.7%) vs. 87.1% (82.1%-90.8%), HR 15.8 (3.8-66.1), p=NR [Upper bound of CI exceeded the prespecified noninferiority margin of 3.2] **PET- Unfavorable (n=594) (De-escalation)** 2 ABVD + INRT vs. 4 ABVD: 92.1% (88.0%-94.8%) vs. 89.6% (85.5%-92.6%), HR 1.45 (0.8-2.5), p=NR [Upper bound of CI exceeded the prespecified noninferiority margin of 2.10] **<u>3-year PFS, (95% CI) [ITT]</u>** **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 3 ABVD + INRT [favorable] vs. 4 ABVD + INRT [unfavorable]: 98.9% (95.6%-99.7%) vs. 95.5% (92.5%-97.3%), HR=NR **<u>Mortality</u>** **PET+ Favorable and Unfavorable (n=361) (Escalation)** 1 or 2 cycles ABVD + INRT vs. 2 eBEACOPP + INRT: (18/192) vs.	

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
		(7/169), RR 2.26, 95% CI 0.97-5.29, p=0.051 **PET- Favorable (n=465) (De-escalation)** 1 ABVD + INRT vs. 2 ABVD: (0/227) vs. (3/238), RR=NR **PET- Unfavorable (n=594) (De-escalation)** 2 ABVD + INRT vs. 4 ABVD: (10/292) vs. (6/302), RR 1.72, 95% CI 0.63-4.68, p=0.2796 **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 3 ABVD + INRT [favorable] vs. 4 ABVD + INRT [unfavorable]: (0/185) vs. (1/420), RR=NR	

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; CI = Confidence Interval; F/U = Follow-up; F =Female; HL = Hodgkin's lymphoma; HR= Hazard ratio; INRT = Involved node radiotherapy; iPET = interim PET; ITT = Intention to Treat; M = Male; NR = Not reported; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial; RR = Risk Ratio

*All early PET-negative patients who were included after the August, 2010 safety amendment received treatment with ABVD + INRT, as the independent data monitoring committee recommended to close the ABVD only arm. Thus, randomization no longer occurred in this proportion of patients and are therefore reported separately from the randomized patients.

Appendix Table F12. Detailed data abstraction: PET-adapted therapy in early Hodgkin Lymphoma, de-escalation, interim PET

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
RCTS			
André 2017 *EORTC/LYSA/FIL H10 Trial* **Raemakers 2014** *Interim Analysis of EORTC/LYSA/FIL H10 Trial* **RCT w/ Observational Cohort** RoB Low	**Treatment prior to iPET**: ABVD chemo, 2 cycles **Groups** **PET + Favorable and Unfavorable (n=361) (Escalation)** 3. 1 or 2 cycles ABVD + INRT (n=192) 4. 2 eBEACOPP + INRT (n=169) **PET- Favorable (n=465) (De-escalation)** 3. 1 ABVD + INRT (n=227) 4. 2 ABVD (n=238) **PET- Unfavorable (n=594) (De-escalation)** 3. 2 ABVD + INRT (n=292) 4. 4 ABVD (n=302) **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 3. 1 ABVD + INRT [favorable] (n=185) 4. 2 ABVD + INRT [unfavorable] (n=320) **Median F/U:** PET+ favorable and unfavorable patients: 54 months (4.5 years) PET- favorable patients: 60 months (5 years) PET- unfavorable patients: 61.2 months (5.1 years) PET- favorable patients treated per safety amendment: 39.6 months (3.3 years) PET- unfavorable patients treated per safety amendment: 42 months (3.5 years)	**5-year OS, (95% CI) [ITT]** **PET+ Favorable and Unfavorable (n=361) (Escalation)** 1 or 2 cycles ABVD + INRT vs. 2 eBEACOPP + INRT: 89.3% (83.4%-93.2%) vs. 96.0 (91.1%-98.2%), HR 0.45 (0.19-1.07), p=0.62 **PET- Favorable (n=465) (De-escalation)** 1 ABVD + INRT vs. 2 ABVD: 100.0% (NR) vs. 99.6% (97.0%-99.9%), HR=NR **PET- Unfavorable (n=594) (De-escalation)** 2 ABVD + INRT vs. 4 ABVD: 96.7% (93.7%-98.3%) vs. 98.3% (96.0%-99.3%), HR=NR **3-year OS, (95% CI)** **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 3 ABVD + INRT [favorable] vs. 4 ABVD + INRT [unfavorable]: 100% (NR) vs. 99.7% (97.7%-100.0%), HR=NR **5-year PFS, (95% CI) [ITT]** **PET+ Favorable and Unfavorable (n=361) (Escalation)** 1 or 2 cycles ABVD + INRT vs. 2 eBEACOPP + INRT: 77.4% (70.4%-82.9%) vs. 90.6 (84.7%-94.3%), HR 0.42 (0.23-0.74), p=0.002	**PET-specific:** **Treatment-Related:** Grade 3/4 Hematologic Toxicities **PET+ Favorable and Unfavorable (n=361) (Escalation)** 1 or 2 cycles ABVD + INRT vs. 2 eBEACOPP + INRT • Neutropenia: 30.3% vs. 53.5% • Anemia: 0.0% vs. 4.9% • Thrombocytopenia: 0.0% vs. 19.7% • Febrile neutropenia episodes: 1.1% vs. 23.9% • Infection without neutropenia: 1.1% vs. 5.6% Secondary Malignancy **PET+ Favorable and Unfavorable (n=361) (Escalation)** 1 or 2 cycles ABVD + INRT vs. 2 eBEACOPP + INRT: 2.1%(4/192) vs. 2.4% (4/169), RR 0.88, 95% CI 0.22-3.47, p=0.8553 **PET- Favorable (n=465) (De-escalation)** 1 ABVD + INRT vs. 2 ABVD: 1.3% (3/227) vs. 2.9% (7/238), RR 0.45, 95% CI 0.12-1.7, p=0.2293 **PET- Unfavorable (n=594) (De-escalation)** 2 ABVD + INRT vs. 4 ABVD: 3.4% (10/292) vs. 3.0% (9/302), RR 1.14, 95% CI 0.47-2.79, p=0.758 **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 3 ABVD + INRT [favorable] vs. 4 ABVD + INRT [unfavorable]: 0.54% (1/185) vs. 1.25% (4/320), RR 0.43, 95% CI 0.05-3.84, p=0.4383

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
		PET- Favorable (n=465) (De-escalation) 1 ABVD + INRT vs. 2 ABVD: 99.0% (95.9%-99.7%) vs. 87.1% (82.1%-90.8%), HR 15.8 (3.8-66.1), p=NR [Upper bound of CI exceeded the prespecified noninferiority margin of 3.2] **PET- Unfavorable (n=594) (De-escalation)** 2 ABVD + INRT vs. 4 ABVD: 92.1% (88.0%-94.8%) vs. 89.6% (85.5%-92.6%), HR 1.45 (0.8-2.5), p=NR [Upper bound of CI exceeded the prespecified noninferiority margin of 2.10] **<u>3-year PFS, (95% CI) [ITT]</u>** **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 3 ABVD + INRT [favorable] vs. 4 ABVD + INRT [unfavorable]: 98.9% (95.6%-99.7%) vs. 95.5% (92.5%-97.3%), HR=NR **<u>Mortality</u>** **PET+ Favorable and Unfavorable (n=361) (Escalation)** 1 or 2 cycles ABVD + INRT vs. 2 eBEACOPP + INRT: (18/192) vs. (7/169), RR 2.26, 95% CI 0.97-5.29, p=0.051 **PET- Favorable (n=465) (De-escalation)**	

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
		1 ABVD + INRT vs. 2 ABVD: (0/227) vs. (3/238), RR=NR **PET- Unfavorable (n=594) (De-escalation)** 2 ABVD + INRT vs. 4 ABVD: (10/292) vs. (6/302), RR 1.72, 95% CI 0.63-4.68, p=0.2796 **PET- Treated Per Safety Amendment (n-505) [Observational Study, non-comparative]** 3 ABVD + INRT [favorable] vs. 4 ABVD + INRT [unfavorable]: (0/185) vs. (1/420), RR=NR	
Radford 2015 RAPID trial **RCT**	**Treatment prior to iPET**: ABVD, 3 cycles **Groups** **PET + (n = 145)** 1. Additional cycle ABVD (4 total) + RT **PET – (randomized) (n=426, n=420 actually randomized)** 1. Involved-field RT (n=209) 2. No further treatment (n=211) **Median F/U: 60 months (5 years)**	**3-year OS, (95% CI) [ITT]:** PET- Radiotherapy vs. PET- No further treatment: 97.1% (94.8%-99.4%) vs. 99.0% (97.6%-100%), RR 0.51 (0.15-1.68), p=0.27 per authors **3-year PFS, (95% CI) [ITT]:** PET- Radiotherapy vs. PET- No further treatment: 94.6% (91.5%-97.7%) vs. 90.8% (86.9%-94.8%), RR 1.57 (0.84-2.97), p=0.16 per authors **3-year PFS, (95% CI) [per-protocol]:** PET- Radiotherapy vs. PET- No further treatment: 97.1% (94.7%-99.6%) vs. 90.8% (86.8%-94.7%) RR 2.36 (1.13-4.95), p=0.02 per authors	**PET-specific:** NR **Treatment-Related:** NR

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
		3-year Absolute Risk Difference, (95% CI) PET- Radiotherapy vs. PET- No further treatment: −3.8 percentage points (−8.8 to 1.3) [Lower bound of CI exceeds the designated noninferiority margin of -7 percentage points] **Proportion alive after follow-up without Disease Progression** PET+ vs. PET- Radiotherapy vs. PET- No further treatment: 87.6% vs. 92.3% vs. 88.6% **Proportion of Episodes of Disease Progression** PET+ vs. PET- Radiotherapy vs. PET- No further treatment: 6.9% vs. 3.8% vs. 9.5% **Deaths after Disease Progression** PET + vs. PET- Radiotherapy vs. PET- No further treatment: 3.4% vs. 2.4% vs. 0.9%	

5PS = 5 point scale; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; CI = Confidence Interval; F/U = Follow-up; F = Female; HL = Hodgkin's lymphoma; HR = Hazard ratio; INRT = Involved node radiotherapy; iPET = interim PET; ITT = Intention to Treat; M = Male; NR= Not reported; OS = Overall Survival; PFS = Progression Free Survival; RCT = Randomized controlled trial; RR = Risk Ratio; RT = Radiation therapy; Tx = treatment

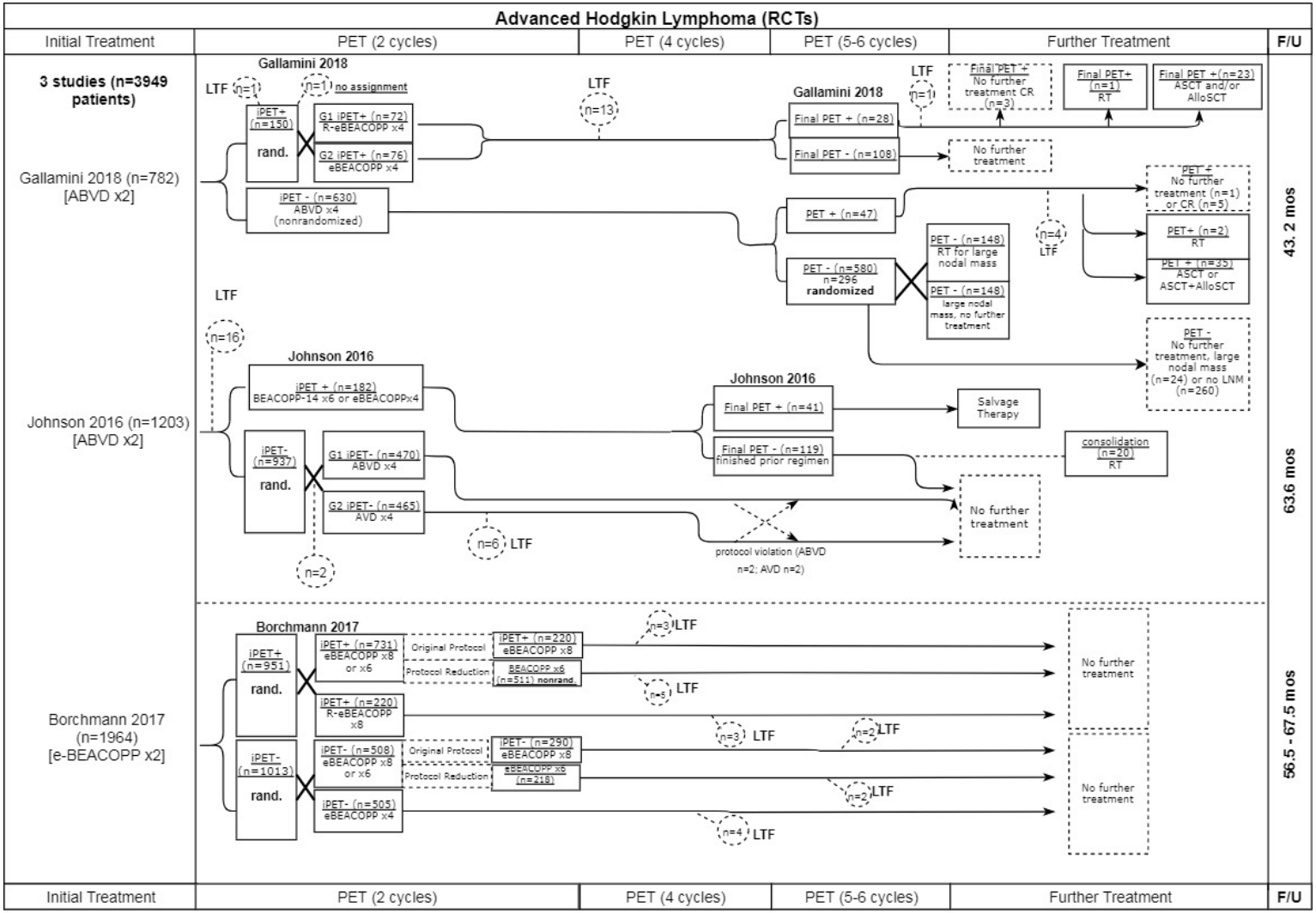
*All early PET-negative patients who were included after the August, 2010 safety amendment received treatment with ABVD + INRT, as the independent data monitoring committee recommended to close the ABVD only arm. Thus, randomization no longer occurred in this proportion of patients and is therefore reported separately from the randomized patients.

Appendix Table F13. Detailed data abstraction: PET-adapted therapy in early Hodgkin Lymphoma, unclear escalation/de-escalation, interim PET

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
Prospective Observational			
Dann 2017 **Prospective Cohort** RoB Moderately High *[includes results for early HL only, see table F16 for advanced HL results]*	**Treatment prior to iPET**: ABVD chemo, 2 cycles (EF-HL, EUF-HL, and advanced HL with IPS 0-2) Escalated BEACOPP, 2 cycles: (Advanced HL with IPS 3-7) **Groups** **EF-HL (n=24) [De-escalation]** **PET+ (n=5)** Two additional ABVD courses (4 total) followed by ISRT **PET– (n=19)** ISRT **OR** two additional cycles (4 total) of ABVD† **EUF-HL (n = 146) [De-escalation]** **PET+ (n=15)** Four additional ABVD courses (6 total) then ISRT **PET– (n=131)** Two additional ABVD courses (4 total) then ISRT **OR** four additional ABVD courses (6 total)‡ **All Early HL (n=170) [De-escalation]** **PET+ (n=20)** Two or four additional courses of ABVD **PET- (n=150)** ISRT (n=87) Two additional courses of ABVD (n=83) **Median F/U: 60 months (5 years)**	**5-year OS, (95% CI)** **All Early-HL** PET+ vs. PET-: 95% (85.4%-104.6%) vs. 100% (NR) **5-year PFS, (95% CI)** **All Early-HL** PET+ vs. PET-: 69.2% (48.6%-89.8%) vs. 91.4% (86.7%-96.1%), HR 3.69 (1.4-9.7), p=0.008 [according to dynamic scoring system], HR 7.63 (2.7-21), p=0.000 [according to Deauville scoring system] PET- no ISRT vs. ISRT: 93.5% (87.9%-99.1%) vs. 88.6% (80.7%-96.6%)	*All patients, not reported separately for early and advanced stage* **PET-specific:** **Treatment-related:** **Evaluated for menstrual status (n = 114):** **Preserved or regained menstrual period**: 78% **Premature ovarian failure during follow-up**: 22% (with somewhat higher rates (33% vs. 20%) in those receiving any EB compared to ABVD only (P = 0.52). **Pregnancy following treatments**: n = 37 **Dose Intensity:** ABVD (75%) ABVD 32–4 + EB 32–4 (21%) 6 EB cycles (12%) Cardiac ischemic events: n = 4 (1 fatal) **Secondary Malignancies:** n=7 (1.9%) (Single cases of lymphoblastic lymphoma, acute Ph+ lymphoblastic leukemia, papillary thyroid cancer, cutaneous B cell follicular lymphoma, and breast cancer. Two cases of secondary leukemia; one had EB 32 + ABVD 34 and the other received one EB cycle and was then withdrawn from the study due to a suicidal attempt and drug abuse.)

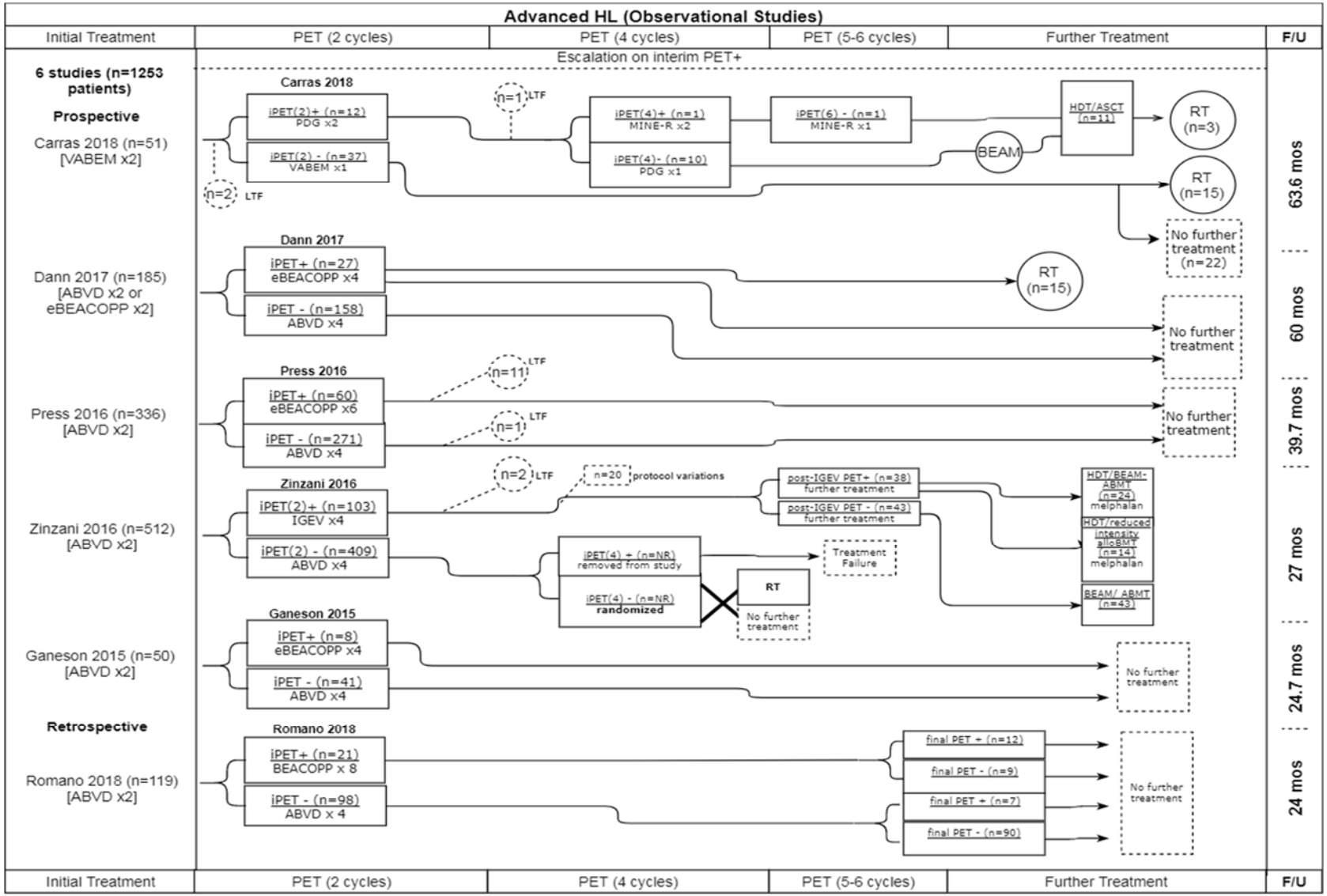
ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CI = Confidence Interval; COI: Conflicts of interest; EB = Escalated BEACOPP; EF = Early favorable; EUF = Early unfavorable; HL = Hodgkin's lymphoma; HR = Hazard ratio; iPET = interim PET; IPS = International Prognostic Score; ISRT = Involved Site Radiation Therapy; NS = Not significant; OS = Overall Survival; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial
*Unclear from the text as to what this p-value represents.2
†PET- patients with multiple or extensive disease sites or fields overlapping breast tissue (women), could forego radiotherapy and receive two further courses of ABVD instead.
‡ PET- patients with multiple or extensive disease sites or fields overlapping breast tissue (women), could forego radiotherapy and receive four further courses of ABVD instead.
§Patients progressing during the study were withdrawn and received salvage therapy.

Appendix Figure F4. Flowchart of Treatment Adaptations: PET-adapted therapy in Advanced Hodgkin Lymphoma, RCTs



ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AlloSCT = allogenic stem cell transplant ; ASCT = autologous stem cell transplant; CR = complete response; eBEACOPP = escalated bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; F/U = follow-up; iPET = interim positron emission tomography; LNM = large nodal mass; LTF = loss to follow-up; mos. = months; R = rituximab; Rand. = randomized; PET = positron emission tomography; RCTs = randomized controlled trials; RT = radiation therapy

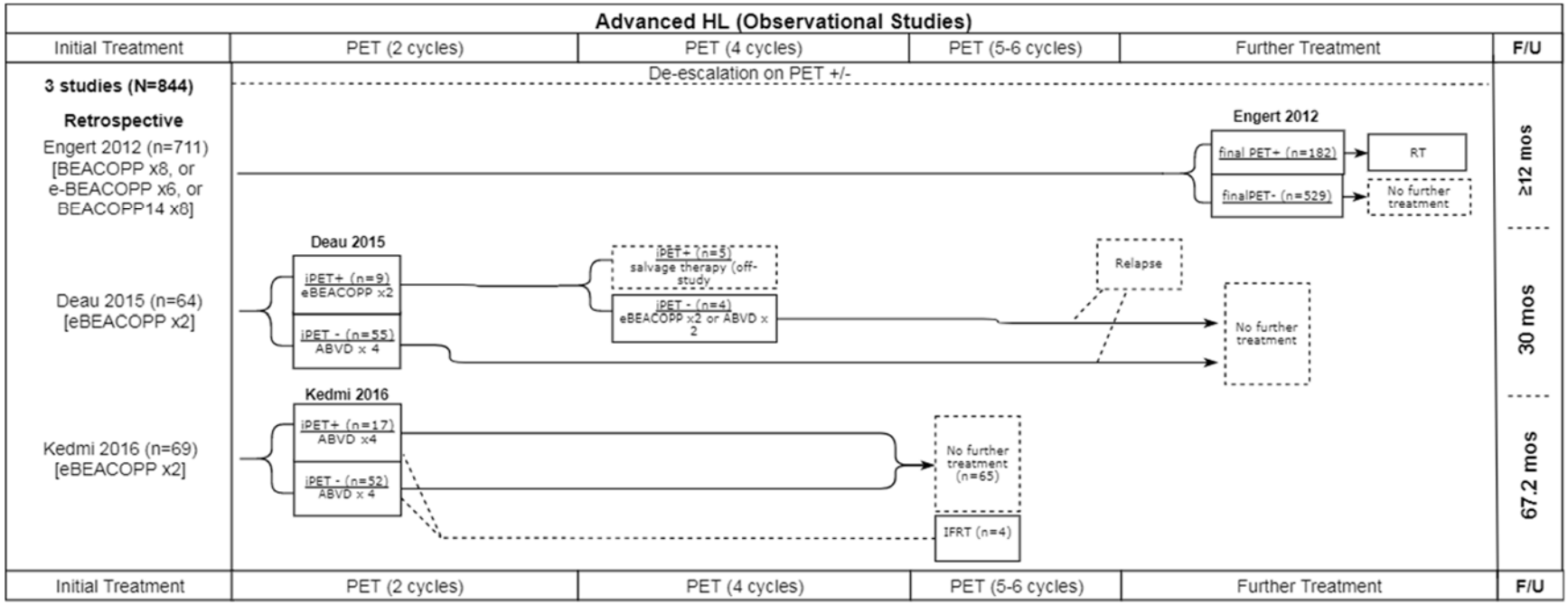
Appendix Figure F5. Flowchart of Treatment Adaptations: PET-adapted therapy in Advanced Hodgkin Lymphoma, Observational Studies, escalation



ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AlloSCT = allogenic stem cell transplant ; ASCT = autologous stem cell transplant; BEAM = carmustine, etoposide, cytarabine, and melphalan; CR = complete response; eBEACOPP = escalated bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; F/U = follow-up; HDT = high dose therapy; IGEV = gemcitabine, vinorelbine, prednisolone; iPET = interim positron emission tomography; LTF = loss to follow-up; mos. = months; PDG = gemcitabine, dexamethasone, cisplatin; PET = positron

emission tomography; RT = radiation therapy; VABEM = vindesine, doxorubicin, carmustine, etoposide and methylprednisolone;
ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; eBEACOPP = escalated bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; F/U = follow-up; HL = Hodgkin Lymphoma; IFRT = involved field radiation therapy; iPET = interim positron emission tomography; mos. = months; PET = positron emission tomography; RT = radiation therapy; VABEM = vindesine, doxorubicin, carmustine, etoposide and methylprednisolone;

Appendix Figure F6. Flowchart of Treatment Adaptations: PET-adapted Therapy in Advanced Hodgkin Lymphoma, Observational Studies, de-escalation



Appendix Table F14. Detailed data abstraction: PET-adapted therapy in advanced Hodgkin Lymphoma, interim PET, escalation

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
RCTS			

Gallamini 2018
GITIL/FIL HD 0607 Trial
 	
RCT
 	
RoB Moderately High
	Treatment prior to iPET: ABVD, 2 cycles
	
	Interim PET
	Groups
	PET + (randomized) (n=150)
	n=148* actually randomized to treatment:
	1. BEACOPP + IV rituximab given on day 1 of each course, 8 cycles (n=72)
	2. BEACOPP, 8 cycles (n = 76)
	In both groups, BEACOPP given as 4 cycles of escalated + 4 cycles of baseline
	3. Death due to progressive disease (n=1)
	4. No random assignment (n = 1)
	
	PET – (n = 630)
	n=629 actually randomized to treatment:
	Standard ABVD for 4 additional cycles (6 cycles total)
	
	Median F/U: 3.6 years
		Interim PET
		3-year OS (95% CI):
		• PET+ vs. PET-: 89% (82%–93%) vs. 99% (97%–99%), p<0.001
		• PET+ randomized to BEACOPP + rituximab vs. BEACOPP alone: 89% (79%–95%) vs. 90% (78%–95%), p=0.895
		
		3-year PFS (95% CI):
		• PET+ vs. PET-: 60% (51%–68%) vs. 87% (84%–89%), p= <0.001
		• PET+ randomized to BEACOPP + rituximab vs. BEACOPP alone: 63% (50%–74%) vs. 57% (45%–68%), p=0.534
		
		Mortality, % (n/N):
		• Overall: 3.8% (30/780)
		  ○ Disease progression and cardiac failure: n=2
		  ○ Resistant or progressive disease: n=18
		  ○ Transplant-related toxicity: n=5
		  ○ Infections: n=4
		  ○ Pulmonary fibrosis: n=1
		PET+ vs. PET-: 11% (16/150) vs. 2% (12/630), RR 5.6, 95% CI 2.7-11.6, p<0.0001
			PET-specific:
			Proportion of PET- patients under treated due to nature of the negative predictive value of interim PET during ABVD treatment: 13%
			
			Treatment-Related:
			Toxicity (Grade 3 to 4 Adverse Events), % (n/N):
			PET+ vs. PET-:
			Blood/Bone Marrow: 76% (114/150) vs. 30% (189/630), RR 2.5, 95% CI 2.2-2.9, p<0.0001
			Infection: 10% (16/150) vs. 1% (5/630), RR 13.4, 95% CI 5.0-36.1, p<.0.0001
			Pulmonary/Upper Respiratory: 1% (1/150) vs. 2% (11/630), RR 0.38, 95% CI 0.05-2.9, p=0.335
			GI: 0% (0/150) vs. 1% (6/630), RR 0, 95% CI NR, p=0.231

Borchmann 2017b HD18 trial **RCT**	**PET Timing:** Interim (2 cycles) **PET + (randomized) (n=951)**	**ITT Data Set (n=2073)**† **3-Year OS:**	**Randomized ITT-Set (n=1439)**§ **PET-specific, PET+ vs. PET-:** None reported

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
Advanced classic HL (stage IIB-IV) RoB Low ITT data set includes all PET+, PET- patients, regardless of protocol change. 'Nonrandomized' are group from baseline that did not get randomized but are included in ITT (though given separate data). After protocol change, randomization ceased for PET+ group; that group is not included in available safety data (from the "randomized" ITT set)	Randomized to standard therapy or rituximab escalation: 1a. Standard therapy escalated BEACOPP x8 (n=220) OR 2. escalated BEACOPP + rituximab x8 (n=220) **PET + subgroup (allocated after protocol change)** A protocol change occurred after which standard therapy was reduced from x8 to x6 eBEACOPP. Randomization ceased at this point: 1b. Reduced Standard Therapy (escalated BEACOPP x6) (n=511) **PET - (randomized) (n=1013)** Randomized to standard therapy/reduced therapy (after protocol change) or de-escalation therapy: 1.Standard therapy escalated BEACOPP x8 (n=220) or x6 reduced standard (n=218) OR 2. de-escalation: escalated BEACOPP x4 (n=505) **Median F/U 67.5 mos. (PET +)** **Median F/U 56.5 mos. (PET -)**	PET+ vs. PET-: 97.1% (95% CI 95.9 to 98.2) vs. 97.3% (95% CI 96.2 to 98.3) **3-Year PFS:** PET+ vs. PET-: 92.5% (95% CI 90.7 to 94.3) vs. 93.5% (95% CI 91.9 to 95.1) **5-Year OS:** PET+ vs. PET-: 88.3% (95% CI 85.8 to 90.8) vs. 91.4% (95% CI 89.5 to 93.4), p=0.49; **5-Year PFS:** PET+ vs. PET-: 95.5% (95% CI 93.9 to 97.1) vs. 96.3% (95% CI 95.0 to 97.6), p=0.30; **Nonrandomized‡ (n=115)** **3-Year OS:** 77.6% (95% CI 68.6 to 86.6), **3-Year PFS:** 91.0% (95%CI 85.4 to 96.7), **5-Year OS:** 77.6 (68.6 to 86.6), **5-Year PFS:** 89.2% (95%CI 82.6 to 95.8), **Randomized ITT Set (n=1439)**§ **Mortality, PET + vs. PET-, % (n/N)** All Causes: 5.3% (23/434) vs 3.4% (34/1005) Mortality, Second Malignancy: 0.9% (4/434) vs 1.3% (13/1005)	**Treatment-Related, PET + vs. PET-, % (n/N); ES (95%CI), p-value:** Mortality due to Toxicity of Study Treatment: 0.9% (4/434) vs 0.6% (6/1005); RR 1.54 (95%CI 0.74 to 2.12), p=0.396 Mortality due to Toxicity of Salvage Therapy: 1.6% (7/434) vs 0.4% (4/1005) RR 4.05 (95%CI 0.93 to 2.56), p=0.089 Any Toxicities CTCAE Grade III or IV: 97% (426/438) vs 93.5% (940/1005); RR 1.04 (95%CI 1.02 to 1.07), p=0.007 Organ Toxicities CTCAE Grade III or IV : 51.6% (226/438) vs 12.8% (129/1005); RR 4.02 (95%CI 2.96 to 4.18), p<0.001 Anemia, Thrombopenia or Infection, CTCAE Grade IV: 83.1% (364/438) vs 46.9% (471/1005); RR 1.77 (95%CI 1.61 to 1.88), p<0.001 Treatment-Related Morbidity: NR vs 52.2% (525/1005) **Tumor-Related, PET + vs. PET-:** Any tumor event: 7.1% (31/434) vs 6.0% (60/1005); RR 1.20 (95%CI 0.85 to 1.68), p=0.303 Tumor Progression: 1.2% (5/434) vs. 0.4% (4/1005); RR 2.89 (95%CI 0.83 to 2.36), p=0.200 Early Relapse (< 1 year after end of treatment): 2.5% (11/434) vs 1.9% (19/1005); RR 1.34 (95%CI 0.796 to 1.97), p=0.331 Late Relapse: 3.5% (15/434) vs 3.7% (37/1005); RR 0.94 (95%CI 0.69 to 1.58) p=0.820

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
			Secondary Malignancies, PET+ vs PET-: Acute Myeloid Leukemia or myelodysplastic syndrome: 2.1% (9/434) vs 0.9% (10/1005); RR 2.08 (95%CI 0.88 to 2.30) p=0.147 Non-Hodgkin's Lymphoma: 1.2% (5/434) vs 1.3% (13/1005); RR 0.89 (95%CI 0.66 to 1.82) p=0.716 Solid Tumor: 2.3% (10/434) vs 3.1% (31/1005); RR 0.747 (95%CI 0.615 to 1.50) p=0.858
Observational studies (prospective)			
Carras 2018 *GOELAMS LH 2007 trial* **Prospective Cohort** RoB Moderately High	**Treatment Prior to iPET**: VABEM chemo, 2 cycles **PET+ (n=12)** n=11** actually treated with salvage therapy: 2 courses of PDG (cisplatin, gemcitabine, and dexamethasone) After 2 courses of PDG: • PET+ (n=1) patients received 2 courses of a MINE-R • PET- (n=10) patients received 1 course of PDG chemo All n=11 patients received HDT and ASCT following the above treatments • n=3 received Radiotherapy, 30Gy, IFRT for initial bulky lesions **PET- (i.e., complete remission) (n = 37)** Additional (3rd) course of VABEM chemo • n=15 received Radiotherapy, 30Gy, IFRT for initial bulky lesions **Median F/U: 63.6 months (5.3 years)**	**5-year OS, (95% CI):** PET+ vs. PET-: 91.7% (77.3%-100%) vs. 88.2% (78.0%-99.8%) **5-year EFS (95% CI):** PET+ vs. PET-: 81.5% (61.1%-100%) vs. 77.8% (65.3%-92.7%) **Mortality, % (n/N)**: All: 6% (3/51)	**PET-specific:** NR **Treatment-Related:** **Severe AE During Front-line Therapy, % (n/N)** ≥ 1 G3-4 acute hematologic event: 98% (50/51) ≥ 1 G3-4 non-hematologic event: 38% (19/51) ≥ 1 G3-4 mucositis event: 35% (18/51) ≥ 1 G3-4 gastrointestinal event: 8% (4/51) **Main Toxicities (VABEM) During Front-line Therapy (All Grades, All Patients), % (n events/n courses)** Neutropenic fever: 61% (83/136) Mucositis: 50% (79/136) Gastrointestinal (diarrhea): 61% (80/136) Hepatic (cytolysis): 17% (23/136) Renal: 8% (11/136) **Severe AE During PDG Therapy, % (n events/n courses)** At least 1 G3 or G4 acute hematologic adverse event: 34% (11/32) At least 1 G3 or G4 acute non-hematologic adverse event: 0% (0/32)

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
			Main Toxicities (PDG), % (n events/n courses) Neutropenic fever: 19% (6/32) Hepatic (cytolysis): 15.7% (5/32) Renal: 15.7% (5/32) **Death Related to AE, % (n/N)**: 6.1% (3/51) **Secondary Malignancies:** **Secondary Leukemia, % (n/N)**: 2% (1/51)
Press 2016 *The Southwest Oncology Group S0816 study* **Prospective Cohort** RoB Moderately Low	**Treatment prior to iPET:** ABVD chemo, 2 cycles **Groups** **PET+ (n=60)** n=49†† actually treated per protocol: Escalated BEACOPP for 6 cycles **PET- (n = 271)** n=270 actually treated: Additional 4 cycles (6 cycles total) of AVBD **Median F/U: 39.7 months (3.3 years)**	**2-year OS (All):** 98% **2-year PFS** PET+ vs. PET-: 64% (95% CI, 50% to 75%) vs. 82% (95% CI, 77% to 86%)	**PET-specific:** NR **Treatment-related:** **Proportion Grade 4 to 5 toxicities:** PET+ (eBEACOPP) vs. PET- (AVBD): 85.7% (42/49) vs. 36.7% (99/270), p<0.001 per authors, RR 2.34, 95% CI 1.93-2.84, p<0.0001 **Dose Intensity:** 98% to 99% in ABVD cycles 1 to 2 87% to 96% in ABVD cycles 3 to 6 **Treatment Related Deaths, % (n/N):** PET+ (eBEACOPP) vs. PET- (AVBD): 4% (2/49) vs. 0.4% (1/270), RR 11.02, 95% CI 1.02-119.21, p=0.0134 **Secondary Malignancies:** PET+ (eBEACOPP) vs. PET- (AVBD): 6.1% (3/49) vs. 1% (3/270), p=0.0487 per authors, RR 16.53, 95% CI 1.76-155.69, p=0.0009 (2 non-HLs, 2 kidney cancers, 1 melanoma, and 1 skin cancer)

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
Zinzani 2016 *HD0801 study* **Prospective Cohort** RoB Moderately Low	**Treatment Prior to iPET:** ABVD chemo, 2 cycles **Groups** **PET+ (n=103)** n=81‡‡ received treatment per protocol: Four cycles IGEV salvage • PET+ after salvage treatment (n=38): 1. High-dose melphlan BEAM-conditioned ABMT (n=24) 2. High-dose melphanlan reduced-intensity alloBMT (n=14) • PET- after salvage treatment (n=43): 1. BEAM-conditioned ABMT (n=43) **PET- (n = 409)** Additional 4 cycles of ABVD (6 cycles total) **Median F/U from enrollment: 27 months (2.3 years)** **Median F/U from iPET scan: 25 months (2.1 years)**	**2-year OS, (95% CI):** All: 97% (94%-98%) **2-year PFS (95% CI):** All: 80% (76%-83%) PET+ vs. PET-: 74% (62%-82%) vs. 81% (76%-84%) [per protocol] PET+ (excluding those with Deauville score of 3) vs. PET-: 75% (57%-86%) vs. 81% (76%-84%) [ITT]	**PET-specific:** **Treatment-related:** **Grades of Adverse Hematologic Events for PET+ patients (n=81):** Grade 0: 20% (16/81) Grade 1: 1% (1/81) Grade 2: 7% (6/81) Grade 3: 9% (7/81) Grade 4: 63% (51/81) **Grades of Adverse Non-hematologic Events for PET+ patients (n=81):** Grade 0: 25% (20/81) Grade 1: 6% (5/81) Grade 2: 19% (15/81) Grade 3: 46% (37/81) Grade 4: 59% (48/81)
Ganesan 2015 **Pro Cohort** RoB Moderately High	**Treatment Prior to iPET**: ABVD chemo, 2 cycles **Groups** **PET+ (n=8)** Four cycles of escalated BEACOPP **PET- (n=41)** Four additional ABVD cycles (6 total) **Median F/U: 24.7 months (2.1 years)**	**Estimated 2-year OS, (95% CI)** All: 87.7% (81.6%-93.8%) **Estimated 2-year EFS. (95% CI)** All (N = 47): 75.7% (68.4%-83.0%) PET+ vs. PET-: 50% vs. 82%, p=0.013 §§ PET+ vs. PET-: 50% vs. 81%,p=0.019 *** **Mortality, % (n/N)** 8% (4/50): 3 due to progressive disease, 1 due to unknown cause	**PET-specific:** **Proportion of PET- patients suffering from disease progression:** 13% (5/39) **Treatment-related:** **Acute grade 3/4 toxicities of patients receiving EB chemotherapy, n=7 (28 cycles):** Acute grade 3/4 toxicities: Non-hematological: 0% (0/28) Neutropenia: 85% (24/28) Febrile neutropenic episodes: 50%(14/28)

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
			Required red cell transfusions for grade IV anemia: n=2 **Required platelet transfusion for grade IV thrombocytopenia**: n=1 **Deaths due to toxicity from treatment**: n=0 **Median Relative Dose Intensity:** ABVD, 6 cycles: 94% EB, 4 cyles: 95%
Observational (retrospective)			
Romano 2018 **Retrospective Cohort** RoB Moderately High	**Number of cycles: ABVD chemo, 6 cycles (followed by involved field RT if clinically indicated)** **Groups** **PET+ (n=21)** n=16, actually treated: BEACOPP for 8 cycles (and in case of persistent disease, bone marrow autologous transplant) **PET- (n=98)** Continued ABVD for 4 additional cycles, followed by consolidation RT on initial bulky nodal site of disease in a subset **Median F/U: 68 months (5.7 years)**	**5-year PFS:** Univariable analysis: PET+ vs PET-: 40.1% vs. 84.7% (HR 4.3, 95% CI 1.5-12.4, p<0.0001) Multivariable analysis:††† PET+ vs PET-: 40.1% vs. 84.7% (HR 3.8, 95% CI 1.7-8.3, p=0.0008)	**PET-specific:** **Treatment-related:** **Early death from infection, % (n/N):** 1% (1/119) **Treatment failure within 2 years, % (n/N)‡‡‡:** PET+ vs. PET-: 66.7% (14/21) vs. 9.3% (9/97), RR 7.19, 95% CI 3.60-14.35, p<0.0001

5PS = 5 point scale; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AE = Adverse Event; ASCT = autologous stem cell transplant; BEACOPP = bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BEAM = carmustine, etoposide, cytarabine, and melphalan; CI = Confidence Interval; EB = Escalated BEACOPP; ECOG = Eastern Cooperative Oncology Group; EFS = Event Free Survival; F/U = Follow-up; F = Female; G = Grade; GOELAMS = Groupe d'étude des Leucémies Aigues et des Maladies du Sang; HDT = High-dose therapy; HL = Hodgkin's lymphoma; HR = Hazard ratio; IFRT = Involved field radiation therapy; iPET = interim PET; IPS = International Prognostic Score; ITT = Intention to Treat; M = Male; MINE-R = mesna, ifosfamide, mitoxantrone, etoposide, and rituximab; OS = Overall Survival; PDG = cisplatin, gemcitabine, and dexamethasone; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial; RR = Risk Ratio; RT = Radiation therapy; VABEM = vindesine, doxorubicin, carmustine, etoposide, and methylprednisolone
*Death due to progressive disease (n=1) No random assignment on basis of medical decision (n = 1)

† ITT Data set group includes all PET+ and PET- patients in ITT analysis, regardless of protocol changes.
‡ The 'nonrandomized' portion of this data refers to a group of 115 recruited at baseline who were not randomized due to a variety of reasons (protocol deviations, etc.) but who were included in ITT set. These are not the same as the group who entered after the protocol change. Of the original 2101 recruited, 22 dropped out, and 115 patients did not get randomized for a variety of reasons (including staging revisions, toxicity, protocol deviations etc.) but are still included in the ITT analysis set.
§ After a protocol change, PET- patients continued to be randomized into x6 regimen (into group with those receiving x8) or into x4 regimen group, whereas PET+ group discontinued randomization at protocol change because their target sample size was reached for the R-eBEACOPP group, and thus new patients were allocated (not randomized) to x6 regimen. Outcomes data here capture all those randomized in the ITT set, excluding those PET+ patients (n=506) allocated to the x6 standard regimen.
** 1 exclusion owing to a local investigator decision
†† 3 were treated with ABVD and 3 denied any protocol treatment
‡‡2 patients had diagnostic failure, 15 patients received four more cycles of ABVD, and 5 patients shifted to a different salvage treatment.
§§Results reported based on Figure 1B.
***Results are reported based on Table 2.
†††Backward elimination was used to isolate predictors in the multivariable model.
‡‡‡This statistic is based on an end-of-treatment PET scan.

Appendix Table F15. Detailed data abstraction: PET-adapted therapy in Advanced Hodgkin Lymphoma, de-escalation, interim PET

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
RCTS			
Johnson 2016 **RCT** RoB Moderately Low	**Treatment prior to iPET:** ABVD, 2 cycles **Groups** **PET+** (n = 182) n=172* actually received treatment: Either BEACOPP-14 (n = 94) or escalated BEACOPP (n = 78) **PET -** (randomized) (n= 937) n=935† actually randomized to treatment: additional cycles (cycles 3-6) 1. Continue ABVD for 4 cycles (n=470 [ITT]/468 [per-protocol]) 2. Omit bleomycin (AVD) for 4 cycles (n=465 [ITT]/456 [per-protocol]) **Median F/U: 41 months (3.4 years)**	**3-year OS (95% CI):** • PET+: 87.8% (81.5%–92.1%) • PET- randomized to ABVD vs. AVD: 97.2% (95.1%–98.4%) vs. 97.6% (95.6%–98.7%); HR 0.09 (95% CI, 0.47 to 1.74), p=0.76 [ITT analysis] **3-year PFS (95% CI):** • PET+: 67.5% (59.7%–74.2%) • PET- randomized to ABVD vs. AVD: 85.7% (82.1% –88.6%) vs. 84.4% (80.7%–87.5%); HR 1.13 (95% CI, 0.81 to 1.57, p=0.48) [ITT analysis]; HR 1.10 (95% CI, 0.79 to 1.53, p=0.58) [per-protocol analysis] **Mortality, % (n/N)**: • PET+ vs. PET-: 12.8% (22/172) vs. 3.9% (36/935) (In the PET+ group: 10 from HL, 4 owing to initial therapy, 5 owing to salvage therapy, 0 from secondary cancer, 1 from cardiac event, and 1 from cause unrelated to HL or treatment. In the PET- group: 14 from HL, 4 owing to initial therapy, 5 owing to salvage therapy, 10 from secondary cancer, 2 from cardiac event, and 3 from cause unrelated to HL or treatment.) • PET- randomized to ABVD vs. AVD: 4.0% (19/470) vs. 3.7% (17/465) **3-year PFS Absolute Risk Difference, (95% CI) [ITT]:**	**PET-specific:** **Treatment-Related:** **Any Grade 3 or 4 adverse event, % (n/N):** • PET+ vs. PET-: 81.4% (140/172) vs. 67.1% (621/925), RR 1.21, 95% CI 1.11-1.32, p=0.0002 • PET+ receiving BEACOPP-14 vs. escalated BEACOPP: 80% (75/94) vs. 83% (65/78), RR 0.96, 95% CI 0.83-1.11, p=0.553 • PET- randomized to ABVD vs. AVD: 69% (322/468) vs. 65% (299/457), RR 0.95, 95% CI 0.87-1.04 **Any clinical adverse event‡, % (n/N):** • PET+ vs. PET-: 57.6% (99/172) vs. 25.8% (239/925), RR 2.23, 95% CI 1.88-2.64, p<0.0001 • PET+ receiving BEACOPP-14 vs. escalated BEACOPP: 55% (52/94) vs. 60% (47/78), RR 0.92, 95% CI 0.71-1.19, p=0.5155 • PET- randomized to ABVD vs. AVD: 31% (143/468) vs. 21% (96/457), p<0.005 per authors, RR 0.69, 95% CI 0.55-0.86, p=0.0009 **Secondary Malignancy, % (n/N):** • PET+ vs. PET-: 1.7% (3/172) vs. 2.6% (24/935), RR 0.68, 95% CI 0.21-2.23, p=0.5205 • PET- randomized to ABVD vs. AVD: 2.8% (13/470) vs. 2.4% (11/465), RR 0.86, 95% CI 0.39-1.89, p=0.6989

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
		PET- randomized to ABVD vs. AVD: 1.6 percentage points (-3.2 to 5.3)	
Borchmann 2017b *GHSG HD18 trial* **RCT** Advanced classic HL (stage IIB-IV) RoB Low ITT data set includes all PET+, PET- patients, regardless of protocol change. 'Nonrandomized' are group from baseline that did not get randomized but are included in ITT (though given separate data). After protocol change, randomization ceased for PET+ group; that group is not included in available safety data (from the	[***data not reported according to escalation and de-escalation, results repeated here for convenience***] **PET Timing:** Interim (2 cycles) **PET + (randomized) (n=951)** Randomized to standard therapy or rituximab escalation: 1a. Standard therapy escalated BEACOPP x8 (n=220) OR 2. escalated BEACOPP + rituximab x8 (n=220) **PET + subgroup (allocated after protocol change)** A protocol change occurred after which standard therapy was reduced from x8 to x6 eBEACOPP. Randomization ceased at this point: 1b. Reduced Standard Therapy (escalated BEACOPP x6) (n=511) **PET - (randomized) (n=1013)** Randomized to standard therapy/reduced therapy (after protocol change) or de-escalation therapy: 1.Standard therapy escalated BEACOPP x8 (n=220) or x6 reduced standard (n=218) OR 2. de-escalation: escalated BEACOPP x4 (n=505) **Median F/U 67.5 mos. (PET +)** **Median F/U 56.5 mos. (PET -)**	[***data not reported according to escalation and de-escalation, results repeated here for convenience***] **ITT Data Set (n=2073)**§ **3-Year OS:** PET+ vs. PET-: 97.1% (95% CI 95.9 to 98.2) vs. 97.3% (95% CI 96.2 to 98.3) **3-Year PFS:** PET+ vs. PET-: 92.5% (95% CI 90.7 to 94.3) vs. 93.5% (95% CI 91.9 to 95.1) **5-Year OS:** PET+ vs. PET-: 88.3% (95% CI 85.8 to 90.8) vs. 91.4% (95% CI 89.5 to 93.4), p=0.49; **5-Year PFS:** PET+ vs. PET-: 95.5% (95% CI 93.9 to 97.1) vs. 96.3% (95% CI 95.0 to 97.6), p=0.30; **Nonrandomized (n=115)**** **3-Year OS:** 77.6% (95% CI 68.6 to 86.6), **3-Year PFS:** 91.0% (95%CI 85.4 to 96.7), **5-Year OS:** 77.6 (68.6 to 86.6), **5-Year PFS:**	[***data not reported according to escalation and de-escalation, results repeated here for convenience***] **Randomized ITT-Set (n=1439)** †† **PET-specific, PET+ vs. PET-:** None reported **Treatment-Related, PET + vs. PET-, % (n/N); ES (95%CI), p-value:** Mortality due to Toxicity of Study Treatment: 0.9% (4/434) vs 0.6% (6/1005); RR 1.54 (95%CI 0.74 to 2.12), p=0.396 Mortality due to Toxicity of Salvage Therapy: 1.6% (7/434) vs 0.4% (4/1005) RR 4.05 (95%CI 0.93 to 2.56), p=0.089 Any Toxicities CTCAE Grade III or IV: 97% (426/438) vs 93.5% (940/1005); RR 1.04 (95%CI 1.02 to 1.07), p=0.007 Organ Toxicities CTCAE Grade III or IV : 51.6% (226/438) vs 12.8% (129/1005); RR 4.02 (95%CI 2.96 to 4.18), p<0.001 Anemia, Thrombopenia or Infection, CTCAE Grade IV: 83.1% (364/438) vs 46.9% (471/1005); RR 1.77 (95%CI 1.61 to 1.88), p<0.001 Treatment-Related Morbidity: NR vs 52.2% (525/1005) **Tumor-Related, PET + vs. PET-:** Any tumor event:

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
"randomized" ITT set)		89.2% (95%CI 82.6 to 95.8), **<u>Randomized ITT Set (n=1439)</u>**†† **Mortality, PET + vs. PET-, % (n/N)** All Causes: 5.3% (23/434) vs 3.4% (34/1005) Mortality, Second Malignancy: 0.9% (4/434) vs 1.3% (13/1005)	7.1% (31/434) vs 6.0% (60/1005); RR 1.20 (95%CI 0.85 to 1.68), p=0.303 Tumor Progression: 1.2% (5/434) vs. 0.4% (4/1005); RR 2.89 (95%CI 0.83 to 2.36), p=0.200 Early Relapse (< 1 year after end of treatment): 2.5% (11/434) vs 1.9% (19/1005); RR 1.34 (95%CI 0.796 to 1.97), p=0.331 Late Relapse: 3.5% (15/434) vs 3.7% (37/1005); RR 0.94 (95%CI 0.69 to 1.58) p=0.820 **Secondary Malignancies, PET+ vs PET-:** Acute Myeloid Leukemia or myelodysplastic syndrome: 2.1% (9/434) vs 0.9% (10/1005); RR 2.08 (95%CI 0.88 to 2.30) p=0.147 Non-Hodgkin's Lymphoma: 1.2% (5/434) vs 1.3% (13/1005); RR 0.89 (95%CI 0.66 to 1.82) p=0.716 Solid Tumor: 2.3% (10/434) vs 3.1% (31/1005); RR 0.747 (95%CI 0.615 to 1.50) p=0.858
Observational studies (retrospective)			
Deau 2015 **Retrospective Cohort** RoB High	**Treatment prior to iPET: e**BEACOPP, 2 cycles **Groups** **<u>PET +</u>** (n = 9) Escalated BEACOPP for 2 additional rounds (4 cycles total) • **PET +** (n=5) Salvage therapy • **PET –** (n=4) ABVD for 2 cycles **<u>PET –</u>** (n = 55) Standard ABVD for 4 cycles	**<u>OS at median follow-up:</u>** PET+ vs. PET-: 100% vs. 100% **<u>2-year PFS:</u>** PET+ vs. PET-: 47% vs. 87%, p=0.0059	**<u>PET-specific:</u>** NR **<u>Treatment-Related:</u>** **Infection-related toxicity:** 8%

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
	Median F/U: 30 months (2.5 years)		
Kedmi 2016 **Retrospective Cohort** RoB Moderately High Funding: NR COI: NR	**PET Timing:** Interim (2 cycles) **<u>iPET + (n=17)</u>** Patients in Partial Response (PR): De-escalation to ABVD x4 **<u>iPET - (n=52)</u>** Patients in Complete Response (CR): De-escalation to ABVD x4 **Median F/U (range): 67.2 (4.8 to 132) mos**	**Interim Treatment Response:** -CR: 75.4% (52/69) -PR: 24.6% (17/69) **5-Year OS, all patients:** 93% **5-Year OS, PET+ vs PET-:** 79% vs 93%, p=0.015 **5-Year PFS, all patients** 76% **5-Year PFS, PET+ vs PET-** 60% vs 80%, p=0.200 **Mortality, All Patients:** -mortality, all causes: 5.8% (4/69) -mortality, tumor-related: 2.9% (2/69) -mortality, catastrophic antiphospholipid syndrome: 1.5% (1/69) -mortality, lung carcinoma: 1.5% (1/69) **Mortality, PET+ vs PET-:** -mortality, catastrophic antiphospholipid syndrome: % 0% (0/17) vs 1.9% (1/52) ; RR IC -mortality, lung carcinoma: % 0% (0/17) vs 1.9% (1/52) ; RR IC	**PET-specific, PET+ vs. PET-:** NR **First-line Treatment-Related, all patients** -grade 4 neutropenia: majority ‡‡ -hospitalized for Febrile Neutropenia: 23.2% (16/69) -Febrile neutropenia with bacteremia: 6.3% (1/16) - Febrile neutropenia with sepsis: 6.3% (1/16) - Cyclophosphamide/bleomycin-induced pneumonitis: 1.5% (1/69) -severe bone pain: 1.5% (1/69) **Adapted Treatment-Related, all patients:** -Grade 3/4 Neutropenia: 7.2% (5/69) -febrile neutropenia: 1.5% (1/69) -peripheral neuropathy and pneumonitis: 1.5% (1/69) **Tumor-Related, PET + vs. PET-:** -relapse or PD: 35.3% (6/17) vs 21.2% (11/52), p=ns; RR 1.67 (95% CI 0.81 to 2.10), p=0.272 -mortality, tumor-related: 2.9% (2/69) **Secondary Malignancies, PET+ vs PET-:** -mortality, lung carcinoma: 0% (0/17) vs 1.9% (1/52); RR IC

5PS = 5 point scale; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AVD = doxorubicin, vinblastine, dacarbazine; CI = Confidence Interval; ECOG = Eastern Cooperative Oncology Group; F/U = Follow-up; F = Female; HL = Hodgkin's lymphoma; HR = Hazard ratio; IC, incalculable; iPET = interim PET; IPS = International Prognostic Score; ITT = Intention to Treat; M = Male; mos. = months; NR = Not reported; NS = not significant; OS = Overall Survival; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial; RR = Risk Ratio
*10 patients stopped the trial prior to treatment.

†1 patient had toxic effect of adverse event and another patient had a second cancer.
‡Excluding blood or bone marrow events and laboratory events.
§ ITT Data set group includes all PET+ and PET- patients in ITT analysis, regardless of protocol changes.
** The 'nonrandomized' portion of this data refers to a group of 115 recruited at baseline who were not randomized due to a variety of reasons (protocol deviations, etc.) but who were included in ITT set. These are not the same as the group who entered after the protocol change. Of the original 2101 recruited, 22 dropped out, and 115 patients did not get randomized for a variety of reasons (including staging revisions, toxicity, protocol deviations etc.) but are still included in the ITT analysis set.
†† After a protocol change, PET- patients continued to be randomized into x6 regimen (into group with those receiving x8) or into x4 regimen group, whereas PET+ group discontinued randomization at protocol change because their target sample size was reached for the R-eBEACOPP group, and thus new patients were allocated (not randomized) to x6 regimen. Outcomes data here capture all those randomized in the ITT set, excluding those PET+ patients (n=506) allocated to the x6 standard regimen.
‡‡ Authors report "almost all" patients developed grade 4 neutropenia but did not report the specific number.

Appendix Table F16. Detailed data abstraction: PET-adapted therapy in Advanced Hodgkin Lymphoma, unclear escalation/de-escalation, interim PET

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
Observational studies (prospective)			
Dann 2017 **Prospective Cohort** RoB Moderately High *[includes results for advanced HL only, see table F13 for advanced HL results]*	**Treatment prior to iPET**: ABVD chemo, 2 cycles (EF-HL, EUF-HL, and advanced HL with IPS 0-2) Escalated BEACOPP, 2 cycles: (Advanced HL with IPS 3-7) **Groups** **Advanced HL, IPS 0-2 (n=111) [Escalation]** **PET+ [without evidence of disease progression§] (n=13)** Four additional escalated BEACOPP courses (6 total) with ISRT to residual masses **PET– (n=98)** Four additional ABVD courses (6 total) **Advanced HL, IPS ≥3 (n=74) [De-escalation]** **PET+ [without evidence of disease progression§] (n=14)** Four additional escalated BEACOPP courses (6 total) with ISRT to residual masses **PET– (n=60)** Four ABVD courses	**5-year OS, (95% CI)** **Advanced-HL** PET+ vs. PET-: 91.4% (79.9%-102.9%) vs. 97.8% (95.4%-100.3%), p=NS* Advanced HL IPS 0-2 PET+ vs. PET: 92% (77%-107%) vs. 97.6% (94.3%-100.9%), p=NS* Advanced HL IPS≥3 PET+ vs. PET-: 91.3% (75%-107%) vs. 98.2% (94.6%-101.7%), p=NS* **5-year PFS, (95% CI)** **Advanced-HL** PET+ vs. PET-: 68.4% (49.8%-86.9%) vs. 80.8% (74%-87.7%), p=0.007*	*Overall (not reported for early versus advanced HL separately)* **PET-specific:** **Treatment-related:** **Evaluated for menstrual status (n = 114):** **Preserved or regained menstrual period**: 78% **Premature ovarian failure during follow-up**: 22% (with somewhat higher rates (33% vs. 20%) in those receiving any EB compared to ABVD only (P = 0.52). **Pregnancy following treatments**: n = 37 **Dose Intensity:** ABVD (75%) ABVD 32–4 + EB 32–4 (21%) 6 EB cycles (12%)

Author Study Design RoB	Treatments	Responders	Safety PET-specific Treatment-Related
	<u>All Advanced HL Patients (n=185) [Escalation/De-escalation]</u> **PET+ (n=27)** Four additional escalated BEACOPP courses (6 total) with ISRT to residual masses **PET- (n=158)** Four ABVD courses **Median F/U: 60 months (5 years)**	Advanced HL IPS 0-2 PET+ vs. PET-: 59% (30.8%-87.1%) Advanced HL IPS≥3 PET+ vs. PET-: 78.6% (57.1%-100.1%) vs. 81.5% (71%-92%), p=NS*	Cardiac ischemic events: n = 4 (1 fatal) **<u>Secondary Malignancies:</u>** n=7 (1.9%) (Single cases of lymphoblastic lymphoma, acute Ph+ lymphoblastic leukemia, papillary thyroid cancer, cutaneous B cell follicular lymphoma, and breast cancer. Two cases of secondary leukemia; one had EB 32 + ABVD 34 and the other received one EB cycle and was then withdrawn from the study due to a suicidal attempt and drug abuse.)

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CI = Confidence Interval; COI: Conflicts of interest; EB = Escalated BEACOPP; EF = Early favorable; EUF = Early unfavorable; HL = Hodgkin's lymphoma; HR = Hazard ratio; iPET = interim PET; IPS = International Prognostic Score; ISRT = Involved Site Radiation Therapy; NS = Not significant; OS = Overall Survival; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial

*Unclear from the text as to what this p-value represents.2
†PET- patients with multiple or extensive disease sites or fields overlapping breast tissue (women), could forego radiotherapy and receive two further courses of ABVD instead.
‡ PET- patients with multiple or extensive disease sites or fields overlapping breast tissue (women), could forego radiotherapy and receive four further courses of ABVD instead.
§Patients progressing during the study were withdrawn and received salvage therapy.

Appendix Table F17. Detailed data abstraction: PET-adapted therapy in advanced Hodgkin Lymphoma, escalation, end-of-treatment PET

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
RCTS			
Gallamini 2018 *GITIL/FIL HD 0607 Trial* **RCT** RoB Moderately High	**Treatment prior to EOT PET**: ABVD, 6 cycles **End-of-treatment PET** Patients in CR after six ABVD cycles w/ large nodal mass (n=320) n=296* actually randomized to treatment: **Groups** 1. Radiotherapy (n=148) 2. No Radiotherapy (n=148) **Median F/U:** 3.6 years	**End-of-treatment PET** **3-year PFS (95% CI)** Radiotherapy vs. No Radiotherapy: 97% (92%-99%) vs. 93%(87%-96%), p=0.29 **3-year OS (95% CI)** Radiotherapy vs. No Radiotherapy: 100% vs. 99% (95%-100%), p=NR **Mortality, % (n/N)**: • Overall: 3.8% (30/780) ○ Disease progression and cardiac failure: n=2 ○ Resistant or progressive disease: n=18 ○ Transplant-related toxicity: n=5 ○ Infections: n=4 ○ Pulmonary fibrosis: n=1 **PET+ vs. PET-:** 11% (16/150) vs. 2% (12/630), RR 5.6, 95% CI 2.7-11.6, p<0.0001	**PET-specific:** **Proportion of PET- patients under treated due to nature of the negative predictive value of interim PET during ABVD treatment**: 13% **Treatment-Related:** **Toxicity (Grade 3 to 4 Adverse Events), % (n/N):** PET+ vs. PET-: Blood/Bone Marrow: 76% (114/150) vs. 30% (189/630), RR 2.5, 95% CI 2.2-2.9, p<0.0001 Infection: 10% (16/150) vs. 1% (5/630), RR 13.4, 95% CI 5.0-36.1, p<0.0001 Pulmonary/Upper Respiratory: 1% (1/150) vs. 2% (11/630), RR 0.38, 95% CI 0.05-2.9, p=0.335 GI: 0% (0/150) vs. 1% (6/630), RR 0, 95% CI NR, p=0.231
Engert 2012/Engert 2017 HD15 trial **Prospective cohort***:* *technically a RCT, but it did not randomize patients based on PET results and included only a subset of patients with*	**Treatment prior to iPET:** eBEACOPP or BEACOPP14 or BEACOPP, 6 or 8 cycles **Groups** **PET +** (n = 182) Radiotherapy **PET –** (n = 529) No radiotherapy **F/U: 12 months (1 year)**	**4-year PFS (95% CI for the difference):** PET+ vs. PET-: 86.2% vs. 92.6% (0.9%-12.0%, log-rank p=0.022) **Progressive disease or early relapse in PET+ patients (w/in 12 months of follow-up):** 11% **10-year PFS according to response to Chemotherapy (95% CI)**:	**PET-specific:** **Negative predictive value (12 months)**: 94.1% (95% CI, 92.1% to 96.1%) **Treatment-Related:** NR

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
PET scans after initial treatment and who had12 months follow-up; thus, it was considered an observational study for purposes of this HTA RoB High		Complete remission (n = 884) vs. PET+ partial remission (n = 191) vs. PET- partial remission (n = 548): 85.2% (82.4%-87.9%) vs. 84.8% (79.3%-90.3%) vs. 88.1% (85.0%-91.2% **Median observation time: 102 months (8.5 years)** **HR for the 10-year PFS according to response to chemotherapy:** PET+ complete remission vs. PET- complete remission: 1.2 (95% CI, 0.6 to 1.1) vs. 1.2 (95% CI, 0.8 to 1.8) **Median observation time: 102 months (8.5 years)**	

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, docorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; 5PS = 5 point scale; CI = Confidence Interval; COI = Conflicts of interest; CR = Complete Response; CT = Computed tomography; EOT= End of treatment; F/U = Follow-up; F = Female; HR = Hazard ratio; iPET = interim PET; IPS = International Prognostic Score; ITT = Intention to Treat; M = Male; NR = Not reported; OS = Overall Survival; PET = Positron Emission Tomography; PFS = Progression Free Survival; RCT = Randomized controlled trial; RoB = Risk of Bias; RR = Risk Ratio

*24 patients had no assignment based on patient or medical decision.

Appendix Table F18. Detailed data abstraction: PET-adapted therapy in pediatric Hodgkin Lymphoma, interim PET (included for references, not in main body of report)

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
RCTS			
Friedman 2014 **RCT (non-PET randomized)** Early-Advanced HL Risk of bias not assessed for this study* Data reported here represents a subset (those who received PET assessment) of the overall study sample. Data for 389/1135 PET recipients NR	**PET Timing:** Interim PET (4 cycles) **Allocated first according to ER (early responder status) as determined by CT.** **After 1 or 2 additional cycles (4 total), CR status was assessed by CT-gallium or PET-CT. Only groups with PET recipients are detailed below** **Randomized PET recipients (n=746)** RER (Rapid Early Responders): **PET+ RER/CR (n=117)** **randomly** assigned to: • IFRT (n=57) • No IFRT (n=60) **PET- RER/CR (n=433)** **Randomly** assigned to • IFRT (n=224) • No IFRT (n=209) SER (Slow Early Responders): **PET+ SER (n=85)** **randomly** assigned to: • Escalation with DECAx2 + additional ABVE-PCx2 + IFRT (n=46) • Consolidation with additional ABVE-PCx2 + IFRT (n=39)	**4-Year EFS, RER/CR PET+ (IFRT)** 83.1%(95% CI 69.9 to 90.8) **4-Year EFS, RER/CR PET + (no IFRT)** 78.1% (95% CI 62.3 to 87.9) **4-Year EFS, RER/CR PET - (IFRT)** 86.7% (95% CI 80.7 to 90.9) **4-Year EFS, RER/CR PET - (no IFRT)** 87.3% (95% CI 81.7 to 91.3) **4-Year EFS, SER PET+ (DECA escalation)** 70.7% (95% CI 52.7 to 82.9) **4-Year EFS, SER PET + (consolidation)** 54.6% (95% CI 37.3 to 69.0) **4-Year EFS, SER PET- (DECA escalation)** 90.1% (95% CI 77.9 to 95.8) **4-Year EFS, SER PET- (consolidation)** 85.6% (95% CI, 73.2 to 92.5)	No PET-specific safety data was reported

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
	PET- SER (n=111) **Randomly** assigned to • Escalation with DECAx2 + additional ABVE-PCx2 + IFRT (n=52) • Consolidation with additional ABVE-PCx2 + IFRT (n=59) An additional n=389 RER patients were assessed with PET scanning and went on to receive IFRT but were not randomized because of sub-optimal response (< CR) and no data was provided. **Median F/U 50.4 mos.**		

ABVE-PC = Doxorubicin Hydrochloride (Adriamycin) + Bleomycin + Vincristine Sulfate + Etoposide Phosphate + Prednisone + Cyclophosphamide; COI = conflict of interest; CR = complete response; DECA = dexamethasone + etoposide + cisplatin + cytarabine; EFS = event free survival; F/U = follow-up; IFRT = involved field radiation therapy; mos. = months ; NR = not reported; PET = positron emission tomography; RCT = randomized controlled trial; RER = rapid early responders; RoB = Risk of Bias; SER = slow early responders;

* A subset of the study population received PET scanning and provided data relevant to our key questions, however, the portion of the overall study who received PET was less than 80% (threshold for inclusion as per our PICOTS table). Data was abstracted here for reference but is not considered in the main body of the report.

Appendix Table F19. Detailed data abstraction: PET-adapted therapy in Relapsed/Refractory Hodgkin Lymphoma, escalation, interim PET

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
Observational Studies			
Moskowitz 2015, Moskowitz 2017 **Prospective cohort** RoB Moderately High Transplant-eligible, relapsed/refractory Classical HL For pre-ASCT related analysis they used ≥3 as a threshold for PET positivity, whereas ≥2 is used for other analysis.	**PET Timing:** Interim (2 or 3 cycles), pre-ASCT PET (iPET + only) Non-randomized allocation based on PET results: **1. iPET + (n=47)** Two cycles of augmented-ICE before consideration for ACST Pre-ASCT PET + (n=14) Proceeded to ASCT consolidation therapy. n=4 received pre-ASCT RT Pre-ASCT PET - (n=31) Proceeded to ASCT consolidation therapy. n=22 received pre-ASCT RT **2. iPET – (n=19)** N=18 iPET - proceeded directly to ACST consolidation therapy, joined by n=1 iPET + patient. **Median F/U (range): 40 mos**	**Treatment Response, all patients:** -CR from First-Line Treatment: 28% (18/65) -CR from overall treatment program: 75% (49/65) -Proceeded to ASCT: 98.4% (64/65) -Received pre-ASCT IFRT: 41% (26/64) **3-Year OS, all patients** 95% **3-Year EFS, all patients** 82% **3-Year EFS, PET+ (n=10) vs PET- (n=54)** 85.2% vs 60%, p=0.05	**PET-specific:** NR **Treatment-Related Toxicities, cohort 2 patients:** -Rash (grade III): 5% (1/20) -Infusion-related Reaction: 5% (1/20) -Withdrawal due to patient discretion: 5% (1/20) **Tumor-Related, cohort 2 patients:** -unfinished first-line treatment due to PD: 5% (1/20) -relapsed after ASCT (<12 months): 1.5% (1/64) **Secondary Malignancies:** NR
Moskowitz 2012 **Prospective cohort** RoB Moderately High Transplant-eligible, relapsed/refractory classical HL	**PET Timing:** Pre-treatment, Interim (2 cycles) Non-randomized allocation based on PET results: **1. iPET + (n=36)** Extended Salvage therapy with Gemcitabine, vinorelbine, and liposomal doxorubicin (GVD), x2 cycles Restaging with PET/CT after;	**ITT Set (n=97)** **51 mos OS** 80% **51 mos EFS** 70% **51 mos EFS, PET+ vs PET –** 52.6% vs 81.4%	**PET-specific:** NR **Chemotherapy Treatment-Related (Grade III or IV):** -ifosamide-induced confusion: 1% (1/97) -anaphylaxis during liposomal doxorubicin infusion: 1% (1/97)

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
	• Patients with PD were considered protocol failures • Rest proceeded to HDT/ASCT **2. iPET – (n=59)** HDT/ASCT; received 1 of 2 ASCT conditioning regimens (involving varying RT and chemotherapy) based on previous RT and presence of noncontiguous extra nodal sites **Median F/U (range): 51 (16 to 86) mos.**	**51 mos EFS, pre-ASCT PET+ vs pre-ASCT PET-** 29% (6/21) vs 81.6% (62/76); p=0.006, p<0.001* **51 mos EFS, PET+ vs PET-/ENS+ vs PET-/ENS-** 29% (6/21) vs 67% (20/30) vs 91.3% (42/46); p<0.001* **Mortality** -Sudden Death: 1% (1/97)	-Febrile Neutropenia: 25 events -Catheter-related infection/thrombosis: 9 events -Acute Renal Failure: 2 events -Clostridium difficile: 1 event -viral meningitis: 1 event - Pneumonia: 2 events - Pulmonary embolism: 1 event - Cellulitis: 1 event - Anaphylaxis: 1 event **Total Lymphoma Irradiation Treatment-Related Toxicities** - Radiation esophagitis: 1.8% (1/56) - Depression: 1.8% (1/56) - Radiation pneumonitis: 1.8% (1/56) - Disseminated zoster: 1.8% (1/56) - Autologous graft vs host: 1.8% (1/56) - Pericardial tamponade: 1.8% (1/56) - Multisystem organ failure: 1.8% (1/56) **CBV Treatment-Related Toxicities:** -*Clostridium difficile*: 6.9% (2/29) -Depression: 3.4% (1/29) -Myelodysplasia: 3.4% (1/29) **Transplant Treatment-Related:** -received NMT instead of ASCT based on physician preference: 1% (1/97) **Tumor-Related, All Patients** -PD after salvage therapy: 4.1% (4/97) -PD after first-line therapy requiring emergent RT: 2.1% (2/97)

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
			Unclear Adverse Events -sudden death: 1% (1/97) -septic shock: 1% (1/97) **Secondary Malignancies:** NR

ASCT =autologous stem cell transplant; CBV = cyclophosphamide, carmustine, etoposide; CR = complete response; CT = computerized tomography; EFS = event free survival; F/U = follow-up; GVD = Gemcitabine, Vinorelbine, Doxil; HL = Hodgkin lymphoma; IFRT = involve field radiation therapy= mos. = months; NMT = nonmyeloablative allogeneic stem cell transplant; NR = not reported; OS = overall survival; PET = positron emission tomography; PET/CT = positron emission tomography / computerized tomography; PD = progressive disease; RoB = risk of bias; RT = radiation therapy
* P-value reflects comparison across all three groups.

Appendix Table F20. Summary of Inclusion & exclusion criteria: PET-adapted therapy in early or advanced Hodgkin Lymphoma

Study	Inclusion Criteria	Exclusion Criteria
HODGKIN (HL)		
Advanced HL, Interim PET		
Randomized Controlled Trials		
Gallamini 2018	Histopathologic diagnosis of classic HL, age 18 to 60 years, no previous therapy, Ann Arbor stage IIB to IVB, measurable International Prognostic Score (IPS), and signed informed consent.	Patients were excluded in case of concomitant or previously treated (<5 years) neoplasia, psychiatric disorder, impaired cardiac (ejection fraction, 50%) and renal (creatinine clearance, 60 mL/min) functions, HIV or any other active uncontrolled infection, pregnancy; and uncompensated diabetes.
Borchmann 2017b	Newly diagnosed, histology-proven Hodgkin Lymphoma (HL) in Ann-Arbor stage IIB with large mediastinal mass (≥ one third of the maximal thoracic diameter) or extranodal lesions; or in stage III and IV. Between 18 and 60 years of age, previously untreated for HL, with personally signed written informed consent, consent to storage of study data and required tissue samples, organ function (except HL-related impairments), a negative human immunodeficiency virus (HIV)-test, a negative pregnancy test in women, and a life expectancy of more than 3 months.	Exclusion criteria included incomplete staging diagnosis, and prior or concurrent disease disallowing protocol treatment, in particular chronic obstructive pulmonary disease with global insufficiency, symptomatic coronary heart disease, cardiomyopathy or cardiac insufficiency (New York Heart Association value of ejection fraction < 50% or fractional shortening < 25%), serious uncontrolled hypertension, uncontrollable infection, leukocyte concentration < 3,000/mm³ or thrombocyte concentration < 100,000/ mm³ (exception: reduced values related to Hodgkin's disease, e.g. bone marrow infiltration, splenomegaly), creatinine clearance < 60 ml/min, bilirubin > 2 mg/dl or glutamic oxaloacetic transaminase > 100 U/l or glutamic pyruvic transaminase > 100 U/l (exception: elevated values due to HL liver involvement), poorly controlled diabetes mellitus (HbA1c > 7.5 %), elevated fasting blood sugar > 200 mg/dl, HIV-Infection, chronic active hepatitis B and/or hepatitis C, or stability endangering bone involvement that precludes from an FDG-PET examination. Patients were also excluded from the study if they were pregnant or lactating, had HL as part of a composite lymphoma, a previous malignant disease within the last 5 years, prior chemo- or radiotherapy, an Eastern Cooperative Oncology Group performance status >2, long-term ingestion of

Study	Inclusion Criteria	Exclusion Criteria
		corticosteroids or antineoplastic drugs or a known intolerance to any of the study drugs, received antiepileptic treatment, lacked accountability, had conditions indicative of noncompliance to trial procedures, used unsafe contraceptive methods (Pearl index > 1), had a relationship of dependence or employer-employee relationship to the sponsor or the investigator, were committed to an institution on judicial or official order, or participated in another interventional trial that could interact with this trial.
Johnson 2016	Previously untreated patients 18 years of age or older with advanced classic Hodgkin's lymphoma that was confirmed by histologic analysis were eligible if they were fit to receive a full course of combination chemotherapy. Staging comprised clinical assessment; contrast-enhanced computed tomography (CT) of the neck, thorax, abdomen, and pelvis; and bone marrow biopsy. Advanced stage was defined as an Ann Arbor stage of IIB to IV, or stage IIA with adverse features: bulky disease (>33% of the transthoracic diameter or >10 cm elsewhere) or at least three involved sites. Written informed consent was obtained from all patients before trial entry.	NR
Prospective Observational		
Carras 2018 GOELAMS LH 2007 trial	Patients with newly histologically proven HL (age range, 18-65 years) were included and stratified according to the GOELAMS Prognostic Score System (PSS) based on age (≤40 years = 0; > 40 years = 1), number of involved nodes (0-2 = 0; 3-5 = 1; ≥ 5 = 2), and B symptoms (absence = 0, presence = 1) into favorable, intermediate, or advanced (PSS ≥ 4) stage HL. All patients with PSS ≥ 4 were included in this treatment arm.	Patients with prior human immunodeficiency virus or viral B or C hepatitis
Dann 2017 [Includes results for early-HL]	After providing written informed consent, eligible patients with classic HL (age 18–60 years, stages I–IV)	NR
Press 2016 The Southwest Oncology Group S0816	Patients between the ages of 18 and 60 were eligible for this trial if they had stage III-IV HL, as documented by central review of a diagnostic excisional or core needle biopsy. Fine needle aspirations and bone marrow biopsies were inadequate for entry onto this trial.	Patients could not be sero-positive for Hepatitis B or Hepatitis C. HIV testing was required prior to registration. HIV-positive patients could not have multi-drug resistant

Study	Inclusion Criteria	Exclusion Criteria
	Patients were required to have measurable disease with lymph nodes measuring at least 2 cm in longest diameter, no prior therapy for lymphoma, a performance status of 0-2 (Zubrod), no other serious medical ailments, and not be pregnant or nursing. Patients with a history of hypertension or cardiac symptoms were required to have an echocardiogram or multi-gated acquisition scan (MUGA scan) demonstrating no significant abnormalities, with a cardiac ejection fraction ≥ 45% within 42 days prior to registration. A second registration to this trial was performed after patients completed the first two cycles of ABVD. To continue on the trial, patients must not have experienced disease progression during the first two cycles of ABVD, must have submitted baseline and interim PET/CT scans for centralized review to the CALGB Imaging Core Laboratory (CALGB ICL), and must have agreed to begin either continued ABVD or BEACOPP (escalated dose BEACOPP3 for HIV-negative patients, standard dose BEACOPP9 for HIV-positive patients) within 10 days after the interim PET/CT was performed.	HIV infection, CD4 counts < 150/mcL or other concurrent AIDS-defining conditions.
Zinzani 2016 HD0801 study	Patients age 18 to 70 years were considered eligible if they had previously untreated and histologically documented HL (with the exception of nodular lymphocyte–predominant subtype) in clinical stage IIB to IV according to Ann Arbor staging and at least one bidimensionally measurable target lesion (even if extranodal only).	Patients were excluded from the study if they had a severe disease that impaired normal life, presented an active infection, or had an inadequate liver or renal function, unless this was a result of the lymphoma. Those with a history of previous malignancy (except basal cell skin carcinoma and in situ carcinoma of the cervix) were considered ineligible.
Ganesan 2015	Newly diagnosed patients (12–65 years) with advanced stage HL (Ann Arbor stages IIB–IVB) were included. Patients had to have histological diagnosis of HL with adequate bone marrow function (white blood cell count ≥ 4000/cmm, platelet count ≥100 000/cmm, unless deranged due to involvement by HL) and adequate organ function (serum creatinine ≤2mg/dL and serum bilirubin, SGOT and SGPT ≤2.5 times upper limit of normal).	Patients with co-existent cardiac or pulmonary diseases or uncontrolled diabetes and hypertension were excluded. Female patients could not be pregnant and had to consent to use effective contraception during the study.
Retrospective Observational		
Romano 2018	Newly diagnosed HL	History of HIV or immune-suppression therapy

Study	Inclusion Criteria	Exclusion Criteria
Advanced HL, End-of-Treatment PET		
Randomized Controlled Trials		
Engert 2012 HD15 trial	Entry criterion for the trial was a newly diagnosed, histology-proven Hodgkin Lymphoma (HL) in Ann-Arbor stage IIB with large mediastinal mass (≥ one third of the maximal thoracic diameter) or extranodal lesions; or in stage III and IV. Patients had to be between 18 and 60 years of age, previously untreated for HL, with personally signed written informed consent, normal organ function (except HL-related impairments), and a life expectancy of more than 3 months. **Criteria for PET assessment objective:** Inclusion: partial response after six to eight cycles of BEACOPP and at least one involved nodal site of 2.5 cm or larger in the transverse or longitudinal diameter as measured by CT.	Exclusion criteria included incomplete staging diagnosis, and prior or concurrent disease disallowing protocol treatment, in particular chronic obstructive pulmonary disease with global insufficiency, symptomatic coronary heart disease, cardiomyopathy or cardiac insufficiency (New York Heart Association value of ejection fraction < 50% or fractional shortening < 25%), serious uncontrolled hypertension, uncontrollable infection, leukocyte concentration < 3,000/mm³ or thrombocyte concentration < 100,000/ mm³ (exception: reduced values related to Hodgkin's disease, e.g. bone marrow infiltration, splenomegaly), creatinine clearance < 60 ml/min, bilirubin > 2 mg/dl or glutamic oxaloacetic transaminase > 100 U/l or glutamic pyruvic transaminase > 100 U/l (exception: elevated values due to HL liver involvement), or human immunodeficiency virus (HIV)-Infection. Patients were also excluded from the study if they were pregnant or lactating, had HL as part of a composite lymphoma, a previous malignant disease within the last 5 years, prior chemo- or radiotherapy, an Eastern Cooperative Oncology Group performance status >2, long-term ingestion of corticosteroids or antineoplastic drugs or a known intolerance to any of the study drugs, received antiepileptic treatment, lacked accountability, or had conditions indicative of non-compliance to trial procedures. **Criteria for PET assessment objective:** Exclusion: Diabetes mellitus, elevated fasting blood sugar level of more than 130 mg/dL, and skeletal; involvement with risk of instability.

Study	Inclusion Criteria	Exclusion Criteria
Early HL, Interim PET		
Randomized Controlled Trials		
Andre 2017/Raemakers 2014 EORTC/LYSA/FIL H10 Trial	Eligibility criteria included previously untreated patients with histologically proven classical HL, supradiaphragmatic Ann Arbor stage I/II disease, age 15 to 70 years, WHO performance status of 0 to 3, and written informed consent.	NR
Radford 2015 RAPID trial	Previously untreated male or female patients 16 to 75 years of age with histologically confirmed classic Hodgkin's lymphoma of clinical stage IA or IIA, as determined by means of clinical history and examination and computed tomographic (CT) scan of the thorax, abdomen, and pelvis, were eligible for trial entry. A baseline PET scan was not mandated and in most cases was not performed. Patients with mediastinal bulk (maximal mediastinal diameter ≥33% of the internal thoracic diameter at T5–T6) were not eligible. Written informed consent was obtained from all patients before trial entry.	NR
Prospective Observational Studies		
Dann 2017 [Includes results for advanced-HL]	After providing written informed consent, eligible patients with classic HL (age 18–60 years, stages I–IV)	NR
Relapsed/Refractory HL, Interim PET		
Prosepctive Observational Studies		
Moskowitz 2017	We recruited patients aged 12 years or older with relapsed or refractory Hodgkin's lymphoma who were eligible for transplantation and had already been treated with a doxorubicin-containing regimen. All patients underwent tissue biopsies to confirm relapsed or refractory Hodgkin's lymphoma and were required to have PET-positive disease. Additionally, patients had to have adequate organ function (defined as a cardiac ejection fraction >45%, a haemoglobin-adjusted diffusion capacity for carbon monoxide >50% on pulmonary function testing, a serum creatinine concentration ≥15 mg/L or creatinine clearance >60 mL/min, an absolute neutrophil count >1000/µL, a platelet count >50 000/µL, and bilirubin ≤20 mg/L).	Patients with HIV, hepatitis B, baseline peripheral neuropathy greater than grade 1, or history of receipt of more than one previous treatment programme for Hodgkin's lymphoma were excluded. All patients underwent staging tests including 18F-FDG PET, diagnostic CT scans of their chest, abdomen, and pelvis, and a bone marrow biopsy sample taken before initiation of treatment.
Moskowitz 2012	All patients had a repeat biopsy confirming relapsed or refractory HL before enrolling in this study. Primary refractory disease is defined as a repeat biopsy confirming active HL during or at the conclusion of front-	Patients with all 3 risk factors (10% of the relapsed or refractory HL patients) were excluded from this study and treated on another Institutional Review Board-approved

Study	Inclusion Criteria	Exclusion Criteria
	line therapy. Eligibility criteria included a diagnosis of classic HL confirmed by the Department of Hematopathology at MSKCC. In all cases, primary refractory or relapsed disease was proven by biopsy or fine needle aspiration (cytology) of an involved site. In addition, patients needed to have relapsed or progressed after receiving either a doxorubicin- or nitrogen mustard-containing front-line regimen. All patients were required to have FDG-PET–positive disease, a cardiac ejection fraction of greater than 45%, measured since last chemotherapy, as well as an adjusted diffusing capacity of greater than 50% on pulmonary function testing, as measured since last chemotherapy was required. In addition, serum creatinine had to be less than or equal to 1.5 mg/dL or, if creatinine more than 1.5 mg/dL, then the measured 12- or 24-hour creatinine clearance must be more than 60 mL/minute; other laboratory values necessary were a neutrophil count more than 1000/_L, platelets more than 50 000/_L, and total bilirubin less than or equal to 2.0 mg/dL in the absence of a history of Gilbert disease. The age range was 18 to 72 years; all patients needed to be hepatitis C virus, hepatitis B virus, and HIV I and II negative. Lastly, patients were not allowed to previously be treated with ifosfamide, carboplatin, cisplatin, gemcitabine, vinorelbine, or liposomal doxorubicin. Patients or their guardians must have been capable of providing informed consent.	HL protocol with the intention of proceeding to nonmyeloablative allogeneic stem cell transplant (NMT) as consolidation

APPENDIX G. Aggressive Non-Hodgkin's Lymphoma

Appendix Table G1. Study characteristics and patient demographics: clinical studies of aggressive Non-Hodgkin Lymphomas

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
Initial Staging				
Fujiwara 2011	Retrospective cohort Population N = 19 Mixed adults and pediatric (median 61, range 13-90) M(%)/F(%): 11(58)/8(42) Natural killer/T-cell lymphoma Stage I-II: (42%) III-IV: (58%) Comparator (both modalities used in the same patients) PET/CT vs Conventional methods (physical exam, CT with IV contrast, biopsies from primary sites, and bone marrow examinations) Median follow-up: NR	NR	Proportion of patients where PET resulted in a change in clinical stage compared to CT: 10.5% (2/19); both upstaged from I-II to II-IV Proportion of patients where PET altered treatment strategy compared to CT: 10.5% (2/19) Outcome after treatment: Complete Response: 36.8% (7/19) Partial Response: 10.5% (2/19) Relapse: 5.3% (1/19) Death: 36.8% (7/19) PD*: 10.5% (2/19)	NR
Casulo 2013 [same as below for interim]	Retrospective cohort [database] Population N = 95 (n=50, interim)	See interim section below	Proportion of patients where PET resulted in a change in clinical stage compared to CT(Initial staging only) 5.2% (5/95) Up-staged: 2.1% (2/95)	NR

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	Adults Median age 54 years (range: 24–89) T-cell or natural killer, peripheral T cell Stage NR Comparator (both modalities used in the same patients) PET vs CT Median follow-up: 40.8 months.		Down-staged: 3.2% (3/95) Proportion of patients where PET altered treatment strategy compared to CT (Initial staging only) 0% (0/95) [largely due to the use of combination chemotherapy regardless of stage, and short course chemotherapy was not performed]	
Interim				
Casulo 2013 [same as above for initial staging]	Retrospective cohort [database] Population N = 95 (n=50, interim) Adults Median age 54 years (range: 24–89) T-cell or natural killer, peripheral T cell Stage NR Comparator (both modalities used in the same patients) PET vs CT Median follow-up: 40.8 months.	OS iPET+ vs iPET-: 47% vs. 76% (p=0.16) Proportion alive at median follow-up PET+ vs. PET-: 26% vs. 63% (p=0.171) PFS (at median follow-up) iPET- vs. iPET+: 5.1 years vs. 10 months (p=0.03) Pearson χ2 for iPET status for association between iPET status and PIR score, IPI score, and other consolidative treatment with ASCT or Allo, respectively: p=0.415, 0.356, 0.260	See initial staging section above	NR

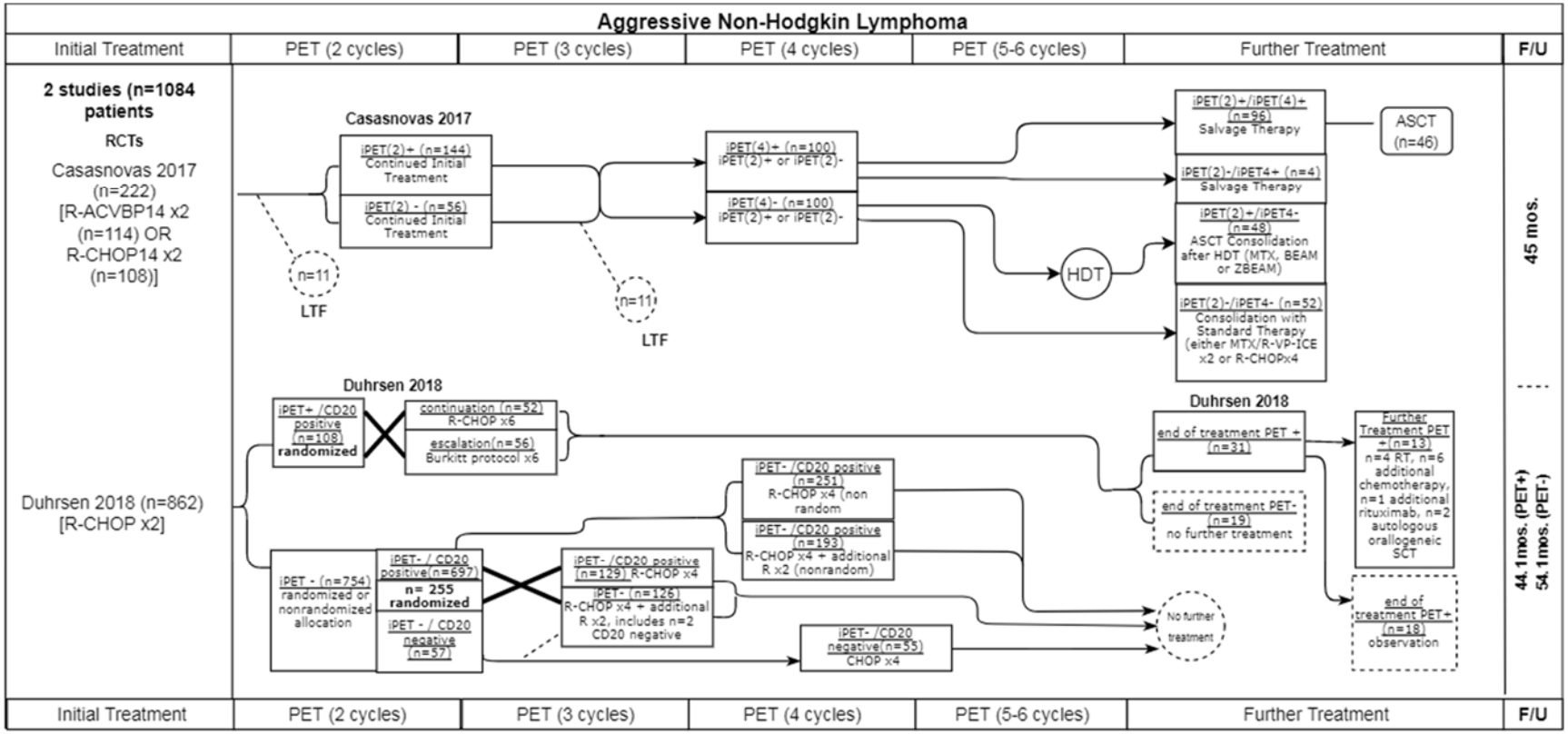
Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
Surveillance				
Epperla 2016	Retrospective cohort Population N = 160 Adults (median 55, range 18-70) M(%)/F(%): 19(59)/13(41) DLBCL [patients in complete remission on CT and/or PET on first post-transplant evaluation] Stage I-II: 24% (6/32) III-IV: 76% (26/32) Comparator Imaging (CT and/or PET) vs Clinical f/u (signs, symptoms, lab findings) Median follow-up: NR	Median OS in those who relapse after auto-HCT Imagining detected relapse vs. clinically detected relapse: 643 (range, 131-4533 days) vs. 586 days (range, 146-3060 days), p = 0.68	All of the 45 relapses were detected at a scheduled follow-up visit; 8 were detected by CT scan, 24 were detected by PET or PET/CT scan, and 13 were detected clinically. Therefore, surveillance imaging identified 32 [24 PET, PET/CT] symptomatic relapses, representing 71% (32/45) [53%; 24/45] of all relapses after day +100. Median time to relapse Imagining detected relapse vs. clinically detected relapse: 191 days [range, 120-3059 days] vs. 492 days [range, 128-2102 days], p= 0.35 Median post relapse survival after auto-HCT Imagining detected relapse vs. clinically detected relapse: 359 days [range, 9-4241 days] vs. 123 days [range, 5-958], p = 0.36	NR
Hong 2014	Retrospective cohort Population N = 106 Adults (median 54, range 22-85) M(%)/F(%): 53(50)/53(50)	3-year EFS 86.4% 3-year OS 93.6%	Additional tests as a result of false positives on PET (n=23 in 21 patients) vs. CT (n=7 in 7 patients): PET: Biopsy (various): 34.8% (8/23) ENT exam: 4.3% (1/23) Pap with gynecological exam: 8.7% (2/23) Correlation with CT: 2.2% (5/23) Correlation with MRI: 4.3% (1/23) Observation: 26.1% (6/23)	False Positive Results PET/CT vs. CT: 21/165 (12.7%) vs. 7/407 (1.7%) (23 visits vs. 7 visits) Sensitivity PET/CT vs. CT: 100% (95% CI 30.5 – 100.0) vs. 100% (95% CI 30.5 – 100.0) Specificity

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	DLBCL Stage III or IV: 39/106 (36.8%) Standard International Prognostic Index: Low: 59.4% (63/106) Low-intermediated: 21.7% (23/106) High-intermediate: 12.3% (13/106) High: 6.6% (7/106) Comparator (both modalities used in the same patients) PET/CT vs CT Median follow-up: NR		CT: Biopsy (various): 28.6% (2/7) Correlation with MRI: 28.6% (2/7) Short-term CT follow-up: 28.6% (2/7) Observation: 14.3% (1/7) Proportion of patients with relapse: 14.2% (15/106)	PET/CT vs. CT: 86.1% (95% CI 79.8 – 91.0) vs. 98.3% (95% CI 96.5 – 99.3) PPV PET/CT vs. CT: 11.5% (95% CI 2.6 – 30.2) vs. 30.0% (95% CI 7.0 – 65.2) NPV PET/CT vs. CT: 100% (95% CI 97.4 – 100.0) vs. 100% (95% CI 99.1 – 100.0)

ALCL = Anaplastic large-cell lymphoma; Allo = Allogenic stem cell transplant; ASCT = Autologous stem cell transplant; auto-HCT = Autologous hematopoietic cell transplantation; CT = Computed Tomography; DLBCL = Diffuse large B-cell lymphoma; EFS = Event Free Survival; f/u = follow up; F = Female; GTV = Gross Tumor Volume; IPI = International Prognostic Index; M = Male; NPV = Negative Predictive Value; NR = Not Reported; NR = Not reported; OS = Overall Survival; PET/CT = Combined Positron Emission Tomography and Computed Tomography; PET = Positron Emission Tomography; PFS = Progression Free Survival; PPV = Positive Predictive Value; RT = Radiation therapy

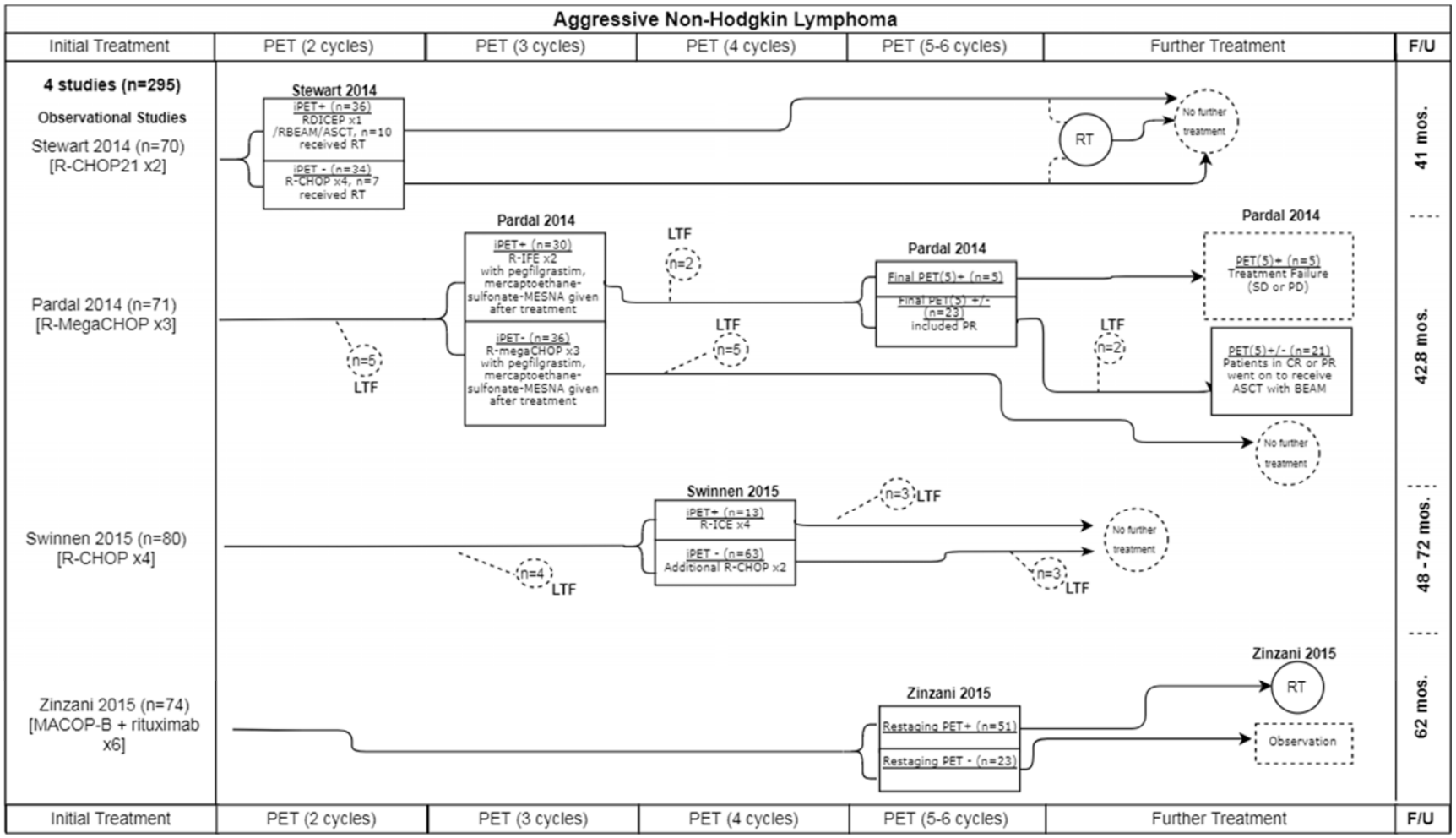
*Study does not define PD anywhere within the text.

Appendix Figure G1. Flowchart of Treatment Adaptations: PET-adapted therapy in aggressive Non-Hodgkin Lymphoma, RCTs



ASCT = autologous stem cell transplant; BEAM = BCNU + etoposide + cytarabine + melphalan ; Burkitt Protocol = HD-MTX + cytarabine, high dose cyclophosphamide and ifosfamide, split-dose doxorubicin and etoposide, vincristine, vindesine, and dexamethasone; CHOP = cyclophosphamide + adriamycin + vincristine + prednisone; F/U = follow-up; HDT = high dose therapy;HL = Hodgkin Lymphoma; iPET = interim positron emission tomography; LTF = lost to follow-up; mos. = months; MTX = methotrexate; PET = positron emission tomography; R-ACVBP14 = rituximab with doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; R-CHOP(14) = rituximab with cyclophosphamide + adriamycin + vincristine + prednisone; RCTs = randomized controlled trials; RT = radiation therapy; Z-BEAM = Zevalin with BCNU + etoposide + cytarabine + melphalan

Appendix Figure G2. Flowchart of Treatment Adaptations: PET-adapted therapy in aggressive Non-Hodgkin Lymphoma, Observational Studies



ASCT = autologous stem cell transplant; BEAM = BCNU + etoposide + cytarabine + melphalan ; CR = complete response; F/U = follow-up; iPET = interim positron emission tomography; LTF = lost to follow-up; MACOP-B = ; mos. = months; PET = positron emission tomography; PR = partial response; R-CHOP(14) = rituximab with cyclophosphamide + adriamycin + vincristine + prednisone; RBEAM = rituximab with BCNU + etoposide + cytarabine + melphalan ; RDICEP = rituximab with dexamethasone + cyclophosphamide + etoposide + cisplatin + mesna + Septra; R-ICE = rituximab + Ifosfamide, carboplatin, etoposide ; R-MegaCHOP = rituximab + Cyclophosphamide 3 g/m2, Vincristine 2 mg, Adriamycin 75 mg/m2, Prednisone; RT = radiation therapy;

Appendix Table G2. Study Characteristics and Patient Demographics: PET-adapted therapy in aggressive Non-Hodgkin Lymphoma, escalation, interim PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
RCTS						
Casasnovas 2017 *GELA/LYSA trial* **RCT (non-PET-randomized)** RoB Moderately High *Funding: funded by the French Government (PHRC 2007), Amgen, and Roche.* *COI: One or more authors received honoraria, research funding, and/or consulted for Roche, Amgen and other industry companies.*	High risk DLBCL (IPI score of 2 or 3) Proportion with Ann Arbor Stage (): -I or II: 3.2% -III or IV: 96.8% Subtypes -DLBCL: 80% -Primary Mediastinal B-Cell: 20% B Symptoms: 50% (112/222) Bone Marrow Involvement: 18.5% (41/222) Extranodal Sites (>1): 65% (145/222) Bulky Disease (>10 cm mass): 25% (55/222)	N = NR recruited 222 randomized, 200 treated, 211 analyzed (ITT) Median Age (range): 46 (18-59) years Male: 59%	Randomized to R-ACVBP14 (Arm A) OR R-CHOP14 (Arm B) Previously treated: No	PET + (SUVmax: PET0-2 >66%; PET0-4 >70%) PET -	**PET Timing:** Interim PET2 (2 cycles) and Interim PET4 (4 cycles) **Groups not randomized by PET rating** **1. PET2 + / PET4 - (n=48)** 2 cycles of high-dose methotrexate, then a high-dose therapy (BEAM or Z-BEAM), followed by ASCT **2. PET2 - / PET4 - (n=52)** Standard immunochemotherapy: • For R-ACVBP14 group: 2 cycles of high-dose methotrexate, 4 cycles rituximab, ifossfamide, etoposide, and 2 cycles cytarabine • For R-CHOP14 group: 4 additional cycles of R-CHOP14 **PET2+/PET4+ (n=96)** Salvage Therapy **PET2-/PET4+ (n=4)** Salvage Therapy **Median F/U 45 mos (range 1 to 63 mos.)**	**Clinical** OS (3-year, 5-year) CR rate EFS PFS **Safety** PET-related: Treatment- Related: Toxicities

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
Duhrsen 2018 *PETAL trial* **RCT (non-PET-randomized)** RoB Moderately Low *Funding: Funded by Deutsche Krebshilfe (Grants No. 107592 and 110515), Amgen Germany, and Roche Pharma* *COI: One or more authors received honoraria, research funding, reimbursements, and/or were consultants/advisors/speakers for the study funders and other industry organizations.*	Aggressive B-cell or T-cell Lymphoma Subtypes -B Cell: 85.4% (736/862) -T Cell: 8.8% (76/862) -Diagnoses Inconsistent with inclusion criteria: 5.8% (50/862) CD20 Lymphoma: -Positive: 91.2% (786/862) -Negative: 8.8% (76/862) Ann Arbor Staging: -III or IV: 59.7% (512/862) Extranodal Sites (>1): 30.1% (258/862)	N= 862 evaluated, 363 randomized (ITT), 499 nonrandom allocation Median Age (range): 60 (18-80) years Male: 56.5%	R-CHOP x2	PET+ (above background) PET-	**PET Timing:** iPET (2 cycles), End of Treatment (iPET+ only, who had PD) **1. iPET+ (randomized) (n=108)** Randomized to: 1a. R-CHOP x6 (n=52, includes n=8 CD20-negative patients) 1b. Burkitt Protocol x6 (HD-MTX + cytarabine, high dose cyclophosphamide and ifosfamide, split-dose doxorubicin and etoposide, vincristine, vindesine, and dexamethasone) (n=56, includes n=11 CD20-negative patients) **2. iPET- CD20-positive (randomized) (n=255)** Randomized to: 2a. additional R-CHOP x4 (n=129) 2b. additional R-CHOP x4 plus additional Rituximab x2 (n=126) includes n=2 CD20-negative patients) iPET+ / End of Treatment PET+ (n=31) N=13 received additional treatment (n=4 RT, n=6 additional chemotherapy, n=1 additional rituximab, n=2 autologous or allogeneic SCT) End of Treatment PET – (n=18) Received no further treatment **Additional non-randomized groups:**	**Clinical** Treatment Response OS PFS EFS Mortality **Safety** PET-related: Treatment- Related: Toxicities

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
					3. iPET- / CD20-positive (nonrandom) (n=444) Received either: a. additional R-CHOP x4 (n=251) b. additional R-CHOP x4 plus additional Rituximab x2 (n=193) 4. iPET- /CD20-negative (n=57) Received CHOP x4 **Median F/U (range): 44.1 mos (iPET+)** **Median F/U (range): 54.1 mos (iPET-)**	
Observational Studies (prospective)						
Pardal 2014 **Prospective cohort** RoB Moderately Low Funding: NR COI: None reported	High-Risk DLBCL or grade 3B follicular lymphoma CD20+ (aaIPI score ≥1) Ann Arbor: -III: 28% (20/71) -IV: 72% (51/71) Subtypes: -DLBCL:90% -Grade 3BFL: 10% Extranodal Sites (>1):	N= 71 recruited, 66 allocated Median age (range): 55 (25 to 69) years Male: 61%	R-MegaCHOP x3 Previously treated: No	PET + (5-PS ≥4) PET -	**PET Timing:** Interim (3 cycles) Non-randomized allocation based on PET results: **1. iPET + (n=30)** R-IFE x2 pegfilgrastim and mercaptoethane-sulfonate-MESNA given after first-line treatment Patient in CR or PR (n=21) went on to receive ASCT with BEAM **2. iPET – (n=36)** Additional R-MegaCHOP x3 pegfilgrastim and mercaptoethane-sulfonate-MESNA given treatment	**Clinical** OS (3-year, 4-year) PFS (3-year, 4-year) CR, PR, PD **Safety** PET-related: Overtreatment Treatment- Related: Toxicities (CTCAE), Tumor-Related

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
	52% (37/71) B Symptoms: 49% (35/71) Bulky Disease (>10cm): 38% (27/71) Bone Marrow Involvement: 23% (15/71)				**Median F/U (range): 42.8 (7.2 to 58.4) mos**	
Stewart 2014 **Prospective cohort** RoB Moderately High *Funding: Grant from Roche, independently monitored by Scimega Research Inc.* *COI: Data controlled and analyzed by investigators. One or more authors reported grants/personal fees from study funder outside the conduct of this study.*	High risk DLBCL (stage III/IV) Ann Arbor Stage: -III: 29% -IV: 79% Proportion with ECOG status 2 to 4: 51% (36/70) Bone Marrow Involvement: 34% (24/70) Extranodal Sites (>1): 59% (41/70)	N=71 enrolled, 70 treated, 70 analyzed Median Age (range): 53.5 (19-65) years Male: NR	R-CHOP21 x2 Previously treated: No	PET+ (5-PS ≥4) PET-	**PET Timing:** Pre-treatment PET (not performed), Interim (2 cycles) Non-randomized allocation based on PET Rating: **1. iPET+ (n=36)** RDICEP x1 followed by BEAM/ASCT **2. iPET- (n=34)** Additional R-CHOP x4 **Median F/U: 41 mos**	**Clinical** OS (3-year) PFS (3-year) Mortality **Safety** PET-related: NR Treatment- Related: Toxicities, ASCT-related, Tumor-related, Secondary Malignancies

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
	Bulky Disease (>10cm): 46% (32/70) B Symptoms: 51% (36/70)					
Swinnen 2015 *ECOG-ACRIN Cancer Research Group* **Prospective cohort** RoB Moderately High Funding: Supported partly by grants from Public Health Service, National Cancer Institute, National Institutes of Health and Department of Health and Human Services. COI: NR	DLBCL (stage III/IV or bulky stage II) IPI Scores: -0 or 1: 14% -2: 31% -3: 36% -4 or 5: 19% modified Ann Arbor Staging: -II/IIE: 10% -III/IV: 90% ECOG Status: -0: 53% (42/80) -1: 36% (29/80) -2: 10% (8/80) -3: 1% (1/80) Subtypes -DLBCL: 82.5% (66/80) Extranodal Sites (≥1): 67.5% (54/80)	N=100 enrolled, 80 eligible and recruited, 76 treated, 68 completed Median Age (range): 62 (20-74) years Male: 58% (46/80)	R-CHOP x4 Previously Treated: No	PET+ (3 or 4 on modified 'ECOG criteria') PET-	**PET Timing:** Pre-treatment, Interim (during 3rd cycle), End of Treatment Allocation based on PET rating: **<u>1. iPET + (n=13)</u>** R-ICE x 4 **<u>2. iPET- (n=63)</u>** Additional RCHOP x2 **Median F/U: 48-72 mos**	**Clinical** OS (2-year, 3-year, 4-year) PFS (2-year, 3-year, 4-year) CR, PR, SD, PD NPV Mortality **Safety** PET-related: Treatment- Related: Toxicities (CTCAE)

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
	Bulky Disease (>10cm): 33% (26/80) Bone Marrow Involvement: 16% (13/80) B Symptom: 29% (23/80)					

5-PS = five point scale; ASCT = ; BEAM = BCNU + etoposide + cytarabine + melphalan; cGy = centigrays; cm = centimeter; COI = conflict of interest; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DFS = disease free survival; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; Gy = Grays; HD-MTX = High Dose Methotrexate; IPI = International Prognostic Index; ITT = intention to treat; mos. = months; NHL = non hodgkin lymphoma; NPV = negative predictive value; NR =not reported; OS = overall survival; PET =positron emission tomography; PD = progressive disease; PFS = progression free survival; PR = partial response; R-ACVBP = rituximab with doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone ; RCHOP = rituximab + cyclophosphamide + adriamycin + vincristine + prednisone; RDICEP = rituximab with dexamethasone + cyclophosphamide + etoposide + cisplatin + mesna + Septra; R-ICE = rituximab + Ifosfamide, carboplatin, etoposide ; R-IFE = rituximab, ifosfamide, etoposide; R-MegaCHOP = rituximab + Cyclophosphamide 3 g/m2, Vincristine 2 mg, Adriamycin 75 mg/m2, Prednisone; RoB = risk of bias; RT = radiation therapy; SD = stable disease; SUVmax = standardized uptake value maximum; Z-BEAM = BEAM with Zevalin;

Appendix Table G3. Study Characteristics and Patient Demographics: PET-adapted therapy in aggressive Non-Hodgkin Lymphoma, de-escalation, interim PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
RCTS						
Lamy 2018 *LYSA/GOELAMS trial* **RCT (PET- randomized)** RoB Moderately Low *Funding: Supported by Roche* COI: T.L. received grants from Genentech. G.D. received an unrestricted research grant from Roche; G.C. served as a consultant for Celgene and Roche, and received honoraria from Bristol-Myers Squibb, Sanofi, Gilead Sciences, Roche, and Janssen Pharmaceutical. S.L.G. received grants, personal fees, and nonfinancial support from Genentech, received personal fees from Celgene, and received grants and personal fees from Janssen-Cilag outside the present work. E.D. received grants from Genentech. The remaining authors declare no competing financial interests.	Non-bulky DLBCL Stage I and II limited-stage vs. activated B-cell phenotype: 57% vs 27% Favorable IPI score (0 or 1): 94% (315/334) Extranodal involvement: 39%	N=334 enrolled, 319 evaluable patients [ITT] (n=281 achieved CR and were treated according to initial random assignment, n=38 achieved PR and were treated according to a different treatment plan) Age >60: 36% (121/334)	4-cycles of R-CHOP	A negative scan was defined as having no abnormally increased 18F-FDG at any site	**PET Timing**: Interim PET4 (4 cycles) **1. PET4+ (n=38)** 1a. No additional therapy (n=3) 1b. R-CHOP x2 (n=5) 1c. R-CHOP x2 + 40 Gy RT (n=27) 1d. DHAP consolidation (n=2) 1e. DHAP consolidation + RT (n=1) **2. PET4- (randomized) (n=281)** Randomized to: 2a. R-CHOP x2 (n=137) 2b. R-CHOP x2 + 40 Gy RT (n=144) *[For ITT analysis: R-CHOP arm, n=159; R-CHOP plus RT arm, n=160]* **Median follow-up: 64 months (range, 24-132)**	5-year EFS 5-year OS Relapse rate Mortality Toxicity (including RT specific toxicities)

CR = Complete Response, PR = Partial response, DLBCL = Diffuse Large B-cell Lymphoma, RT = Radiotherapy.

Appendix Table G4. Study Characteristics and Patient Demographics: PET-adapted therapy in aggressive Non-Hodgkin Lymphoma, escalation, end of treatment PET

Author Study Design RoB	Diagnosis, Stage	Population N, Age, Sex	First-Line Treatment, Previous Treatment	Criteria for PET+ and PET -	Number treatment cycles before iPET, Treatment groups after iPET, Follow-up (post allocation)	Outcomes
Observational Studies (retrospective)						
Zinzani 2015 **Retrospective Cohort** RoB Moderately High *Funding: Funded partly by Italian Association for Leukemias, Lymphomas and Myeloma (AIL, Bologna, Italy). Authors declare funder had no role in design, collection, analysis or interpretation of data or writing of report.* COI: None declared.	aggressive NHL [Primary mediastinal large B-cell lymphoma (PMLBCL)] Ann Arbor Staging: -II/IIE: 68%, -III/IV: 32% B Symptoms: 35% (26/74) Bulky Mass (>10cm): 93% (69/74) Bone Marrow Involvement: NR Extranodal Sites (>1): NR	N=74 Median Age (range): 34 (18 to 63) years Male: 40.5%	MACOP-B plus rituximab x6 Previously Treated: No	PET+ (5-PS ≥3) PET-	**PET Timing:** restaging (6 cycles) and 3 mos. post-treatment Allocation based on PET rating **1. PET+ (n=51)** Mediastinal RT (tumor dose ranging from 30–36 Gy over 4–5 weeks at 180 cGy/day for 5 days/week) **2. PET- (n=23)** Observation **Median F/U (range): 62 (28-112) mos**	**Clinical** OS DFS PFS CR/disease progression Relapse **Safety** PET-related: NR Treatment-Related: Toxicities (CTCAE)

5-PS = five point scale; cGy = centigrays; cm = centimeter; COI = conflict of interest; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DFS = disease free survival; Gy = Grays; mos. = months; NHL = non hodgkin lymphoma; NR =not reported; OS = overall survival; PET =positron emission tomography; PFS = progression free survival; RoB = risk of bias; RT = radiation therapy;

Appendix Table G5. Detailed data abstraction: PET-adapted therapy in aggressive Non-Hodgkin Lymphoma, escalation, interim PET

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
RCTS			
Casasnovas 2017 *GELA/LYSA trial* **RCT** High risk DLBCL (aaIPI score of 2 or 3) RoB Moderately High	**PET Timing:** Interim PET2 (2 cycles) and Interim PET4 (4 cycles) **Groups not randomized by PET rating** **1. PET2 + / PET4 - (n=48)** 2 cycles of high-dose methotrexate, then a high-dose therapy (BEAM or Z-BEAM), followed by ASCT **2. PET2 - / PET4 - (n=52)** Standard immunochemotherapy: • For R-ACVBP14 group: 2 cycles of high-dose methotrexate, 4 cycles rituximab, ifossfamide, etoposide, and 2 cycles cytarabine • For R-CHOP14 group: 4 additional cycles of R-CHOP14 **PET2+/PET4+ (n=96)** Salvage Therapy **PET2-/PET4+ (n=4)** Salvage Therapy **Median F/U 45 mos (range 1 to 63 mos.)**	**First-Line Treatment Response** -CR: 43% (91/211) -PR: 47% (99/211) -SD: 2% (4/211) -PD: 3% (7/211) -not evaluable: 5% (10/211) **CR Rate, all patients:** 47.4% (100/211) **4-Year OS** Interim PET2 only: iPET2+ (n=48) vs iPET2 – (n=52) 90.4 (95%CI 81.0 to 95.1) vs 89.6 (85.0 to 92.2), p=0.210; Interim PET4 only: iPET4+ (n=100) vs iPET4 – (n=100) 88.9 (82.1 to 94.4) vs 80 (69 to 87.5), p=0.080 Interim PET 2/4: iPET2+ / iPET 4- vs iPET2- / iPET4- 90.2 vs 89.8, p=0.900 **4-Year PFS** Interim PET2 only: iPET2+ vs iPET2 - 85% (95% CI 71.1 to 92.6) vs 75% (95%CI 60.9 to 84.6), p=0.260;	**PET-specific, PET+ vs. PET-:** None reported. **Treatment-Related, all patients:** -received ≥1 red blood cell transfusion for hematological toxicity: 47.9% (101/211) -received ≥ 1 platelet transfusion for hematological toxicity: 10.9% (23/211) **Tumor-Related, PET + vs. PET-:** NR **Secondary Malignancies, All Patients:** Secondary Primary Cancers: 2% (4/211)

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
		Interim PET4 only: iPET4+ (n=100) vs iPET4 – (n=100) 79.8 (95%CI 79.4 to 86.4) vs 72.9 (95%CI 63.1 to 80.6), p=0.160 Interim PET2/4: iPET2+ /iPET 4- vs iPET2- /iPET4- 74.5% vs 87.2%, p > 0.14 **Mortality Rate, all patients** -All Causes: 18% (39/222) -lymphoma progression: 10% (22/222) -toxicity of study treatment: 2/222 -subsequent treatment: 1% (1/222) -unknown: 1.4% (3/222) **Outcomes According to ΔSUVmax** **4-Year OS, patients with PET0-2 ΔSUVmax >66% vs patients ≤66%** 87% (95% CI 80% to 92%) vs 69% (95% CI 49% to 83%), p=0.0034 **4-Year PFS, patients with PET0-2 ΔSUVmax >66% vs patients ≤66%** 80% (95% CI 73% to 86%) vs 56% (95% CI 37% to 72%), p=0.005	
Duhrsen 2018 *PETAL trial* **RCT** RoB Moderately Low	**PET Timing:** iPET (2 cycles), End of Treatment (iPET+ only, who had PD) **1. iPET+ (randomized) (n=108)** Randomized to: 1a. R-CHOP x6 (n=52, includes n=8 CD20-negative patients)	**Randomized (ITT) Data Set** **Treatment Response** **iPET+ (n=108) vs iPET – (n=255)** -ORR: 69.2% (54/78) vs 92.1% (220/239) -CR: 39.7% (31/78) vs 68.6% (164/239) **Mortality, iPET+ vs iPET-**	**PET-specific, PET+ vs. PET-:** NR **Treatment-Related (Grade III or IV), iPET+ vs iPET-:** -Anemia: 35.1% (38/108) vs 13.7% (35/255); RR 2.56 (95%CI 1.41 to 2.69), p<0.001

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
Aggressive NHL (B-Cell and T-Cell)	1b. Burkitt Protocol x6 (HD-MTX + cytarabine, high dose cyclophosphamide and ifosfamide, split-dose doxorubicin and etoposide, vincristine, vindesine, and dexamethasone) (n=56, includes n=11 CD20-negative patients) **2. iPET- / CD20-positive (randomized) (n=255)** Randomized to: 2a. additional R-CHOP x4 (n=129) 2b. additional R-CHOP x4 plus additional Rituximab x2 (n=126) includes n=2 CD20-negative patients) End of Treatment PET+ (n=31) N=13 received additional treatment (n=4 RT, n=6 additional chemotherapy, n=1 additional rituximab, n=2 autologous or allogeneic SCT) End of Treatment PET – (n=18) Received no further treatment **Additional non-randomized groups:** 3. iPET- / CD20-positive (nonrandom) (n=444) Received either: a. additional R-CHOP x4 (n=251) b. additional R-CHOP x4 plus additional Rituximab x2 (n=193) 4. iPET- /CD20-negative (n=57) Received CHOP x4 **Median F/U (range): 44.1 mos (iPET+)** **Median F/U (range): 54.1 mos (iPET-)**	-Mortality, Treatment-Related: 3.7% (4/108) vs 2% (5/255); RR 1.88 (95%CI 0.77 to 2.19), p=0.332 **iPET+ (group 1a, n=52) vs iPET+ (group 1b, n=56) vs iPET – (group 2a, n=129) vs iPET- (group 2b, n=126)** **Treatment Response,** -ORR: 69.8% (30/43) vs 68.6% (24/35) vs 93.3% (111/119) vs 90.8% (109/120) -CR: 30.2% (13/43) vs 51.4% (18/35) vs 67.2% (80/119) vs 70% (84/120) **2-year OS** 63.6 (95% CI 48.5 to 75.3) vs 55.4 (95% CI 40.7 to 67.8) vs 88.2 (95% CI 81.2 to 92.7) vs 87.2 (95% CI 79.9 to 91.9) **2-year PFS** 49.4 (95% CI 34.7 to 62.4) vs 43.1 (95% CI 29.2 to 56.2) vs 82.0 (95% CI 74.2 to 87.7) vs 77.5 (95% CI 69.1 to 83.9) **2-year EFS** 42.0 (95% CI 28.2 to 55.2) vs 31.6 (95% CI 19.3 to 44.6) vs 76.4 (95% CI 68.0 to 84.2) vs 73.5 (95% CI 64.8 to 80.4) **Full Population Set (n=862)** **2-year OS** 59.3 (95%CI 49.0 to 68.2) vs 88.2 (95%CI 85.6 to 90.3)	-Leukopenia: 70.4% (76/108) vs 57.2% (146/255); RR 1.23 (95%CI 1.04 to 1.44), p=0.022 -Neutropenia: 28.7% (31/108) vs 19.6% (50/255); RR 1.46 (95%CI 0.99 to 1.88), p=0.060 -Thrombocytopenia: 40.7% (44/108) vs 11.4% (29/255); RR 3.58 (95%CI 1.73 to 3.31), p<0.0001 -Infection: 36.1% (39/108) vs 12.9% (33/255); RR 2.79 (95%CI 1.48 to 2.83), p<0.0001 -Mucositis: 25% (27/108) vs 2% (5/255); RR 12.75 (95%CI 1.90 to 4.44), p<0.0001 -Diarrhea: 7.4%(8/108) vs 2% (5/255); RR 3.77 (95%CI 0.96 to 2.58), p=0.070 -Creatinine*: 3.7% (4/108) vs 2% (5/255); RR 1.88 (95%CI 0.77 to 2.19), p=0.332 -Mortality, Treatment-Related: 3.7% (4/108) vs 2% (5/255); RR 1.88 (95%CI 0.77 to 2.19), p=0.332 **Treatment-Related (Grade III or IV), iPET+ (group 1b: escalation with Burkitt protocol) vs iPET+ (group 1a: standard continuation)** -Anemia: 44.6% (25/56) vs 25% (13/52), p=0.044; RR 1.79 (95%CI 0.98 to 2.16) -Leukopenia: 80.4% (45/56) vs 59.6% (31/52), p=0.022; RR 1.35 (95%CI 1.00 to 1.67), p=0.046 -Neutropenia: 33.9% (19/56) vs 23.1% (12/52); RR 1.47 (95% CI 0.86 to 1.99), p=0.206 -Thrombocytopenia: 58.9% (33/56) vs 21.2% (11/52), p<0.001; RR 2.79 (95%CI 1.23 to 2.72)

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
		2-year PFS 46.1 (95%CI 36.1 to 55.6) vs 79.4 (95%CI 76.3 to 82.1) **2-year EFS** 36.7 (95%CI 27.4 to 46.2) vs 75.6 (95%CI 72.3 to 78.5) **<u>Post-Hoc Analysis (n=844)</u>** **Survival, iPET+ vs iPET – (when PET+ is 3-5 on 5-PS)** **2-year OS** 83.0 (95%CI 79.7 to 85.8) vs 88.9 (95%CI 84.2 to 92.2) **2-year PFS** 73.9 (95% CI 70.2 to 77.3) vs 78.8 (95%CI 73.1 to 83.4) **2-year EFS** 68.7 (95%CI 64.7 to 72.3) vs 76.0 (95%CI 70.2 to 80.9)	-Infection: 50% (28/56) vs 21.2% (11/52), p=0.002; RR 2.36 (95%CI 1.11 to 2.49) -Mucositis: 37.5% (21/56) vs 11.5% (6/52), p=0.003; RR 3.25 (95%CI 1.10 to 2.76) -Diarrhea: 5.4% (3/56) vs 9.6% (5/52); RR 0.56 (95%CI 0.62 to 1.77), p=0.870 -Creatinine*: 1.8% (1/56) vs 5.8% (3/52); RR 0.31 (95%CI 0.61 to 1.83), p=0.843 **Tumor-Related, PET + vs. PET-:** NR **Secondary Malignancies, All Patients:** NR
Observational Studies (prospective)			
Pardal 2014 **Prospective cohort** RoB Moderately Low High-Risk DLBCL or grade 3B follicular lymphoma CD20+	**PET Timing:** Interim (3 cycles) and End of Treatment (4 cycles) Non-randomized allocation based on PET results: **<u>1. PET + (n=30)</u>** R-IFE x2 pegfilgrastim and mercaptoethane-sulfonate-MESNA given after treatment	**<u>ITT Data Set</u>** **Treatment Response, PET+ vs PET-** -CR: 53% (16/30) vs 78% (28/36) -PR: 10% (3/30) vs 0% (0/36) -PD: 23% (7/30) vs 8% (3/36) -Not Evaluable: 14% (4/30) vs 14% (5/36)	**PET-specific, PET+:** -Proportion of PET1 + patients who may have been overtreated: 56.6% (17/30) **Treatment-Related, all patients:** Serious Adverse Event leading to dropout: 1.4% (1/71) Mortality, Toxicity of Study Treatment: 2.8% (2/71)

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
Includes retrospective semi-quantitative analysis of 51 patients	patient in CR or PR went on to receive ASCT with BEAM **2. PET – (n=36)** Additional R-MegaCHOP x3 pegfilgrastim and mercaptoethane-sulfonate-MESNA given after treatment **Median F/U (range): 42.8 (7.2 to 58.4) mos**	**4-Year OS, All Patients** 78% **3 –Year OS, PET+ vs PET-** 73% vs 89%, p=0.11 **4-Year PFS, All Patients** 67% **3 –Year PFS, PET+ vs PET-** 57% vs 81%, p=0.023 **Mortality** -All Causes: 21.1% (15/71) -Lymphoma Progression: 15.5% (11/71) -Toxicity of Study Treatment: 2.8% (2/71) -other:2.8% (2/71)	**Tumor-Related, all patients:** -Mortality, Lymphoma Progression: 15.5% (11/71) **Secondary Malignancies, PET+ vs PET-:** -Adenocarcinoma: 0% (0/30) vs 2.8% (1/36)
Stewart 2014 **Prospective cohort** RoB Moderately High High risk DLBCL	**PET Timing:** Pre-treatment PET (not performed), Interim (2 cycles) **1. PET+ (n=36)** RDICEP x1 followed by BEAM/ASCT **2. PET- (n=34)** Additional R-CHOP x4 **Median F/U: 41 mos**	**3-Year OS, PET+ vs PET-** 70.5% vs 68.4% **3-Year PFS, PET+ vs PET-** 52.7% vs 65.2% **Mortality:** Non-Relapse Death: 8.3% (3/36) vs 0% (0/34); RR IC Relapse Death: 25% (9/36) vs 23.5% (8/34); RR 1.06 (95%CI 0.72 to 1.84), p=0.562	**PET-specific, PET+ vs. PET-:** NR **Treatment-Related, PET+ vs. PET -:** Febrile Neutropenia: 27.7% (10/36) vs 8.8% (3/34); RR 3.15 (95%CI 0.895 to 2.48), p=0.120 Bacteremia: 2.7% (1/36) vs (0/34); RR IC Transient Pancreatitis: 2.7% (1/36) vs (0/34); RR IC Transient Pericarditis: 2.7% (1/36) vs (0/34); RR IC Transient Atrial Fibrillation: 2.7% (1/36) vs (0/34); RR IC Transient renal insufficiency: 2.7% (1/36) vs (0/34); RR IC

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
			RBEAM/ASCT Treatment-Related: -Febrile Neutropenia: 33.3% (12/36) -Late Onset Neutropenia: 11.1% (4/36) -Late Onset Neutropenia leading to fever: 8.3% (3/36) -Late Onset Neutropenia leading to Pneumonia: 6% (2/36) -Early Non-Relapse Mortality: 3% (1/36) -Low levels of ≥1 Antibody Level: 44.4% (16/36) -Late Pulmonary Infection-related Mortality: 6% (2/36) -Recurrent Pneumonia treated with with monthly immunoglobulin: 6% (2/36) **Radiation Treatment-Related Events, PET+ (n/N) vs PET- (n/N):** -patients with bulky disease who received RT: 1 event (1/4) vs 0 events (0/8) -patients with bulky disease who did not receive RT: 7 event (7/12) vs 5 events (5/8) **Tumor-Related, PET+ vs. PET -:** -Relapse: 25% (9/36) vs 44.1% (15/34); RR 0.57 (95%CI 0.58 to 1.38), p=0.618 **Secondary Malignancies, PET+ vs PET-:** Relapse with development of CNS involvement: 2.7% (1/36) vs 14.7% (5/34); RR 0.19 (95%CI 0.56 to 1.64), p=0.884
Swinnen 2015 *ECOG-ACRIN Cancer Research Group* **Prospective cohort**	**PET Timing:** Pre-treatment, Interim (during 3rd cycle), End of Treatment **Number of cycles before iPET:** 3 Allocation based on PET rating	**Mid-Treatment Response Assessment(by CT), PET+ vs PET-:** -CR: 0% (0/13) vs 33.3% (21/63) -PR: 46.2% (6/13) vs 38.1% (24/63) -SD: 0% (0/13) vs 3.2% (2/63)	**PET-specific, PET+ vs. PET-:** NR **Treatment-Related Toxicities, PET+ vs. PET – (proportions calculated from percentages):**

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
RoB Moderately High DLBCL (stage III/IV or bulky stage II) 4/80 did not receive interim PET, and 4/74 did not receive end of treatment PET	**1. iPET + (n=13)** R-ICE x 4 **2. iPET- (n=63)** Additional RCHOP x2 **Median F/U: 48-72 mos**	-Unevaluable (scan not conducted): 0% (0/13) vs 4.8% (3/63) **End of Treatment Response Assessment (by CT), PET+ vs PET -:** -CR: 30% (3/10) vs 71.7% (43/60) -CR unconfirmed: 20% (2/10) vs 18.3% (11/60) -PR: 0% (0/10) vs 6.7% (4/60) -PD: 50% (5/10) vs 3.3% (2/60) **All Patients:** **2-Year OS** 90% (90% CI 83% to 94%) **3-Year OS** 89% (90% CI 81% to 93%) **4-Year OS** 86% (90% CI 78% to 91%) **2-Year PFS** 70% (90% CI 60% to 78%) **3-Year PFS** 69% (90% CI 59% to 77%) **4-Year PFS** 64% (90% CI 53% to 73%) **iPET+ (n=13) vs iPET- (n=61)** **2-Year OS** 77% (90% CI 51% to 90%) vs 93% (90% CI 86% to 97%)	-Anaemia: 54% (7/13) vs 5% (3/61); RR 10.9 (95%CI 1.09 to 2.84), p=0.020 -Neutropenia: 69% (9/13) vs 15% (9/61); RR 4.69 (95%CI 1.12 to 2.70), p=0.015 -Thrombocytopenia: 92% (12/13) vs 5% (3/61); RR 18.77 (95%CI 1.42 to 3.43), p<0.001 -Febrile (fever) Neutropenia: 0% (0/13) vs 3% (3/61); RR IC -Nausea/Vomiting: 8% (1/13) vs 0% (0/61); RR IC -Fatigue: 8% (1/13) vs 2% (1/61); RR 4.69 (95%CI 0.72 to 2.20), p=0.411 -Mortality, Treatment Toxicity: 0% (0/13) vs 1.6% (1/61); RR IC -withdrawal from treatment: 3 vs 3 **Tumor-Related, PET + vs. PET -:** NR **Secondary Malignancies, PET+ vs PET-:** NR

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
		3-Year OS 69% (90% CI 43% to 85%) vs 93% (90% CI 86% to 97%) **4-Year OS** 69% (90% CI 43% to 85%) vs 90% (90% CI 81% to 95%) **2-Year PFS** 42% (90%CI 19% to 63%) vs 76% (90%CI 65% to 84%) **3-Year PFS** 33% (90%CI 13% to 55%) vs 71% (90%CI 59% to 80%) **4-Year PFS** 33% (90%CI 13% to 55%) vs 71% (90%CI 59% to 80%) **NPV, % (n/N) (90% CI), (n/N)** NPV of iPET 75% (43/57) (90% CI 64% to 84%) NPV of End of Treatment PET 79% (45/57) (90% CI 68% to 87%) **Mortality, iPET+ vs iPET-** -Treatment Toxicity: 0% (0/13) 1.6% (1/61); RR IC	

5-PS = five point scale; ASCT = autologous stem cell transplantation; BEAM = BCNU + etoposide + cytarabine + melphalan; cGy = centigrays; cm = centimeter; CI = confidence interval; COI = conflict of interest; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DFS = disease free survival; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; Gy = Grays; HD-MTX = High Dose Methotrexate; IC = incalculable; iPET= interim positron emission tomography; IPI = International Prognostic Index; ITT = intention to treat; mos. = months; NHL = non-Hodgkin lymphoma; NPV = negative predictive value; NR =not reported; OS = overall survival; PET =positron emission tomography; PD = progressive disease; PFS = progression free survival; PR = partial response; R-ACVBP = rituximab with doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone ; RCHOP = rituximab + cyclophosphamide + adriamycin +

vincristine + prednisone; RDICEP = rituximab with dexamethasone + cyclophosphamide + etoposide + cisplatin + mesna + Septra; R-ICE = rituximab + Ifosfamide, carboplatin, etoposide ; R-IFE = rituximab, ifosfamide, etoposide; R-MegaCHOP = rituximab + Cyclophosphamide 3 g/m2, Vincristine 2 mg, Adriamycin 75 mg/m2, Prednisone; RoB = risk of bias; RR = risk ratio; RT = radiation therapy; SD = stable disease; SUVmax = standardized uptake value maximum; Z-BEAM = BEAM with Zevalin;
* Authors do not make clear what this outcome (creatinine) implies (abnormal high or low levels, or else).

Appendix Table G6. Detailed data abstraction: PET-adapted therapy in aggressive Non-Hodgkin Lymphoma, de-escalation, interim PET

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
RCTS			
Lamy 2018 *LYSA/GOELAMS trial* **RCT (PET- randomized)** RoB Moderately Low	**Treatment prior to iPET**: 4-cycles of R-CHOP **Groups** **1. PET4- (randomized) (n=281)** Randomized to: 1a. R-CHOP x2 (n=137) 1b. R-CHOP x2 + 40 Gy RT (n=144) **2. PET4+ (n=38)** 2a. No additional therapy (n=3) 2b. R-CHOP x2 (n=5) 2c. R-CHOP x2 + 40 Gy RT (n=27) 2d. DHAP consolidation (n=2) 2e. DHAP consolidation + RT (n=1) **Median F/U**: 64 months (range, 24-132) *[For ITT analysis: R-CHOP arm, n=159; R-CHOP plus RT arm, n=160]*	**5-year OS (95% CI)** • *All patients [ITT]* R-CHOP vs. R-CHOP + RT: 92% ± 2.5% vs. 96% ± 1.7%; HR 0.62 (95% CI, 0.3 to 1.5); p=0.28 • *PET4- patients** R-CHOP vs. R-CHOP + RT: 92% vs. 92%; p=NR **5-year EFS (95% CI)** • *All patients [ITT]* R-CHOP vs. R-CHOP + RT: 89% ± 2.9% vs. 92% ± 2.4%; HR 0.61 (95% CI, 0.3 to 1.2); p=0.18 • *PET4+ vs. PET4-*: 82.5% vs. 92.5%; p=NS† **Proportion of PET4- Patients Experiencing Relapse** *R-CHOP vs. R-CHOP + RT*: 7.3% (10/137) vs. 6.9% 10/144	**PET-specific:** **Treatment-related:** Mortality‡ R-CHOP vs. R-CHOP + RT: 7.5% (12/159) vs. 5.6% (9/160) Toxicity - Febrile neutropenia: 15.7% (50/319) [66 episodes] - Severe infection: 1.3% (4/319) - Death from septic shock: 0.3% (1/319) - red blood cell transfusion: 5.6% (18/319) - Severe cardiac toxicity: 1.6% (5/319) - Moderate cardiac toxicity: 2.5%(8/319) Toxicity (resulting from RT) - Grade 3 mucositis: 0.6% (2/319) - Jaw radionecrosis: 0.3% (1/319)

*Statistics are estimated from Figure 3
† Statistics are estimated from Supplemental Figure 3, p-value obtained from text
‡Deaths were the result of progressive disease (n=11), secondary malignancies (n=3 [1 patient with acute myeloid leukemia, 1 with colon cancer, and 1 with pancreatic adenocarcinoma]), accident (n=2), stroke (n=1), late onset infection (n=1), and unknown (n=3).

Appendix Table G7. Detailed data abstraction: PET-adapted therapy in aggressive Non-Hodgkin Lymphoma, escalation, end of treatment PET

Author Study Design and Stage RoB, Notes	Treatments	Clinical Outcomes	Safety PET-specific Treatment-Related
Observational Studies			
Zinzani 2015 **Retrospective Cohort** RoB Moderately High aggressive NHL [Primary mediastinal large B-cell lymphoma (PMLBCL)] Patients were divided in complete responders, and PET+ and PET- after first line treatment (immunochemotherapy).	**PET Timing:** restaging (6 cycles) and 3 mos. post-treatment **Number of cycles before PET:** Allocation based on PET rating **1. PET+ (n=51)** Mediastinal RT (tumor dose ranging from 30–36 Gy over 4–5 weeks at 180 cGy/day for 5 days/week) **2. PET- (n=23)** Observation **Median F/U (range): 62 (28-112) mos**	**10-Year OS** 82% **10-Year DFS (n=61)** 90.5% **10-Year PFS** 87.6% **10-Year DFS, PET+ vs PET-** 90.7% (4/51) vs 90% (1/23), p=0.850 **CR, End of First-Line Treatment, all patients:** 82.4% (61/74) **Continuous CR, post-treatment, all patients:** 92% (56/61) **Post-RT CR, PET+ patients:** 74.5% (38/51)	**PET-specific, PET+ vs. PET-:** NR **Treatment-Related Toxicities, All Patients:** -Neutropenia(Grade III or IV): 5.5% (4/74) -Thrombocyopenia(Grade III or IV): 1.4% (1/74) -Nausea/Vomiting (Grade I or II): 25% -Hepatic Toxicity (Grade I or II): 3% (2/74) **Tumor-Related, patients with CR after end of first-line treatment:** -Relapses (<12 months): 8.2% (5/61) **Tumor-Related, post-RT PET+ patients:** Persistent Disease: 25.5% (13/51) Progression of Disease: 38.5% (5/13) Minor Reduction in SUV: 61.5% (8/13) **Secondary Malignancies, PET+ vs PET-:** NR

cGy = centigrays; cm = centimeter; COI = conflict of interest; CR = complete response; DFS = disease free survival; F/U = follow-up; Gy = Grays; mos. = months; NHL = non-Hodgkin lymphoma; NR =not reported; OS = overall survival; PET =positron emission tomography; PFS = progression free survival; RoB = risk of bias; RT = radiation therapy; SUV = standardized uptake value;

Appendix Table G8. Summary of Inclusion & exclusion criteria: PET-adapted therapy in aggressive non-Hodgkin Lymphoma

Study	Inclusion Criteria	Exclusion Criteria
Aggressive NHL, Interim PET		
RCTs		
Casasnovas 2017	Patients 18 to 59 years old with previously untreated histologically proven CD201DLBCL; aaIPI score of 2 or 3; baseline PET scan (PET0) was mandatory, with at least 1 evaluable hypermetabolic lesion; all patients had to be fit for ASCT;	Patients with known positive HIV status, active viral hepatitis B and C, or central nervous system involvement were excluded
Duhrsen 2018	Patients age 18 to 80 years with newly diagnosed aggressive B-cell or T-cell lymphomas, including follicular lymphoma grade 3 and an Eastern Cooperative Oncology Group performance status of 0 to 3 were eligible for registration.	Patients with a negative baseline PET scan were excluded. Burkitt's, transformed, and primary cerebral lymphomas were excluded
Prospective Observational Studies		
Pardal 2014	Age between 18 and 70 years; untreated, histologically proven DLCBL or grade 3B follicular lymphoma CD20+; aaIPI >1 or aaIPI = 1 with high beta 2-microglobulin (>30 mg/l); eligible for high-dose therapy; and baseline PET scan (PET0) positive with at least 1 evaluable hypermetabolic lesion.	NR
Stewart 2014	Age 18 to 65 years; stage 3 – 4 DLBCL associated with an elevated serum LDH level at diagnosis; no more than one cycle of RCHOP; no central nervous system (CNS) lymphoma and adequate organ function (left ventricular ejection fraction of at least 45%, pulmonary function tests over 50% predicted, normal serum creatinine and liver transaminases < 3 times upper limit of normal unless caused by lymphoma).	NR
Swinnen 2015	Previously untreated patients between the ages of 18 and 70 years with DLBCL stage III, IV or bulky stage II (bulky: any lesion ≥10 cm); histological diagnosis (central pathology review and measurable disease defined by CT imaging were required); adequate organ reserve (absolute neutrophil count ≥1.5 X 109/liter); platelet count >100 x 109/liter, creatinine <176.8 µmol/l; total bilirubin <34.2 µmol/l or ≤51.3 µmol/l if due to liver involvement); documentation of left ventricular ejection fraction >50% in patients over 50 years of age and Eastern Cooperative Oncology Group (ECOG) Performance Status ≤3.	Exclusion for positivity of human immunodeficiency virus, pregnancy or breastfeeding, primary large B-cell mediastinal lymphoma, primary central nervous system lymphoma, primary testicular diffuse large B-cell lymphoma, immunodeficiency-related lymphomas and prior malignancy, unless in situ or treated with curative intent ≥5 years prior to enrolment.
Zinzani 2015	NR	NR

APPENDIX H. Indolent Hodgkin's Lymphoma

Appendix Table H1. Study characteristics and data abstraction: clinical studies in Indolent Non-Hodgkin Lymphomas

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
Initial staging				
Abou-Nassar 2013	Retrospective cohort (NCCN database) Population N = 953 Adults (median, 56.4 years) M/F: 52%/48% Grade 1-2 follicular lymphoma Stage I-II: 25% II-IV: 75% Bulky disease: 16% Comparator PET/CT (n=532) (95% [n=503]; 5% had PET only) vs. CT only (No PET for initial stating) (n=421); (89% [n=374] had CT w/in 90 days of diagnosis) Median follow-up: NR	NR	Undergoing PET for initial staging significantly increased likelihood of receiving early therapy: • PET vs. no PET: 80% vs. 60% (20% vs. 40% observation only)* • adjusted† odds ratio for early treatment: 1.87, 95% CI 1.31-2.66, p=0.0006 Use of PET for initial staging was associated with significant differences in choice of initial therapy (p=0.02) • More anthracycline based chemotherapy ± immunochemotherapy(50% vs. 40%) and less radiation only therapy (5% vs. 15%)‡	NR
Bakhshi 2012 [same as below for interim]	Prospective cohort Population N = 34 Pediatric (mean 10.6 ± 3.1 years)	See interim section below	PET/CT resulted in a change in clinical stage compared to CT Upstage: 14.7% (5/34) • from I to II: 2.9% (1/34) • from III to IV; 11.8% (4/34) Downstage: 0% (0/34)	Sensitivity **Interim CT**: 7/9 (77.8) [95% CI, 47.8, 94.2] **Interim PET/CT**: 7/9 (77.8) [95% CI, 44.9, 95.9] **Posttreatment CT**: 6/7 (85.7) [95% CI, 46.3, 99.2]

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	nonlymphoblastic NHL Stage I-II: (9%) III-IV: (91%) Comparator (both modalities used in the same patients) PET-CT vs. contrast enhanced CT Median follow-up: 20.3 months.		Detection of additional disease sites Baseline PET/CT and contrast enhanced CT showed concordance in depiction of 112 disease sites; PET/CT depicted 18 more disease sites and two fewer disease sites than contrast-enhanced CT (p=0.0003)	**Posttreatment PET/CT:** 3/4 (75.0) [95% CI, 23.5, 98.7] Specificity **Interim CT**: 10/22 (45.5) [95% CI, 32.2, 52.9] **Interim PET/CT**: 12/22 (54.5) [95% CI, 41.1, 62.0] **Posttreatment CT**: 18/24 (75.0) [95% CI, 63.5, 78.9] **Posttreatment PET/CT**: 18/24 (75.0) [95% CI, 66.4, 78.9] PPV **Interim CT**: 7/19 (36.8) [95% CI, 21.5, 45.4] **Interim PET/CT**: 7/17 (41.2) [95% CI, 23.8, 50.8] **Posttreatment CT**: 6/12 (50.0) [95% CI, 27.0, 57.9] **Posttreatment PET/CT**: 3/9 (33.3) [95% CI, 10.4, 43.9] NPV **Interim CT**: 10/12 (83.3) [95% CI, 59.0, 96.9] **Interim PET/CT**: 12/14 (85.7) [95% CI, 64.6, 97.4] **Posttreatment CT**: 18/19 (94.7) [95% CI, 80.2, 99.7] **Posttreatment PET/CT**: 18/19 (94.7) [95% CI, 83.9, 99.9]
Carrillo-Cruz 2015 [same as below for end-of-treatment]	Retrospective cohort Population N = 25 (N = 17 patients for whom results of both imagings are available) Adults	See interim section below	**Initial Staging** Discrepancies between PET/CT and CT scans 70% (12/17)	**Initial Staging** Sensitivity PET/CT vs. CT: 96% vs. 76%

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	(median 60 years, range 26 to 81) Marginal zone B cell Stage I-II: (32%) III-IV: (68%) Comparator (both modalities used in the same patients) PET/CT vs. contrast-enhanced CT Median follow-up: 50 months.		Detection of additional disease sites by PET/CT not identified by CT 67% (8/12) PET/CT resulted in a change in clinical stage compared to CT Upstage: 29.4% (5/17)	
Friedberg 2012	Retrospective cohort Population N = 206§ Adults ≤60: 48% (99/206) >60: 52% (107/206) Follicular Lymphoma Stage I: All B symptoms: 23/206 (11.2%) Comparator PET (n=128) vs No PET (n=78) Median follow-up: 57 months.	OS No difference (data not provided) PFS PET vs. No PET: HR 0.87, 95% CI 0.47-1.62 (no other data provided)	*Treatment given according to staging with PET vs. without PET:* • *Watchful waiting: 15% (19/128) vs. 21% (61/78)* • *Rituximab monotherapy: 12% (15/128) vs. 13% (10/78)* • *Rituximab/chemotherapy: 25% (32/128) vs. 32% (25/78)* • *Radiation therapy: 30% (38/128) vs. 23% (18/78)* • *Combined modality with radiation therapy: 14% (18/128) vs. 10% (8/78)* • *Other: 5% (6/128) vs. 1% (1/78)* • *p=0.47 (Fisher's exact test)*	NR
Metser 2017	Prospective Registry Population N = 197	NR	**All patients** PET/CT resulted in a change in clinical stage	NR

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	Adults (median 63 years, range 17-90) M(%)/F(%): 53(50)/53(50) Follicular Lymphoma (76%); marginal zone lymphoma (11%), other subtypes of iNHL (13%) <u>Stage</u> I-II: (88%) III-IV: (12%) <u>Comparator (both modalities used in the same patients)</u> PET/CT vs Conventional clinical and radiological staging procedures (pre-PET/CT) <u>Median follow-up:</u> NR		**Any change** in disease state: 55.8% (110/197) • Migration from either limited (I-II) to advanced (III-IV) stage or vice versa: 25.9% (51/197) **Upstage**: 36.5% (72/197) • Migration from limited to advanced stage disease: 65.3% (47/72) • Within stage (from I to II or from III to IV): 34.7% (25/72) **Downstage**: 5.1% (10/197) • Migration from advanced to limited stage: 40% (4/10) **Equivocal findings** requiring further evaluation: 14.2% (28/197) <u>Proportion of patients assessed as having limited stage disease</u> Before PET/CT vs. after PET/CT: 88.3% (174/197) vs. 63.9% (108/169), 95% CI 0.16 to 0.33, p<0.0001 <u>Treatment plan for all patients (n=155)** pre-PET/CT was RT. After PET/CT:</u> • <u>Proportion of patients planned for active treatment:</u> 61.3% (95/155), 95% CI, -1.0 to -0.32, p<0.0001 ○ <u>Chemotherapy only:</u> 19.3% (30/155) ○ <u>Radiation only:</u> 38.1% (59/155)	

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
			○ Combined modality: 3.9% (6/155) • No treatment: 38.7% (60/155) • Proportion of patients actually treated: 42.6% (65/155) (95% CI, 0.08 to 0.30), p=0.001 ○ Chemotherapy only: 18.1% (28/155) ○ Radiation only: 21.9% (34/155) ○ Combined modality: 2.6% (4/155) ○ No treatment: 57.4% (89/155) **Follicular Lymphoma Cohort (n=150)** **Any change:** • Migration from either limited (I-II) to advanced (III-IV) stage or vice versa: 32.7% (49/150) **Upstage**: 40.7% (61/150) • Migration from limited to advanced stage disease: 73.8% (45/61) **Proportion of patients with limited stage disease** Before vs. after PET: 88.7% (133/150) vs. 57.9% (77/133), 95% CI 0.21-0.47, p>0.0001	

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
Interim				
Bakhshi 2012 [same as above for initial staging and below of end-of-treatment]	Prospective cohort Population N = 31 Pediatric (median 10.5) nonlymphoblastic NHL Stage I-II: (9%) III-IV: (91%) Comparator (both modalities used in the same patients) PET-CT vs. contrast enhanced CT Median follow-up: 20.3 months.	**OS (95% CI)** • In patients with complete remission on PET/CT vs. CT: 78.6% (47.2%–92.5%; SE 11.0) vs. 83.3% (48.2%–95.5%; SE 10.8) In patients without complete remission on PET/CT vs. CT: 50.4% (24.9%–71.4%, SE 12.5) vs. 49.7% (25.4%– 70.0%; SE 11.9) **PFS (95% CI)** • In patients with complete remission on PET/CT vs. CT: 85.7% (53.9%–96.2%; SE 9.3) vs. 82.5% (46.1%–95.3%; SE 11.3) • In patients without complete remission on PET/CT vs. CT: 57.0% (30.1%–76.9%, SE 12.4) vs. 62.3% (36.7%– 80.0%; SE 11.3) For both OS and PFS, on the basis of the exact symmetry test, there was no significant discordance between interim contrast enhanced	See initial staging section above	Sensitivity **Interim CT**: 7/9 (77.8) [95% CI, 47.8, 94.2] **Interim PET/CT**: 7/9 (77.8) [95% CI, 44.9, 95.9] Specificity **Interim CT**: 10/22 (45.5) [95% CI, 32.2, 52.9] **Interim PET/CT**: 12/22 (54.5) [95% CI, 41.1, 62.0] PPV **Interim CT**: 7/19 (36.8) [95% CI, 21.5, 45.4] **Interim PET/CT**: 7/17 (41.2) [95% CI, 23.8, 50.8] NPV **Interim CT**: 10/12 (83.3) [95% CI, 59.0, 96.9] **Interim PET/CT**: 12/14 (85.7) [95% CI, 64.6, 97.4]

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
		CT and PET/CT results (p=0.47). *See below section for data on end-of treatment PET*		
End-of-treatment				
Bakhshi 2012 [same as above for initial staging, and interim]	Prospective cohort Population N = 31 Pediatric (median 10.5) nonlymphoblastic NHL Stage I-II: (9%) III-IV: (91%) Comparator (both imaging in same patients) PET/CT vs. contrast enhanced CT Median follow-up: 20.3 months.	**OS (95% CI)** • In patients with complete remission on PET/CT vs. CT: 84.2% (58.6%–94.6%; SE 8.4) vs. 84.2% (58.6%–94.6%; SE 8.4) In patients without complete remission on PET/CT vs. CT: 55.6% (20.4%–80.4%, SE 16.6) vs. 50.0% (20.8%– 73.6%; SE 14.4) **PFS (95% CI)** • In patients with complete remission on PET/CT vs. CT: 94.7% (68.1%–99.2%; SE 5.1) vs. 94.7% (68.1%–99.2%; SE 5.2) • In patients without complete remission on PET/CT vs. CT: 66.6% (28.2%–87.8%, SE 15.7) vs. 50% (20.8%– 73.6%; SE 14.4) For both OS and PFS, on the basis of the exact symmetry test,	See above section on initial staging	Sensitivity **Posttreatment CT**: 6/7 (85.7) [95% CI, 46.3, 99.2] **Posttreatment PET/CT:** 3/4 (75.0) [95% CI, 23.5, 98.7] Specificity **Posttreatment CT**: 18/24 (75.0) [95% CI, 63.5, 78.9] **Posttreatment PET/CT**: 18/24 (75.0) [95% CI, 66.4, 78.9] PPV **Posttreatment CT**: 6/12 (50.0) [95% CI, 27.0, 57.9] **Posttreatment PET/CT**: 3/9 (33.3) [95% CI, 10.4, 43.9] NPV **Posttreatment CT**: 18/19 (94.7) [95% CI, 80.2, 99.7] **Posttreatment PET/CT**: 18/19 (94.7) [95% CI, 83.9, 99.9]

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
		there was no significant discordance between interim contrast enhanced CT and PET/CT results (p>0.99). *See above section for data on interim PET*		
Carrillo-Cruz 2015 [same as above for initial staging]	Retrospective cohort Population N = 25 (N = 17 patients for whom results of both imagings are available) Adults (median 60 years, range 26 to 81) Marginal zone B cell Stage I-II: (32%) III-IV: (68%) Comparator (both modalities used in the same patients) PET/CT vs. contrast-enhanced CT Median follow-up: NR	3-year OS Post-treatment PET+ vs. Post-treatment PET-: 80% vs. 100% 3-year disease free survival 86%	**End-of-treatment** Discrepancies between PET/CT and CT scans 27% (3/11)	**End-of-treatment** PPV PET/CT: 83.3% NPV PET/CT: 100%

CI = Confidence interval; CT = Computed Tomography; F = Female; M = Male; NCCN = National Comprehensive Cancer Network; NPV = Negative Predictive Value; NR =Not reported; OS = Overall Survival; PET/CT = Combined Positron Emission Tomography and Computed Tomography; PET = Positron Emission Tomography; PFS = Progression Free Survival; PPV = Positive Predictive Value; RT = Radiation therapy; SE = Standard error

*Percent estimated from Figure 3 in article.

†Adjusted for FLIPI score, participation in a study protocol and NCCN center.

‡Percent estimated from Figure 4 in article.

§Results are reported on those patients within the rigorously staged group who had PET with those who did not.

**Per registry criteria, the pre-PET/CT treatment plan for all patients was RT. Treatment data available for 155 of the 197 patients.

APPENDIX I. Mixed (and Transformed) Lymphoma

Appendix Table I1. Study characteristics and data abstraction: clinical studies in mixed populations of early and advanced Hodgkin Lymphoma

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
Initial Staging				
Angelopoulou 2017	Population N = 162 Adults (median 33, range 17-82) M(%)/F(%): 83(51)/79(49) Stage I: 10% (16/162) II: 42% (69/162) II: 24% (39/162) IV: 24% (38/162) B symptoms: 44% (71/162) Comparator (both modalities used in the same patients) PET/CT staging vs. Clinical Staging Median Follow-up: 56.7 months	**5-year OS** Overall: 93% **5 year FFP** • Overall: 81% • For patients without stage modification vs. upstaged patients vs. downstaged patients: 79% vs. 89% vs. 78% (p=0.547) (no prognostic significance based on univariate analysis) • For patients with vs. without treatment modification according to PET staging: 80% vs. 92% (p=0.427)* • For patients with vs. without IFRT modification according to PET: 80% vs. 90% (p=0.48)†	PET resulted in a change in stage compared to clinical staging Upstage: 16% (26/162) Downstage: 6% (9/162) Theoretical proportion of patients where PET could have altered treatment strategy 14% (23/162) Proportion of patients where treatment strategy was actually altered by PET 6% (10/162)	NR
Bednaruk-Mlynski 2015	Retrospective cohort Population N = 96 Adults (median 36, range 19-78 years) M(%)/F(%): 51(53)/45(47)	NR	Concordance of results between PET/CT and CT 66% (63/96) PET resulted in a change in clinical stage compared to CT Upstage: 28% (27/96) Downstage: 6% (6/96)	NR

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	Stage IA - IVB Comparator (both modalities used in the same patients) PET/CT vs Contrast CT Median follow-up: NR		Proportion of patients where PET would have altered treatment strategy had the PET results been included in the initial staging procedure 21% (20/96) (16/20 would have had extended treatment; 4/20 would have had shortened treatment) (details regarding treatment were not provided)	
Cerci 2011	Prospective cohort Population N = 210 Adults (median 33.7, SD ± 14.9 years) M(%)/F(%): 103(49.0)/107(51.0) Stage I-II: 48.1% (101/210) III-IV: 51.9% (109/210) B symptoms: 53.3% (112/210) Comparator (both modalities used in the same patients) PET alone vs CT alone [Dx accuracy; Excluding proportion correctly staged, false positives, and false negatives, which were reported according to an unclear reference standard determined by study authors] AND	NR	Proportion of patients where PET would have altered treatment strategy had the PET results been included in the initial staging procedure 15% (32/210) PET resulted in a change in clinical stage compared to CT 32% (67/210) Upstage: 23.8% (50/210) Downstage: 8.1% (17/210)	**Sensitivity** % (95% CI) PET vs. CT: 97.9% (0.95-0.98) vs. 87.3% (0.84-0.89) **Specificity** % (95% CI) PET vs. CT: 95.3% (0.91-0.97) vs. 96.8% (0.93-0.98) **PPV** % (95% CI) PET vs. CT: 97.9% (0.96-0.98) vs.98.4% (0.96-0.99) **NPV** % (95% CI) PET vs. CT: 93.8% (0.90-0.96) vs. 77.0% (0.72-0.81) **Accuracy** PET vs. CT: 96.6% vs. 90.2% **False Positive (according to reference standard)** PET vs. CT: 7/210 (3.3%) vs 6/210 (2.9%)

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	PET vs. Conventional Clinical Stage (physical exam, blood work, CT bilateral bone marrow biopsy) [Secondary Outcomes] Median follow-up: NR			**False Negative (according to reference standard)** PET vs. CT: 14/210 (6.7%) vs. 55/210 (26.2%) **Concordance of results between PET and CCS** 68% (143/210)
Grellier 2014	Retrospective database Population N = 35 (Nodular lymphocyte-predominant Hodgkin lymphoma; rare type of HL Mixed adults and pediatric (median age 29, range 4-75) M(%)/F(%): 24(69)/11(31) Stage *Initial stage:* I-II: (81%; 22/27) III-IV: (19%; 5/27) *Relapse stage*: I-II: (75%; 6/8) III: (25%; 2/8) Comparator (both modalities used in the same patients) PET/CT (initial staging, n=27; relapse staging, n=8) vs clinical exam, contrast-enhanced CT, and/or biopsy	NR	Proportion of patients where PET resulted in a change in initial/relapse stage compared with clinical examination (to include CT and/or biopsy) *All*: 34.3% (12/35) Upstage: 31.4% (11/35) Downstage: 2.9% (1/35) *Initial stage*: 29.6% (8/27) Upstage: 25.9% (7/27) Downstage: 3.7% (1/27) *Relapse stage*: 50.0% (4/8) Upstage: 50% (4/8) Downstage: 0% (0/8) Proportion of patients where PET resulted in a change in therapeutic procedure compared with clinical examination 11% (4/35); all were converted from local treatment (RT) to systemic treatment (chemotherapy)	**Initial Staging** Sensitivity 100% Specificity 99% PPV 97% NPV 100% Accuracy 99% Out of a total of 455 site analyzed: TP: 104 TN: 349 FP: 2 FN: 0

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	Median follow-up: 34 months.			
Paulino 2012	Retrospective case series Population N = 53 Pediatric (mean 14 years, range 6-21 years) M(%)/F(%): 33(62.3)/20(37.7) Stage IA-IVB (various)- Comparator (both modalities used in the same patients) PET/CT vs Conventional Staging (CT and bone marrow biopsy; some had bone scan, MRI, gallium) Median follow-up: NR	NR	PET resulted in a change in clinical stage compared to conventional staging Upstage: 5.7% (3/53) Downstage: 3.8% (2/53) PET resulted in a change in radiotherapy field in 20.7% (11/53): more extensive in 9 and less extensive in 2	Proportion of Discordant sites where imaging was able to differentiate presence and absence of tumor PET/CT vs. conventional imaging: 11/23 (47.8%) vs. 12/23 (52.2%)
Robertson 2011	Prospective cohort Population N = 30 Pediatric (median 15, range 5-18) M(%)/F(%): (77%)/(23%) Stage II: 47% (14/30) III: 37% (11/30) IV: 17% (5/30)	NR	PET resulted in a change in clinical stage compared to CT Upstage: 27% (8/30) Downstage: 23% (7/30) As a result of PET, 32 sites were added and 15 sites were excluded from IFRT. Proportion of IFRT volumes that needed to be adjusted on the basis of the initial PET findings 70% (21/30)	Concordance of PET and CT 86% Discordance of PET and CT 14% Correlation between PET and CT for all suspected sites of disease 0.64 (95% CI, 0.56 to 0.71) indicating “intermediate” to “good” agreement

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	Comparator (both modalities used in the same patients) PET alone vs CT alone Median follow-up: NR			
Cheng 2013 [HL subgroup only]	Retrospective cohort Population N = 30 Pediatric (mean 14.9, range 6-22) M(%)/F(%): 16(53)/14(47) Stage I: 4 II: 15 III: 5 IV: 6 Comparator (both modalities used in the same patients) PET/CT vs. contract enhanced CT (median 5.2 days apart) Median follow-up: NR	NR	Proportion of additional lesions detected PET/CT vs CT: 50% vs. 16.7% (p=0.0062) Proportion of patients where PET resulted in a change in stage compared to CT Upstage: 23.3% (7/30) Downstage: 0% (0/30)	NR
Surveillance				
Dann 2014	Retrospective cohort Population N = 368 **Group I** (n=305)**:** Adults	3-year PFS Group I vs. Group II: 93% vs. 86% 5-year PFS Group I vs. Group II: 92% vs. 86%	Proportion of relapses reported during 60 months of follow-up Group I vs. Group II: 9% (28/305) vs. 13% (8/68) Median time to relapse (months)	

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	(median 30, range 16-78 years) M(%)/F(%): 155(51)/149(49) <u>Stage</u> Early Stage: 108 (35%) **Group II** (n=63)**:** Adults (median 34, range 16-82 years) M(%)/F(%): 23(36)/30(48) <u>Stage</u> Early Stage: 25 (40%) <u>Comparator</u> **Group I**: Routine clinical f/u + routine and dedicated PET/CT (n=305) (96%; 4% had CT only) vs. **Group II**: Routine clinical f/u + dedicated CT only in case of relapse suspicion (n=63) (98%; 2% had PET/CT) <u>Follow-up:</u> 36 months. (separate analysis at 5-year follow-up)		Group I vs. Group II: 8.6 (range 3-64) vs. 8.6 (range 6-32) <u>No. of imaging tests needed to diagnose/detect a single relapse</u> Group I vs. Group II: 47.5 vs. 4.7 <u>No. of imaging tests required per patients</u> Group I vs. Group II: 3.9 vs. 0.6, p<0.001	
Pingali 2014	Retrospective cohort <u>Population</u> N = 241 Adults in CR at end of first line therapy **RSI (clinical follow-up plus routine imaging, i.e., CT and/or PET scans)** (n=174):	<u>5-year OS</u> RSI vs. CS: 97% (95% CI, 92% to 99%) vs. 96% (95% CI, 86% to 99%), p-value for the log-rank test = p=0.41 <u>Proportion of Deaths</u> RSI vs. CS: 2.9% (5/174) vs. 6% (4/67) *n=1 death from relapsed HL in RSI group	Average number of scans per year: RSI vs. CS: 0.98 (95% CI 0.89-1.08) vs. 0.21 (95% CI 0.18-0.31) Relative risk: 4.5 (95% CI 3.1-5.5); p<0.0001 Number of scans performed per relapse detected: RSI vs. CS: 127 vs. 14.6	NR

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	(mean 36, range 18-77 years) M(%): 79(45) <u>Stage</u> IA, IB, or IIA: 47% (81/174) IIB, III, or IV: 53% (93/174) B symptoms: 35% (61/174) <u>Comparator</u> Clinical f/u + routine imaging (CT and/or PET scans) (RSI) (n=174) vs. Clinical f/u only (imaging done only to evaluation signs or symptoms) (CS) (n=67) **CS (clinical follow-up with imaging done only to evaluate signs or symptoms)** (n=67): (mean 33.4, range 18-76 years) M(%): 26(39) <u>Stage</u> IA, IB, or IIA: 54% (36/67) IIB, III, or IV: 46% (31/67) B symptoms: 28% (19/37) <u>Comparator</u> **RSI** vs. **CS** <u>Follow-up:</u> ≥24 months.	<u>5-year Incidence of Relapse</u> RSI vs. CS: 3.4% vs. 7.4% (p=.39) <u>Proportion of patients experiencing relapse</u> RSI vs. CS: 3.5% (6/174) vs. 7.5% (5/67)		

CCS = Conventional Clinical Staging; CI = Confidence interval; CR = Complete Response; CS = Clinical Surveillance; CT = Computed Tomography; f/u = follow up; F = Female; FFP = Freedom from Progression; FN = False negative; FP = False positive; IFRT = In Field Radiation Therapy; M = Male; MRI = Magnetic Resonance Imaging; NPV = Negative Predictive Value; NR = Not reported; OS = Overall survival; PET/CT = Combined Positron Emission Tomography and Computed Tomography; PET = Positron Emission Tomography; PPV = Positive Predictive Value; RSI = Routine surveillance imaging; TN = True negative; TP = Tue positive
*Among the 23 patients in whom treatment strategy could have been changed according to PET.
†Among the 63 patients in whom IFRT could have been changed according to PET; 20 patients for whom the IF was not actually modified and 36 for whom the IF changed.

Appendix Table I2. Study characteristics and data abstraction: clinical studies in mixed populations of Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
Initial Staging				
Awan 2013	Prospective cohort [Hodgkin (66%) (97% classic HL; one patient was lymphocyte predominant); NHL (ALCL, DLBCL)] Population N = 53 (HL: n=35, NHL: n=18) Adults (median 26, range 18-51 years) M(%)/F(%): 40(75.5)/13(24.5) Stage Actual Stage NR (authors state that most presented with advanced disease) Bone marrow involvement: 15% (8/53) B symptoms: 51% (27/53) Comparator (both modalities used in the same patients) PET/CT vs. contrast enhanced CT Median follow-up: NR	NR	Proportion of patients where PET resulted in a change in stage compared to CT Upstage: 7.5% (4/53) [all changed from III to IV] Downstage: 0% PET did not lead to any changes in the number of chemotherapy cycles since no patient was upstaged from early to advance stage and the treatment recommendations for stage III and IV are similar Complete Response PET vs. CT: 71% (38) vs. 6% (3) Partial Response PET vs. CT: 23% (12) vs. 91% (48) Progressive Disease PET vs. CT: 6% (3) vs. 4% (2)	Concordance of CT and PET Kappa = 0.856, p<0.001

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
van Hamersvelt 2014	Prospective cohort [Hodgkin; NHL (various, including DLBCL, follicular, marginal zone)] Population **HL** N = 6 Adults (mean 36.2, range 22-45) M(%)/F(%): 3(50)/3(50) **NHL** N = 23 Adults (mean 59.5, range 22-74) M(%)/F(%): 15(65)/8(35) Stage NR Comparator (both modalities used in the same patients) PET/CT vs. enhanced CT Median follow-up: NR	NR	PET/CT and CT agreed on staging in 20 of 29 patients Of the 9 patients for which there was disagreement, PET correctly staged 7 (78%) and CT 2 (22%) Proportion of patients where CT either did not change or did not correctly change the stage assigned according to PET/CT 93% (27/29), 95% CI 78%-98%) Proportion of patients where CT correctly provided another stage than PET/CT 7% (2/29), 95% CI 2%-22%) (treatment was not modified in these 2 patients)	NR
Interim				
Terezakis 2014	Prospective cohort [Hodgkin, NHL] Population	NR	Effect of PET on change in management 8.4% (8/95) Addition of a RT site: 2% (2/95)	NR

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	N = 95 with PET(+) scans at time of RT planning [84% with lymphoma (HL: n=10, NHL: n=70); 16% with other hematologic malignancies=15] Adults (median 61, range 20-93 years) M(%)/F(%): 50(52.6)/45(47.4) <u>Stage</u> NR 45% (43/95) presented with relapsed or refractory disease <u>Comparator (both modalities used in the same patients)</u> PET/CT vs. CT alone* <u>Median follow-up: NR</u>		Not treated due to extensive disease not apparent on pre-RT imaging: 6.3% (6/95) Clinically meaningful change (≥5%) in RT volume (per radiation oncology defined GTV): 88.8% (79/89) Increased: 43% (38/89) Decreased: 46% (41/89) Clinically meaningful change in RT volume (per radiation oncology defined GTV) or change in overall treatment plan: 91.6% (87/95)	

ALCL = Anaplastic large-cell lymphoma; CT = Computed Tomography; DLBCL = Diffuse large B-cell lymphoma; F = Female; GTV = Gross Tumor Volume; M = Male; NR = Not reported; PET/CT = Combined Positron Emission Tomography and Computed Tomography; PET = Positron Emission Tomography; RT = Radiation therapy
*Blinded to PET scan.

Appendix Table I3. Study characteristics and data abstraction: clinical studies in mixed populations of Aggressive, Indolent and Transformed Non-Hodgkin Lymphoma

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
Indolent and Aggressive (mixed population) NHL				
Initial Staging				
Papajik 2011b	Prospective cohort Population N = 122 Adults (median 59, range 26-79) M(%)/F(%): 67(55)/55(45) Various, including DLBCL, follicular Stage NR Comparator (both modalities used in the same patients) PET/CT vs CT, bone marrow biopsy, other clinical Median follow-up: NR	NR	PET/CT resulted in a change in clinical stage compared to CT Upstage: 4% (5/117) Downstage: 5% (6/117) Proportion of patients where PET/CT altered treatment strategy 3% (3/117)	Reported, but not relevant (compares sensitivity and specificity of PET/CT and CT by detection in lymph nodes and extranodal organs.
Cheng 2013 [NHL only]	Retrospective cohort NHL (various, including DLBCL, Burkitt) Population N = 21 Pediatric (mean 14.7, range 6-24)	NR	Proportion of additional lesions detected PET/CT vs. CT: 42.9% vs. 23.8% (p=0.19) Proportion of patients where PET resulted in a change in stage compared to CT Upstage: 33.3% (7/21) Downstage: 0% (0/21)	NR

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	M(%)/F(%): 13(62)/8(38) Stage (Murphy staging) I: 3 II: 7 III: 3 IV: 8 Comparator (both modalities used in the same patients) PET/CT vs. contract enhanced CT (median 5.2 days apart) Median follow-up: NR		Proportion of patients where CT resulted in a change in stage compared to PET/CT Upstage: 9.5% (2/21) [due to non-FDG-avid lung nodules in one case and a false negative PET/CT in the other]	
End-of-treatment				
Sohn 2013	Retrospective cohort Population N = 41 Adults (≤40 years (97.6%)) M(%)/F(%): 31(75)/10(25) T-cell NHL Stage I/II: 28/41 (68%) III/IV: 13/41 (32%) Comparator post-ASCT PET (17%) or PET/CT (83%) vs. post-ASCT CT	Adjusted* HR for OS PET− vs. PET+: adjusted HR=0.350, 95% CI=0.139–0.882, p=0.026 Adjusted HR for EFS PET− vs. PET+: adjusted HR=0.232, 95% CI=0.092–0.582, p=0.002 Patients with a CT- scan confirmed by a PET- scan had about a 10% increase in survivals compared to patients with only a CT- scan. 6-month EFS	NR	Concordant responses vs. Discordant responses between PET and CT 73.2% (30/41) vs. 26.9% (11/41) (Cohen's κ=0.465, SE=0.137, 95% CI=0.197–0.733)

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	Median follow-up: NR	CT- scan confirmed by PET- scan (n=16) vs. CT- scan only (n=20): 72.5% ± 11.8% vs. 62.4% ± 11.3% (p=NR) 2-year OS CT- scan confirmed by PET- (n=16) vs. CT- scan only (n=20): 53.0% ± 13.2 % vs. 44.9 ± 12.0 % Patients with a CT+ scan confirmed by a PET+ scan had about a 5% decrease in survivals compared to those with only a CT+ scan. 6-month EFS CT+ scan confirmed by PET+ scan (n=14) vs. CT+ scan only (n=21): 16.3% ± 10.5% vs. 20.4% ± 9.1% 2-year OS CT+ scan confirmed by PET+ scan (n=14) vs. CT+ scan only (n=21): 26.8% ± 12.3% vs. 32.7% ± 10.4%		
Surveillance				

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
Taghipour 2016a	Retrospective cohort (database) Population N = 204 patients (560 scans) Adults Mean, 56 years (range, years) M(%)/F(%): 128(37.3)/ 76(62.7) aNHL and iNHL (DLBCL 42%; follicular 23%; mantel cell 9.3%; other types 26%) Stage I-II: 11/204 (5.4%) III-IV: 62/204 (30.4%) Unknown: 131/204 (64.2%) Comparator PET/CT without prior clinical suspicion vs. PET/CT with prior clinical suspicion Median follow-up: 16.5 months	NR	Proportion of PET/CT patients without prior clinical suspicion that resulted in a change in management (n/N, % scans) **Yes:** 7.5% (29/388 scans) **No:** 85.6% (332/388 scans) **Unknown:** 6.2% (24/388 scans) Proportion of PET/CT patients with prior clinical suspicion that resulted in a change in management (n/N, % scans) **Yes:** 34.3% (59/172 scans) **No:** 50.6% (87/172 scans) **Unknown:** 11.6% (20/172 scans)	**PET/CT without prior clinical suspicion (n/N, % scans)** True Positives 12.4% (48/388) False Positives 7.5% (29/388) True Negatives 71.1% (276/388) False Negatives 2.1% (8/388) **PET/CT without prior clinical suspicion (n/N, % scans)** True Positives 73.8% (127/172) False Positives 1.7% (3/172) True Negatives 16.3% (28/172) False Negatives 0.6% (1/172)
Taghipour 2016b†	Retrospective cohort (database) Population N = 77 patients* (231 first 3 follow-up scans; 208 fourth and subsequent scans) Adults (mean age, 56 years)	NR	**In patients with first 3 follow-up scans** Proportion of PET/CT patients without prior clinical suspicion that resulted in a change in management (n/N, % scans) **Yes:** 7.0% (11/157 scans) **No:** 91.7% (144/157 scans) **Unknown:** 1.3% (2/157 scans)	**In patients with first 3 follow-up scans** **PET/CT without prior clinical suspicion** True Positives 13.4% (21/157) False Positives 5.7% (9/157) True Negatives

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
	M(%)/F(%):49(63.6)/ 28 (36.4) aNHL and iNHL (DLBCL 48%; follicular 12%; mantel cell 7.8%; marginal zone5 5.2% other types 27%) Stage I-II: 9/77 (11.7%) III-IV: 27/77 (35.1%) Unknown: 41/77 (53.2%) Comparator PET/CT without prior clinical suspicion vs. PET/CT with prior clinical suspicion		Proportion of PET/CT patients with prior clinical suspicion that resulted in a change in management (n/N, % scans) **Yes:** 32.4% (24/74 scans) **No:** 66.2% (49/74 scans) **Unknown:** 1.4% (1/74 scans) **In patients with 4th and subsequent follow-up scans** Proportion of PET/CT patients without prior clinical suspicion that resulted in a change in management (n/N, % scans) **Yes**: 9.2% (16/175 scans) **No**: 79.4% (139/175 scans) **Unknown**: 11.4% (20/175 scans) Proportion of PET/CT patients with prior clinical suspicion that resulted in a change in management (n/N, % scans) **Yes:** 36.4% (12/33 scans) **No:** 42.4% (14/33 scans) **Unknown:** 21.2% (7/33 scans)	80.3% (126/157) False Negatives 0.6% (1/157) **PET/CT with prior clinical suspicion** True Positives 74.3% (55/74) False Positives 5.4% (4/74) True Negatives 18.9% (14/74) False Negatives 0% (0/74) **In patients with 4th a subsequent follow-up scans** **PET/CT without prior clinical suspicion** True Positives 5.1% (9/175) False Positives 5.1% (9/175) True Negatives 72.6% (127/175) False Negatives 3.4% (6/175) **PET/CT with prior clinical suspicion** True Positives 57.6% (19/33) False Positives

Study year	Study characteristics	Primary outcomes	Secondary outcomes	Diagnostic accuracy
				3.0% (1/33) True Negatives 27.3% (9/33) False Negatives 3.0% (1/33)
Transformed indolent NHL				
Surveillance				
Cheah 2014	Retrospective database (case series) Population N = 55 Adults (median 59, range 35-83 years) M(%)/F(%): 33(60)/22(40) Transformed indolent NHL (iNHL with a synchronous or subsequent diagnosis of DLBCL) Stage I-II: 11/55 (20%) III-IV: 44/55 (80%) B symptoms: 12/52 (23%) Comparator Detection of relapse sub-clinically (i.e., via PET) or symptomatically (i.e., not via PET) Median follow-up: 34 months.	3-year OS 88 % (95% CI, 75% to 94%) 3-year PFS 77 % (95 % CI, 62% to 86%)	Proportion of patients experiencing relapse 29.1% (16/55) • Detected by PET/subclinical: 12.7% (7/55) • Not detected by PET/symptomatic: 16.4% (9/55) *Surveillance imaging of transformed NHL achieving CMR is not indicated. PET-CT should be reserved for evaluation of suspected relapse.*	True positives 15/180 (9%) False positives 4/180 (2%) Indeterminate 7/180 (4%) True Negatives 153/180 (85%) False negatives 1/180 (0.5%) Specificity: 94 % Sensitivity: 83 %, PPV: 63% NPV: 98%

CI = Confidence interval; CT = Computed Tomography; DLBCL = Diffuse large B-cell lymphoma; EFS = Event Free Survival; F = Female; M = Male; NCCN = National Comprehensive Cancer Network; NPV = Negative Predictive Value; NR = not reported; OS = Overall Survival; PET/CT = Combined Positron Emission Tomography and Computed Tomography; PET = Positron Emission Tomography; PFS = Progression Free Survival; PPV = Positive Predictive Value; RT = Radiation therapy

*Adjusted for histology, disease status at ASCT, and conditioning regimen.
†Subset of Taghipour 2016a; includes 77 patients who had more than 3 follow-up PET/CT scans after the completion of initial therapy. These 77 patients had 231 first three follow-up scans and 208 fourth and subsequent follow-up PET/CT scan

APPENDIX J. List of on-going studies

Appendix Table J1. List of on-going trials and studies of PET-adapted therapy for lymphoma

	Studies	Status
1.	Trial ID: NCT01357733 Title: Interim FDG PET/CT in Diffuse Large B Cell Lymphoma (DLBCL) Patients Link: https://clinicaltrials.gov/ct2/show/NCT01357733	Recruiting; as of April 2018, Estimated Completion: December 2020
2.	Trial ID: NCT03051555 Title: 18F-FDG PET/CT-based Prognostic Model for Predicting Outcome in Patients With Natural Killer/T-cell Lymphoma Link: https://clinicaltrials.gov/ct2/show/record/NCT03051555 Also registered as https://clinicaltrials.gov/ct2/show/record/NCT03051568	Not Yet Recruiting; as of February 2017 Estimated Completion: 2020
3.	Trial ID: NCT03051581 Title: 18F-FDG PET/CT-based Prognostic Model for Predicting Outcome in Patients With Peripheral T-cell Lymphoma Link: https://clinicaltrials.gov/ct2/show/record/	Not Yet Recruiting ; as of February 2017 Estimated Completion: 2020
4.	Trial ID: NCT03121456 Title: 18F-FDG PET Scan and MRI Diffusion : Correlation Study of the Evaluation of the Early Therapeutic Response of Diffuse Large B-cell Lymphoma Link: https://clinicaltrials.gov/ct2/show/record/NCT03121456	Recruiting; as of July 2017 Estimated Completion: 2021
5.	Trial ID: NCT01357733 Title: Early Interim Chemotherapy Response Evaluation by F-18 FDG PET/CT in Diffuse Large B Cell Lymphoma Link: https://clinicaltrials.gov/ct2/show/record/NCT01357733	Recruiting; as of April 2018 Estimated Completion: 2020
6.	Trial ID: NCT02928861 Title: 18F-FDG PET/CT-based Prognostic Model for Predicting Outcome in Patients With Diffuse Large B-cell Lymphoma Link: https://clinicaltrials.gov/ct2/show/record/NCT02928861	Active, not Recruiting; as of October 2016 Estimated Completion: December 2018
7.	Trial ID: NCT03525665 Title: Study on the Role of FDG-PET in Patients With FL at Time of Relapse/Progression Link: https://clinicaltrials.gov/ct2/show/record/NCT03525665	Recruiting; as of May 2018 Estimated Completion: 2018
8.	Trial ID: NCT03065790 Title: Early FDG PET/CT Imaging as a Measure of Response in Patients With Non-Hodgkin Lymphoma on Lenalidomide Link: https://clinicaltrials.gov/ct2/show/record/NCT03065790	Recruiting; as of February 2017 Estimated Completion: 2019
9.	Trial ID: NCT01118026 Title: Response-Based Therapy Assessed By PET Scan in Treating Patients With Bulky Stage I and Stage II Classical Hodgkin Lymphoma Link: https://clinicaltrials.gov/ct2/show/record/NCT01118026	Active, not Recruiting; as of January 2018 Estimated Completion: August 2020

	Studies	Status
10.	Trial ID: NCT02931201 Title: Evaluating Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography /Computed Tomography With Liver SUVmax-based Criteria for Prognosis of Patients With Diffuse Large B-cell Lymphoma Link: https://clinicaltrials.gov/ct2/show/record/NCT02931201	Recruiting; as of October 2016 Estimated Completion: December 2018
11.	Trial ID: NCT00795613 Title: Multicenter Clinical Study With Early Treatment Intensification In Patients With High- Risk Hodgkin Lymphoma, Identified As FDG-PET Scan Positive After 2 Conventional ABVD Courses Link: https://clinicaltrials.gov/ct2/show/record/NCT00795613	Unknown as of October 2015; verified by responsible party
12.	Trial ID: NCT00822120 Title: A Phase II Trial of Response-Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging Link: https://clinicaltrials.gov/ct2/show/record/NCT00822120	Active, not Recruiting; as of April 2018 Estimated Completion: April 2020
13.	Trial ID: NCT00678327 Title: A Randomized Phase III Trial to Assess Response Adapted Therapy Using FDG-PET Imaging in Patients With Newly Diagnosed, Advanced Hodgkin Lymphoma Link: https://clinicaltrials.gov/ct2/show/record/NCT00678327	Active, not Recruiting; as of January 2018 Estimated Completion: December 2018
14.	Trial ID: NCT00784537 Title: Early Salvage With High Dose Chemotherapy and Stem Cell Transplantation in Advanced Stage Hodgkin's Lymphoma Patients With Positive PET After Two Courses of ABVD (PET-2 Positive) and Comparison of RT Versus no RT in PET-2 Negative Patients Link: https://clinicaltrials.gov/ct2/show/record/	Active, not Recruiting; as of March 2018 Estimated Completion: December 2020

APPENDIX K. Lymphoma Classifications

Reference Guide to Lymphoma Types

Lymphoma is heterogeneous group of blood cancers originating from malignant lymphocytes (white blood cells) with dozens of subtypes with many different characteristics. Unless otherwise noted, the following classification of types, subtypes, and associated population and prevalence data is drawn from information provided by overviews of lymphoma from the American Cancer Society (www.cancer.org), and based on the most recent system for lymphoid tissue classification from the World Health Organization (WHO).[1-5] Due to expanding number of lymphoma subtypes, not all subtypes are captured here and classifications may be subject to change over time. References can be found immediately following the table.

Appendix Table K1. Lymphoma Classifications Table

Type/Subtype	Population	Rarity/Prevalence
HODGKIN LYMPHOMA		**8,500 diagnoses/year**
Classic HL (4 subtypes)		**95% of HL**
Nodular Sclerosis HL (NScHL)	Adult and Pediatric, common in teens and young adults (70% of pediatric HL)	60-80% of HL
Mixed Cellularity HL (MCcHL)	Older Adults and Pediatric	15-30% of HL
Lymphocyte-Rich Classic HL (LRcHL)	Older adults	5% of HL
Lymphocyte-Depleted HL (LDcHL)	older adults	1% of HL, aggressive
Nodular Lymphocyte-Predominant HL (NLPHL)	Adult and Pediatric, mostly men	**5% of HL**
NON HODGKIN LYMPHOMA		**75,000 diagnoses/year**
B-cell Lymphomas		**85% of NHL**
Diffuse Large B-Cell Lymphoma (DLBCL)	Primarily adults >60	30% of NHL, aggressive
-Primary Mediastinal Large B-cell Lymphoma (PMBCL)	Primarily younger women	2.5% of NHL, aggressive
-Primary Testicular Lymphoma (PTL)	Men, primarily >60	1-2% of NHL[6], aggressive
Mediastinal Gray-Zone Lymphoma (MGZL)	Primarily adults	<2.5% of NHL
Follicular Lymphoma (FL)	Primarily adults >60 Rare in younger people	20% of NHL, indolent but can be aggressive
Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)	Adults, mostly Western countries[7]	7% of NHL (~21,000 diagnoses/year), indolent[7]
Mantle Cell Lymphoma (MCL)	Primarily men >60	5% of Lymphomas, aggressive

Type/Subtype	Population	Rarity/Prevalence
Marginal Zone Lymphomas (B-Cell)	Primarily older adults	5-10% of lymphomas, mostly indolent
-Extranodal Marginal Zone B-Cell Lymphoma, AKA mucosa-associated lymphoid tissue lymphoma (MALT)	Adults >60	indolent
-Nodal Marginal Zone B-Cell Lymphoma	Primarily older women	indolent
-Splenic Marginal Zone B-cell Lymphoma	Primarily older men	rare
Cutaneous B Cell Lymphomas (CBCLs)		
-Primary Cutaneous Marginal Zone B-Cell Lymphoma (pcMZBCL)	All ages, primarily adults	Indolent
-Primary Cutaneous Follicle Center Lymphoma (pcFCL)	Primarily middle-aged adults	Indolent, most common CBCL
-Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg type	Primarily older women	Aggressive
Burkitt Lymphoma / Burkitt-Like Lymphoma -Endemic Variety -Western variety	Rare in adults, more common in male children	Aggressive, endemic variety is associated with Epstein-Barr virus, rare outside of Africa. Western variety is more commonly seen in US.
Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)	Primarily older men	<2% (1,000-1,500 diagnoses/year) of lymphomas
Hairy Cell Leukemia (HCL)	Primarily men >50	Very rare (700 diagnoses/year), indolent sometimes considered a lymphoma subtype
Primary Central Nervous System Lymphoma (PCNSL)	Primarily older adults	Rare, associated with primary intraocular lymphoma
T-Cell Lymphomas		**15% of NHLs**
Precursor T-lymphoblastic lymphoma/leukemia	Primarily male teens or young adults	1% of lymphomas, aggressive
Cutaneous T-Cell Lymphomas (CTCLs)		5% of lymphomas
-Mycosis Fungoides/Sezary Syndrome (MF/SS) -Foliculotropic MF -Pagetoid reticulosis MF -Granulomatous Slack Skin MF	Any age, primarily men >50	Indolent (MF) or aggressive (SS), 50% of skin lymphomas are MF, has rarer sub-variants;
-Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders	See below	See below
-primary Cutaneous Anaplastic Large Cell Lymphoma (PC-ALCL)	Any age, primarily adults >50	Indolent
-Lymphomatoid Papulosis (LyP) -Type A - Type B - Type C	Primarily men aged ~45	indolent

Type/Subtype	Population	Rarity/Prevalence
-Extranodal natural killer/T-cell lymphoma (ENKTCL or ENKL) -nasal -nasal type	Nearly always Epstein-Barr virus positive-associated; common to Asia, Central and South America[8]	Rare, aggressive, can present in nose (nasal) or in other organs (nasal type)
-Subcutaneous panniculitis-like T-cell lymphoma	All ages, sexes	Rare, indolent
-Primary cutaneous gamma/delta T-cell lymphoma	Only minimal data available	Rare, aggressive
-Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	Only minimal data available	Rare, aggressive
-Primary cutaneous acral CD8+ T-cell lymphoma	Only minimal data available	Very Rare, indolent
-Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	Only minimal data available	Rare, indolent
Other T-Cell Lymphomas		
-Adult T-Cell Leukemia/Lymphoma (ATLL): -smoldering type -chronic type -acute type	Primarily adults	Rare, can be aggressive or indolent
- Hepatosplenic T-cell lymphoma. (HSTL) -Gamma-Delta Type -Alpha-Beta Type	Primarily adolescents and young adults, mostly male	<1% of all NHL[9]; mostly gamma-delta type rather than alpha-beta type
-Angioimmunoblastic T-cell lymphoma	Primarily in older adults	4% of all lymphomas, aggressive
-Enteropathy-associated intestinal T-cell lymphoma (EATL) -Type I -Type II	Primarily men	Rare
Anaplastic large cell lymphomas (ALCL): -Breast Implant-Associated ALCL -Systemic ALCL	More common in young people (children) but can affect older adults (especially women with breast implants)	2% of lymphomas, rare, aggressive
Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) -any unspecified type not fitting in other groups	Primarily in adults >60	aggressive

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APPENDIX L. Summary of Guidelines

A summary table (Appendix Table L1) of guideline consensus can be found below, arranged by lymphoma types and stages, that condenses agreements or disagreements related to PET therapy recommendations. The level of agreement between guidelines is characterized, recommendation strength is described and quality of evidence is summarized, as available. A complete summary of each guideline of PET imaging for Lymphoma follows (Appendix Table L2), including guidelines from the following organizations and groups:

- **International Conference on Malignant Lymphomas Imaging Working Group Consensus Statement and Summary of Recommendations (Barrington et al. 2014 and Cheson et al., 2014)**
- **National Comprehensive Cancer Network (NCCN) Guidelines**
- **NICE UK Guidelines**
- **British Journal of Haematology**
- **European Society for Medical Oncology (ESMO)**
- **American College of Radiology (ACR) Appropriateness Criteria across different lymphomas**
- **British Medical Journal**
- **Alberta Health Services (AHS) Clinical Practice Guideline**
- **Australian Government Medical Services Advisory Committee (MSAC) – Public Summary Document**
- **Spanish Lymphoma Group (GELTAMO)**
- **Clinical Oncology Working Group (Herst 2017): Hodgkin Lymphoma Guidelines**
- **AIM Specialty Health Clinical Appropriateness Guidelines**

A complete bibliography of included guidelines can be found at the end of Appendix L.

Appendix Table L1. Synthesis of recommendations across clinical guidelines of PET staging and response assessment in lymphoma (all types)

Condition	Areas of Consensus	Consensus (Strength of Recommendation)				
		Initial Staging	Interim	End of Treatment	Restaging/Relapse or Refractory	Surveillance/Follow-up
FDG-Avid Lymphomas						
FDG-Avid Lymphomas [2]*	Recommendation	Yes (++)	Yes (++)	Yes (++)	Yes (++)	N (-)
	Quality of Evidence	Low	Low	NR	NR	NR
Hodgkin Lymphoma						
classical HL [6]	Recommendation	Yes (++/-)	Mixed (++/+++)	Yes (-)	Yes (++/-)	Mixed (++/-)
	Quality of Evidence	Low-Moderate	Low-High	NR	Low or NR	Low or NR
Nodular Lymphocyte Predominant HL (NLPHL) [2]	Recommendation	Yes (+)	No (+++)	Mixed (++/+++)	Yes (++)	No (++)
	Quality of Evidence	Moderate	Low	Low	Low	Low
Aggressive Non-Hodgkin Lymphoma (aNHL)						
aggressive/High-Grade Non-Hodgkin Lymphomas [2]*	Recommendation	Yes (-)	Mixed (-)	Mixed (-)	Mixed (-)	No (-)
	Quality of Evidence	NR	NR	NR	NR	NR
Diffuse Large B-Cell Lymphomas (DLBCL) [5]	Recommendation	Yes (++/+++)	Mixed (+++/-)	Yes (+++)	Mixed (+)	No (++/+++)
	Quality of Evidence	Low-Moderate	Low-High	High	Moderate	Low
Extranodal Lymphomas [5]	Recommendation	Yes (++)	NR	Yes (+/++)	NR	NR
[Extranodal Natural Killer/T-Cell Lymphoma (ENKL), Primary Mediastinal Large B-Cell Lymphoma (PMBL), Primary Testicular Lymphoma (PTL)]	Quality of Evidence	Low	NR	Low-Moderate	NR	NR
Peripheral T-Cell Lymphomas [2]	Recommendation	NR	NR	Yes (-)	NR	No (-)
	Quality of Evidence	NR	NR	NR	NR	NR
Primary Central Nervous System Lymphoma [3]	Recommendation	Mixed (+++)	NR	No (-)	N (-)	N (-)
	Quality of Evidence	Low or NR	NR	NR	NR	NR

Condition	Areas of Consensus	Consensus (Strength of Recommendation)				
		Initial Staging	Interim	End of Treatment	Restaging/Relapse or Refractory	Surveillance/Follow-up
Mantle Cell Lymphoma (MCL) [3]	Recommendation	M (+/++)	NR	Mixed (++/-)	NR	NR
	Quality of Evidence	Low-High	NR	High or NR	NR	N (-)
Burkitt Lymphoma [1]	Recommendation	Yes (-)	NR	Yes (-)	NR	NR
	Quality of Evidence	NR	NR	NR	NR	NR
Indolent NHLs						
Indolent NHLs [4]*	Recommendation	Y (-)	NR	Y (-)	M (-)	N (-)
	Quality of Evidence	NR	NR	NR	NR	NR
Other NHL subtypes (various)* [1]	Recommendation	M (+/-)	NR	NR	NR	NR
	Quality of Evidence	NR	NR	NR	NR	NR
Follicular Lymphoma [4]	Recommendation	M (+/++)	NR	U (++)	NR	N (-)
	Quality of Evidence	Low or NR	NR	Moderate	NR	NR
CLL/SLL, Richter's Transformation [3]	Recommendation	M (+/++)	NR	M (+)	M (-)	NR
	Quality of Evidence	Low or NR	NR	Low	NR	NR
Other T-Cell Lymphomas [4] **[Adult T-Cell Leukemia/Lymphoma (ATLL), Breast-Implant Associated or Primary cutaneous Anaplastic Large Cell Lymphoma (BIA-ALCL), T-Cell Prolymphocytic Leukemia (TPLL)]**	Recommendation	ATLL M (+/++) BIA-ALCL Y (+/++) TPLL M (+/++)	ATLL M (++)	ATLL M (+/++)	NR	BIA-ALCL U (++)
	Quality of Evidence	ATLL Low BIA-ALCL Low TPLL Low	ATLL Low	ATLL low	NR	BIA-ALCL +
Cutaneous Lymphomas [4] **[Primary Cutaneous B-Cell Lymphoma (PCBCL), Primary Cutaneous CD30+ T-Cell**	Recommendation	all M (+/++)	NR	PCBCL M (+/++)	NR	NR
	Quality of Evidence	all	NR	PCBCL	NR	NR

Condition	Areas of Consensus	Consensus (Strength of Recommendation)				
		Initial Staging	Interim	End of Treatment	Restaging/Relapse or Refractory	Surveillance/Follow-up
Lymphoproliferative Disorders (PC-CD30+) and Mycosis Fungoides and Sezary Syndrome (MF/SS)]		Low		Low		
Marginal Zone Lymphomas [3]	Recommendation	M (+)	NR	M (+)	NR	NR
	Quality of Evidence	Low	NR	Low	NR	NR
Miscellaneous NHLs [4] **[post-transplant lymphoproliferative disease (PTLD)], Hairy Cell Leukemia (HCL), primary breast lymphoma (PBL), Primary Bone Lymphoma (PBoL)]**	Recommendation	PTLD Mixed (+) HCL Mixed (+/++) PBL Mixed (+/++) PBoL Mixed (+/++)	NR	PBL Mixed (+/-) PBoL Mixed (+/-)	NR	NR
	Quality of Evidence	PTLD Low HCL Low PBL Low PBoL Low	NR	PBL Low or NR PBoL Low or NR	NR	NR

NR = not reported

Strength of Recommendation: + = Low or weak; ++ = Moderate; +++ = High; - = No evidence or not reported; +/++ = ranges between the levels shown

*In cases where a guideline reports on an overarching category of lymphoma (such as all FDG-avid Lymphomas, which includes all HL subtypes and a variety of NHL types, or aggressive or high grade NHL, etc.), its recommendations are not necessarily repeated or tabulated in the summary of consensus for more specific subtypes within this table, even if their recommendations apply.

Appendix Table L2. Summary of PET imaging recommendations from clinical guidelines of Lymphoma

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
International Consensus Statements			
Consensus Statement - International Conference on Malignant Lymphomas Imaging Working Group 2014 And **Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al., 2014)** FDG-Avid Lymphomas (Hodgkin's and Non-Hodgkin's Lymphomas) *Barrington et al., Role of imaging in the staging and response assessment*	Literature review and Expert Consensus Staging: 19 key studies comparing PET or PET/CT with CT alone, type NR (1248 patients) Interim PET: 8 studies (type NR) for HL, 7 studies (type NR) for aggressive NHL, 1 clinical trial (type NR), 8 studies (type NR) for DLBCL End of Treatment PET: Previously cited studies and 8 additional studies (type NR) Additional citations for each stage are reported in Cheson et al., 2014	**FDG-avid, nodal lymphomas** Staging PET-CT is preferred for staging of FDG-avid lymphomas, and CT scan is preferred in the other lymphomas. 1. PET-CT should be used for staging in clinical practice and clinical trials but is not routinely recommended in lymphomas with low FDG avidity; PET-CT may be used to select best site to biopsy **(type 1)** 2. Contrast-enhanced CT when used at staging or restaging should ideally occur during single visit combined with PET-CT, if not already performed; baseline findings will determine whether contrast-enhanced PET-CT or lower-dose unenhanced PET-CT will suffice for additional imaging examinations **(type 2)** 3. Bulk remains an important prognostic factor in some lymphomas; volumetric measurement of tumor bulk and total tumor burden, including methods combining metabolic activity and anatomical size or volume, should be explored as potential prognosticators **(type 3)** Interim PET PET-CT should be used for interim (early) response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity. 1. If mid-therapy imaging is performed, PET-CT is superior to CT alone to assess early response; trials are evaluating role of PET response–adapted therapy; currently, it is not recommended to change treatment solely on basis of interim PET-CT unless there is clear evidence of progression **(type 1)** 2. Standardization of PET methods is mandatory for use of quantitative approaches and desirable for routine clinical practice **(type 1)** 3. Data suggest that quantitative measures (eg, SUVmax) could be used to improve on visual analysis for response assessment in DLBCL, but this requires further validation in clinical trials **(type 2)**	Recommendations were formulated as follows: * **Type 1**: Based on established current knowledge * **Type 2**: To identify emerging applications * **Type 3**: To highlight key areas requiring further research

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. Journal of clinical oncology. 2014 Sep 20;32(27):3048.		End of Treatment PET-CT should be used for end of treatment response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity. 1. PET-CT is standard of care for remission assessment in FDG-avid lymphoma; in presence of residual metabolically active tissue, where salvage treatment is being considered, biopsy is recommended **(type 1)** 2. Investigation of significance of PET-negative residual masses should be collected prospectively in clinical trials; residual mass size and location should be recorded on end-of-treatment PET-CT reports where possible (**type 3**) 3. Emerging data support use of PET-CT after rituximab-containing chemotherapy in high–tumor burden FL; studies are warranted to confirm this finding in patients receiving maintenance therapy **(type 2)** 4. Assessment with PET-CT could be used to guide decisions before high-dose chemotherapy and ASCT, but additional studies are warranted **(type 3)** Surveillance Surveillance scans after remission are discouraged, especially for DLBCL and HL, although a repeat study may be considered after an equivocal finding after treatment. Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease.	
NCCN Guidelines			
National Comprehensive Cancer Network (NCCN) 2018 (Hodgkin Lymphoma)	Systematic Literature Review and Expert Consensus 1 meta-analysis, 13 studies type NR, [26,27], 3 randomized trials, 7 retrospective analyses, 3 prospective studies, , 1 study with 1 long term follow-up study type NR	**Hodgkin Lymphoma** Initial Staging 1. PET recommended for initial staging of HL and for evaluation of residual masses after treatment. An integrated PET scan plus diagnostic CT is recommended for initial staging, although a separate diagnostic CT is not needed if it was part of the integrated PET scan. (**2A**) Interim 2. Interim PET scans may be useful to identify a subgroup of patients with early-stage disease that can be treated by chemotherapy alone. The value of interim PET scans is considered to be unclear for many clinical scenarios and all measures of response should be considered in the context of management decisions. (**2A**)	NCCN Categories of Evidence and Consensus: **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A**: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
		Prognosis 3. Initial results from retrospective analyses have failed to demonstrate the prognostic significance of interim PET scans in stage I-II favorable disease. Surveillance 4. PET scans not recommended for routine post-therapy surveillance, due to the risk of false positives. Management decisions should not be based on PET scan alone, clinical or pathological correlation is needed. Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy. PET/CT only if last PET was Deauville 4-5, to confirm complete response for follow-up after completion of treatment up to 5 years. (**2A**) Restaging/Relapse or Refractory Disease Second-line systemic therapy followed by response assessment with PET is recommended for all patients. Suspected relapse should be confirmed with biopsy. Observation (with short-interval follow-up with PET/CT) is appropriate if biopsy is negative. **Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)** End of Treatment Reevaluation with PET should be done for all patients after completion of initial therapy. Observation is recommended for all asymptomatic patients with a clinical response. Surveillance PET scans are not recommended for routine surveillance due to the risk of false positives. Relapse or Refractory Disease All patients with biopsy-proven NLPHL should be observed or treated with second-line therapy followed by reevaluation with PET.	**Category 2B:** Based upon high-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3**: Based upon high-level evidence, there is major NCCN disagreement that the intervention is appropriate.
National Comprehensive Cancer Network (NCCN) 2018 (Non-Hodgkin Lymphoma: B-Cell Lymphomas)	Systematic Literature Review and Expert Consensus Overview	**Overview of NHL** Initial Staging 1. PET-CT is recommended for initial staging of FDG-avid lymphomas, PET should be done with contrast-enhanced diagnostic CT. (**2A**) 2. Staging imaging with CT is recommended for lymphomas that are minimally FDG-avid (**CLL/SLL, marginal zone lymphomas, HCL, cutaneous B-Cell lymphoma, MF/SS, CD30+**	Outlined above

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
	1 meta-analysis, 1 retrospective study , 1 prospective study FL: 4 studies type NR, 2 studies type NR, 1 retrospective study, 1 retrospective analysis of RCT data, 1 prospective study, 1 retrospective study, 1 prospective study DLBCL: 3 studies, type NR Interim DLBCL 7 studies type NR, 2 prospective studies, 1 retrospective analysis Surveillance DLBCL 1 study type NR, 1 retrospective study, 1 prospective study, 5 retrospective studies, 1 registry study, Relapsed or Refractory 1 RCT, 1 retrospective analysis, 9 studies type NR	**cutaneous lymphomas and T-Cell large granular lymphocytic leukemia**), except in selected circumstances. FDG-avid lymphomas should have response assessed by PET-CT using the Lugano 5-point scale. (**2A**) 3. False-positive PET scans may be observed related to infectious or inflammatory conditions. (**2A**) 4. Biopsy remains gold standard for confirming new or persistent disease at end of therapy. (**2A**) **Follicular Lymphoma** <u>Initial Staging</u> In patients presenting with what appears to be localized disease, a PET scan may be helpful in identifying occult sites of disease or if there is concern about histologic transformation. PET does not replace histologic confirmation of the diagnosis; however, if there are sites with discordant high FDG-avidity, these represent the most likely sites of transformation. The use of PET-CT is considered optional or useful in select patients with FL during workup or post-treatment assessment. (**2A**) **Diffuse Large B-Cell Lymphoma (DLBCL)** <u>Initial Staging</u> PET-CT scan ± chest/abdominal/pelvic CT with contrast of diagnostic quality is recommended for initial workup. As PET scans have now been incorporated into the response criteria, a baseline PET is necessary for optimal interpretation of post-treatment PET scans. Bone marrow biopsy may not be needed if there is clearly positive marrow uptake by PET-CT. BMB may also be omitted in the absence of any skeletal uptake on the staging of PET/CT scan, unless finding another lymphoma subtype (discordant low-grade lymphoma) would be considered important for treatment decisions. (**2A**) <u>Interim</u> Interim PET imaging is not recommended to be used to guide changes in therapy. If treatment modifications are considered on the basis of interim PET scan results, a repeat biopsy of residual masses should be strongly considered to confirm PET-positivity prior to additional therapy. If the biopsy is negative, the planned course of treatment as recommended for PET-negative guidelines should be completed. Patients should undergo evaluation prior to	

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
	PBML 2 studies type NR	receiving RT, including all positive studies. If RT is not planned, interim restaging after 3-4 cycles of R-CHOP is appropriate to confirm response. <u>Interim with Stage I-II</u> If interim restaging demonstrated a PET-Positive, treatment with a higher dose of RT is appropriate. At the present time, there is no data to suggest that a PR with persistent PET positivity after 3 cycles should prompt a change in treatment. (**2A**) <u>End of treatment</u> End of treatment restaging is performed upon completion of treatment. (**2A**) <u>Surveillance</u> NCCN Guidelines do not recommend the use of PET or CT for routine surveillance for patients with stage I-II disease who have achieved a CR to initial therapy. When surveillance imaging is performed, CT scan is preferred over PET/CT for the majority of patients. PET/CT may be preferable for patients with primarily osseous presentations, with the caveat that bone remodeling may also be FDG-avid, so a biopsy is recommended for PET positive sites prior to instituting second line therapy (**2A**) <u>Relapsed or Refractory Disease</u> All patients with relapse or refractory DLBCL should be considered for enrollment in available clinical trials. (**2A**) **Primary Mediastinal Large B-Cell Lymphoma (PMBL)** <u>End of Treatment</u> Post-treatment PET-CT is considered essential; if PET-CT is negative at the end of treatment and initial disease was non-bulky, patients may be observed. Residual mediastinal masses are common. For patients initially treated with R-CHOP, consolidation with RT should be considered, particularly if increased FDG-activity persists in the primary tumor. For patients who are PET-CT negative after more intensive therapies (e.g. DA-EPOCH-R), observation may be appropriate. If PET-CT is positive, biopsy is recommended before additional treatment is contemplated. (**2A**)	

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
National Comprehensive Cancer Network (NCCN) 2018 (CLL/SLL)	Literature Review and Expert Consensus CLL & Richters Transformation: 4 studies type NR	**CLL** PET scan is considered not useful for CLL but can assist in directing nodal biopsy if Histological (Richter's) transformation is suspected. (**2A**) **Richters Transformation** Initial Staging PET/CT scans are recommended to direct nodal biopsy and biopsies should be directed to lesions with highest FDG uptake on PET scans. (**2A**)	Outlined above
NCCN Consensus Guidelines for the Diagnosis and Management of Primary Cutaneous B-Cell Lymphomas (2018)	Literature Review and Expert Consensus Treatment recommendations are derived from management practices of patients with PCBCL at NCCN member institutions based on limited data from retrospective analyses and small studies	**PCBCL** Initial Staging Chest/abdominal/pelvic CT with contrast or PET/CT are considered essential. (**2A**) End of Treatment PET/CT is strongly preferred to assess end of treatment response. It can be repeated if there is clinical suspicion of progressive disease. (**2A**)	Outlined above
NCCN Consensus Guidelines for the Diagnosis and Management of T-Cell Lymphomas (2018) and **NCCN Consensus Guidelines for the Diagnosis**	Literature Review and Expert Consensus Key consensus statements (Lugano criteria) **Overview** Staging: [12] 1 retrospective study [13], 1 prospective study [14]	**Overview** Initial Staging PET/ceCT is recommended for initial staging of FDG-avid lymphomas. FDG-avid lymphomas should have response assessed by PET/CT using the 5-Point Scale. False-positive PET scans may be observed related to infectious of inflammatory conditions. Biopsy of affected sites remains the gold standard for confirming new or persistent disease at the end of therapy. (**2A**) Interim Interim restaging should be done with PET/CT or Chest/abdominal/pelvic CT scan with contrast. (**2A**) End of Treatment	Outlined above

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
and Management of Breast Implant-Associated Anaplastic Large Cell Lymphoma (2017)	MF/SS: 1 prospective study PL-ALCL 1 retrospective analysis ENKL 3 retrospective analyses	At completion of treatment, repeat PET/CT or C/A/P CT scan with contrast. If PET/CT scan positive, rebiopsy before changing course of treatment. (**2A**) **Adult T-Cell Leukemia/Lymphoma** Initial Staging CT scans of chest/abdomen/pelvis should be performed. PET/CT scans are considered useful in selected cases. (**2A**) Interim Usefulness of PET/CT has not been evaluated in [interim] response of patients with ATLL. If nodal disease is present, repeat chest/abdominal/pelvic CT with contrast or PET/CT. (**2A**) End of Treatment Usefulness of PET/CT has not been evaluated in [end of treatment] response of patients with ATLL. If nodal disease is present, repeat chest/abdominal/pelvic CT with contrast or PET/CT. (**2A**) **Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)** Initial Staging For confirmed cases of BIA-ALCL, a PET scan is often beneficial for demonstrating associated capsular masses, chest wall involvement, and is the preferred test to evaluate (**2A**) Surveillance Physicians may include chest abdominal/pelvic computerized tomography (CT) scans with contrast or PET scan every 6 months for 2 years then only as clinically indicated. (**2A**) **T-Cell Prolymphocytic Leukemia (TPLL)** Initial Staging PET/CT scan is considered useful in selected cases **Extranodal Natural Killer/T-Cell Lymphoma, nasal type (ENKL)** Initial Staging Chest/abdominal/pelvic CT with contrast or PET/CT are considered essential. (**2A**)	

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
		End of Treatment Response After radiation therapy evaluation repeat initial imaging of CT, MRI or PET/CT scan. (**2A**) **Mycosis Fungoides and Sezary Syndrome** Initial Staging CT with contrast or PET/CT is recommended for patient with unfavorable features (T2b or higher, FMF or LCT, palpable adenopathy, or abnormal laboratory studies) and should be considered for patients with T2a (patch disease with 10% or more BSA). (**2A**) **Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders** Initial Staging CT with contrast or integrated whole body PET/CT is recommended for primary cutaneous anaplastic large cell lymphoma (PC-ALCL). Bone marrow evaluation has limited value in the staging of patients with PC-ALCL and is not required for disease staging. Bone marrow aspiration and biopsy only recommended for solitary PC-ALCL or PC-ALCL with extra-cutaneous involvement on imaging. (**2A**)	
NCCN Consensus Guidelines for the Diagnosis and Management of Hairy Cell Leukemia (2017)	NA	No PET-specific guidelines are included.	NA
International and National Guidelines			
NICE Non-Hodgkin's lymphoma: diagnosis and management 2016	Literature Review and Expert Consensus Staging: prospective and retrospective data from 27 cross-sectional studies and 16 cohort studies Response to Treatment (DLBCL):	**DLBCL, FL, Burkitt Lymphoma** Initial Staging Offer FDG-PET-CT imaging to confirm staging for people diagnosed with: • stage I diffuse large B-cell lymphoma by clinical and CT criteria • stage I or localized stage II follicular lymphoma if disease is thought to be encompassable within a radiotherapy field • stage I or II Burkitt lymphoma with other low-risk features. For people diagnosed with other subtypes or stages of non-Hodgkin's lymphoma not listed, consider FDG-PET-CT imaging to confirm staging if the results will alter management. (Quality of evidence assessed as **LOW** using QUADAS-2)	QUADAS-2, NICE Checklist and GRADE

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
	17 cohort studies (2326 patients) End of Treatment : 10 retrospective cohort studies (915 patients) Follow-up DLBCL: 1 retrospective case series and 1 retrospective cohort study	**DLBCL** <u>Interim</u> Do not routinely offer FDG-PET-CT imaging for interim assessment during treatment for diffuse large B-cell lymphoma. (Quality of Evidence assessed as **MODERATE** using NICE checklists for prognostic studies) <u>Surveillance</u> For people in complete remission after first-line treatment with curative intent for diffuse large B-cell lymphoma: • do not offer routine surveillance imaging (including chest X-ray, CT and PET-CT) for detecting relapse in people who are asymptomatic. (Quality of Evidence assessed as **VERY LOW** using GRADE methodology) **DLBCL, Burkitt Lymphoma** <u>End of Treatment</u> Offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with: • diffuse large B-cell lymphoma • Burkitt lymphoma. For people with other subtypes of non-Hodgkin's lymphoma not listed, do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management. **High Grade NHL** <u>Restaging</u> Consider FDG-PET-CT imaging to assess response to treatment before autologous stem cell transplantation for people with high-grade non-Hodgkin's lymphoma. (Quality of evidence assess as **MODERATE** using NICE checklists for prognostic studies)	

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
British Journal of Haematology - Guidelines for the investigation and management of nodular lymphocyte predominant Hodgkin lymphoma (2016)	Literature Review and Expert Consensus Pre-treatment evaluation: 2 retrospective case series, other case reports Interim PET: 2 studies (type NR) End of Treatment: None	**NLPHL** Initial Staging Consider pre-treatment staging with FDG-PET, especially for patients with localized disease by CT imaging as upstaging would be likely to result in a change in management (i.e. that radiotherapy would not be offered) **(2B)** Bone marrow biopsy may be deferred in patients with advanced stage disease, with normal laboratory parameters and who have no evidence of bone involvement on FDG-PET scanning **(2C)** Interim PET There is no evidence to support the use of interim PET/ CT imaging in patients with NLPHL outside of a clinical trial (**1C)** End of Treatment There are no published series specifically addressing the use of PET/CT to confirm remission status at the end of first line therapy and, as such, we cannot recommend this at this time **(1C)**	The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations.
British Journal of Haematology - Guidelines for the management of diffuse large B-cell lymphoma	Literature Review and Expert Consensus Staging: 5 studies and or guidelines; 1 meta-analysis; 5 studies (type NR) Interim PET & End of Treatment: 10 studies (type NR)	**DLBCL** Initial Staging Where possible, a staging PET/CT scan is recommended for all patients **(1B)**. Currently a staging bone marrow biopsy remains the standard of care **(1A).** However, emerging evidence suggests PET may be very valuable in assessing bone marrow involvement in DLBCL though it may miss low level or discordant disease (**2B)**. Interim PET The PPV of an interim PET scan is variable with insufficient evidence at present to change standard treatment based on the result of interim PET-CT scan alone. A routine interim PET scan is therefore not recommended **(1C)**. End of Treatment An end of treatment PET scan is strongly recommended **(1A)**. Relapsed/Refractory In transplant eligible patients, response assessment by PET scan prior to ASCT is desirable (**2B)**	The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations.

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
British Journal of Haematology - Guidelines for the investigation and management of mantle cell lymphoma (2012)	Literature Review and Expert Consensus Staging: 2007 IWG statement (Cheson et al., 2007) 2 studies (type NR) Response to Therapy: None	**Mantle Cell Lymphoma (MCL)** <u>Initial Staging</u> Routine use of FDG-PET in the staging of MCL is not recommended. **(Strong, Moderate)** <u>Interim Response Assessment</u> Treatment response should be assessed using conventional CT scanning. FDG-PET and assessment of minimal residual disease are not currently recommended outside the context of a clinical trial. **(Strong, Moderate)** <u>End of Treatment Response Assessment</u> Treatment response should be assessed using conventional CT scanning. FDG-PET and assessment of minimal residual disease are not currently recommended outside the context of a clinical trial. **(Strong, Moderate)**	
ESMO Clinical Guidelines			
Hodgkin's lymphoma: ESMO Clinical Practice Guidelines (2018)	Literature Review and Expert Consensus Initial Staging and Final Staging: Consensus statements and Guidelines Interim PET: 2 studies (type NR)	**Hodgkin Lymphoma** <u>Initial Staging</u> Chest X-ray and a contrast-enhanced computed tomography (CT) scan of neck, chest and abdomen are mandatory. In addition, a baseline positron emission tomography (PET) should be carried out according to the recommendations for staging and response assessment in lymphoma whenever this diagnostic tool is available. Given the high sensitivity of PET/CT for bone marrow involvement, a bone marrow biopsy is no longer indicated in patients undergoing PET/CT evaluation **[III, B]** However, bone marrow biopsy must be carried out if PET/CT is not available. <u>Interim PET</u> All patients should undergo interim staging to exclude disease progression during treatment and to stratify treatment if PET–CT is available. The question of whether RT can be omitted in patients with complete metabolic response at interim PET is currently a matter of debate and cannot be fully answered to date. The available data consistently demonstrate a progression-free survival (PFS) advantage for patients treated with combined-modality approaches despite a negative interim PET (defined as a Deauville score 2 within the	<u>Levels of evidence</u> ▪ I: Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity ▪ II: Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity ▪ III: Prospective cohort studies ▪ IV: Retrospective cohort studies or case–control studies ▪ V: Studies without control

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
		RAPID and H10 studies). Thus, a patient group that can be safely treated with Chemotherapy alone could not yet be defined **[I, A]** <u>End of Treatment</u> Final staging should be carried out after completion of treatment. Physical examination, laboratory analyses and contrast enhanced CT are mandatory. In addition, PET should be carried out at final staging according to the guidelines for staging and response assessment in lymphoma whenever this diagnostic tool is available	<u>Grades of recommendation</u> ▪ A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended ▪ B: Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended ▪ C: Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,…), optional ▪ D: Moderate evidence against efficacy or for adverse outcome, generally not recommended ▪ E: Strong evidence against efficacy or for adverse outcome, never recommended
Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2015)	Literature Review and Expert Consensus Staging: International consensus guidelines Interim: 1 randomized, 1 study, type NR Response Evaluation: 1 study, type NR	**Diffuse large B-cell lymphoma** <u>Initial Staging</u> FDG-PET/CT scan is recommended as the gold standard for staging DLBCL patients **[V, A]**. If CeCT is not carried out before PET/CT, a full diagnostic high-dose CeCT should be carried out when necessary, in combination with PET/CT **[V, B]**. Biopsy may be avoided when PET/CT scans demonstrate bone or marrow involvement indicating advanced-stage disease but is appropriate in the case of negative PET, when its results would change prognosis and treatment, especially when a shortened number of immuno-chemotherapy cycles is proposed **[V, C]**.	<u>Outlined above.</u>

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
	Follow-up: None reported.	<u>Interim PET</u> Changing treatment solely on the basis of interim PET/CT is discouraged **[II, E]**, unless there is clear evidence of progression; Early PET evaluation carried out after one to two cycles of treatment has been shown to be predictive of outcome, but should be reserved for clinical trials at the present time **[II, D]**. The role of interim PET to select patients who could benefit from consolidative ASCT or from radiotherapy is under evaluation **[I, C]**. <u>End of Treatment</u> FDG-PET/CT is the recommended standard for post-treatment assessment in DLBCL **[I, A].** <u>Surveillance</u> Routine surveillance with PET scan is not recommended **[V, E]**.	
Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2016)	Literature Review and Expert Consensus Staging: Consensus guideline and unspecified retrospective cohorts or case-control studies End of Treatment: 1 study (Trotman 2014) Surveillance: Consensus-based, no literature cited	**Follicular Lymphoma** <u>Initial Staging</u> Positron emission tomography (PET) / CT improves the accuracy of staging for nodal and extranodal sites and thus should be recommended for routine staging in FL **[IV, C]** <u>End of Treatment</u> PET–CT after completion of chemotherapy induction has been recommended for prognostic reasons as persistent PET positivity (using appropriate Deauville scales) identifies a small group (20%–25%) of patients with a worse prognosis, but therapeutic consequences remain undefined **[II, B]**. <u>Surveillance</u> PET–CT should be not used for surveillance.	<u>Outlined above</u>
Extranodal diffuse large B-cell lymphoma (DLBCL)	Literature Review and Expert Consensus	**Primary Mediastinal Large B-Cell Lymphomas (PMLBCL)** <u>End of Treatment</u>	<u>Outlined above</u>

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2016)	PMLBCL: Prospective cohorts not otherwise specified. PTL: One ongoing study (NCT00945624) and unspecified prospective cohorts.	FDG-PET/CT scan is mandatory to assess disease extent and to obtain better definition of the residual mediastinal masses at the completion of treatment, because PMBCL shows universal FDG-avidity. Positive post-treatment PET scans require further investigation before modifying planned therapy. A post-treatment PET/CT response evaluation should not be carried out until at least 5–6 weeks from the last infusion of chemotherapy to minimize the incidence of these false-positive scans. In young patients who do not obtain an adequate response (i.e. less than partial response) with an elevated FDG uptake at the post immunochemotherapy PET/CT scan, if residual disease is confirmed by biopsy when feasible, an intensification therapy with HDCT/ASCT is recommended **[III, B]** **Primary Testicular Lymphoma (PTL)** End of Treatment FDG-PET/CT can be considered the recommended standard for post-treatment assessment in PTL. RT to involved nodes could be safely omitted if PET is negative after R-CHOP chemotherapy **[III, C]** **Primary CNS lymphomas** Initial Staging PET/CT is standard for initial staging. **[V, B]** End of Treatment Based on the rarity of systemic progressions, additional systemic evaluation (i.e. CT or CT/PET scans) are indicated only in the case of clinical signs or symptoms of systemic progression. **Primary Breast Lymphoma** Initial Staging PET/CT is standard for initial staging. **[V, B]** End of Treatment FDG PET/CT can be considered the recommended standard for post-treatment assessment in Primary Breast Lymphoma	

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
		Primary Bone Lymphoma Initial Staging PET/CT is standard for initial staging. **[V, B]** End of Treatment FDG PET/CT can be considered the recommended standard for post-treatment assessment in pBoL.	
Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2017) and **ESMO Consensus Conference on malignant lymphoma: general perspectives and recommendations for the clinical management of the elderly patient with malignant lymphoma (2017)**	Literature Review and Expert Consensus Overall: 1 consensus guideline No other PET-specific citations are provided.	**Mantle Cell Lymphoma** Initial Staging Positron emission tomography (PET)-CT scan is especially recommended in the rare limited stages I/II, before localized radiotherapy (RT) **[IV, C]**. Interim PET-CT according to Lugano Classification for response evaluation is optional. Radiological tests should be carried out mid- and post-completion of chemotherapy. End of Treatment PET-CT according to Lugano Classification for response evaluation is optional. Radiological tests should be post-completion of chemotherapy. Surveillance PET-CT should not be used for surveillance. **Mantle Cell Lymphoma (Elderly Patients)** Initial Staging The use of PET-CT imaging is considered optional for fit elderly patients with Mantle Cell Lymphoma. Not recommended for terminally ill patients. **[V, A]** End of Treatment The use of PET-CT imaging is considered optional for fit elderly patients with Mantle Cell Lymphoma **[V, A]** **DLBCL (Elderly Patients)** Initial Staging	Outlined above

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
		Staging should be with PET-CT. **[V,A]**	
Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2015)	Literature Review and Expert Consensus ENKTCL: 4 studies(type NR) PTCL:2 citations(type NR)	**Extranodal Natural Killer T-Cell Lymphoma (ENKTCL)** Initial Staging ENKTCL is FDG-avid, and although the role of PET/CT for response evaluation is not yet fully clarified, PET/CT is the recommended imaging modality in ENKTCL. **Peripheral T-Cell Lymphoma (PTCL)** Interim In systemic PTCL, a midway interim evaluation should be carried out in order to assess chemosensitivity End of Treatment Diagnostic imaging (CT or PET/CT) should be repeated at the end of treatment along with a bone marrow biopsy (only if initially involved). Evidence points to PTCL as consistently FDG-avid tumors, providing the rationale for the use of PET/CT, particularly in the context of residual disease evaluation. Follow-up Routine surveillance with PET scan is not recommended.	Outlined above
ESMO Consensus conferences: guidelines on Malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma (2013)	Literature Review and Expert Consensus PET-specific literature not characterized.	**Marginal Zone Lymphoma (Localized and Disseminated)** Initial Staging The value of positron emission tomography (PET) scan is controversial and has uncertain clinical utility and is not recommended. There are no data supporting the clinical utility of abdominal sonography and PET in the routine staging of disseminated Marginal Zone Lymphoma. PET scan investigation may be considered in selected cases (i.e. if clinical and/or laboratory data suggest a transformation to high-grade histology, or to guide the decision which lymph node should be biopsied).	Outlined above
Hairy cell leukemia: ESMO Clinical Practice Guidelines	NA	**Hairy cell leukemia** No PET-specific guidelines are included.	NA

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
for diagnosis, treatment and follow-up (2015)			
Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2013)	NA	**Gastric marginal zone lymphoma of MALT type** No PET-specific guidelines are included.	NA
Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2013)	NA	**Primary cutaneous lymphomas** No PET-specific guidelines are included.	NA
Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2016)	NA	**Acute lymphoblastic leukaemia** No PET specific guidelines are included.	NA
Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2015)	NA	**Chronic lymphocytic leukaemia** No PET-specific guidelines are included.	NA

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
American College of Radiology Appropriateness Criteria:			
American College of Radiology Appropriateness Criteria: Follow-up of Hodgkin Lymphoma (2014)	Literature review and Expert Consensus 4 studies (type NR), 1 cost-effectiveness analysis, 1 prospective study, 3 retrospective studies	**Hodgkin Lymphoma** Surveillance Though PET scan is a useful tool in defining a subset of patients who require additional therapy after completion of the initial therapy, the routine use of PET for surveillance is not recommended in general due to low positive predictive value, high false-positive rate, and unfavorable cost-effectiveness.	NR
American College of Radiology Appropriateness Criteria: Hodgkin Lymphoma-Favorable Prognosis Stage I and II (2016)	Systematic Literature review (67 references total) and Expert Consensus Response Adapted Therapy: 4 studies, 1 RCT, 3 ongoing trials (EORTC H10F, RAPID trial, and GHSG HD16 trial)	**Favorable Early Hodgkin Lymphoma** Interim For favorable prognosis stage I and II HL, changing chemotherapy or omitting RT based on PET response for early-stage patients may be appropriate with caution after careful consideration and preferably as part of a clinical trial, at least until preliminary data mature.	NR
American College of Radiology Appropriateness Criteria: Hodgkin Lymphoma-Unfavorable Clinical Stage I and II (2015)	Literature Review (83 references total) and Expert Consensus 3 RCTs, international consensus panel (Barrington et al 2014), 1 study (type NR)	**Unfavorable Early Hodgkin Lymphoma** Interim The pediatric regimen ABVE-PC can be used in pediatric, adolescent, and young adult patients without RT when there is a rapid early response after 2 cycles, especially if defined by a negative PET scan and if at the end of chemotherapy there is a complete response by CT criteria.	NR
American College of Radiology Appropriateness	NA	**Advanced Hodgkin Lymphoma** No PET-specific Recommendations	NR

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
Criteria: Hodgkin Lymphoma-Stage III and IV (2016)			
American College of Radiology Appropriateness Criteria: Pediatric Hodgkin Lymphoma (2012)	NA	**Pediatric Hodgkin Lymphoma** No PET-specific Recommendations	NR
American College of Radiology Appropriateness Criteria: Recurrent Hodgkin Lymphoma (2016)	NA	**Recurrent Hodgkin Lymphoma** No PET-specific Recommendations	NR
American College of Radiology Appropriateness Criteria: Diffuse Large B-Cell Lymphoma (2014)	Systematic Literature review (90 references) and Expert Consensus Diagnosis, Staging and Response Evaluation: 7 prospective and retrospective studies, type NR Interim: 2 Case series, 3 studies type NR, 1 retrospective study	**Diffuse Large B-Cell Lymphoma (DLBCL)** Initial Staging: Review of data suggests that PET/CT is well established and should be routinely used for the evaluation of patients with DLBCL. Bone-marrow biopsy is not performed if bone-marrow involvement is indicated on PET/CT conversely, if bone marrow involvement is not indicated by PET/CT, then bone-marrow biopsy should be performed if relevant to clinical trial enrollment or management of the patient Interim (mid-treatment) Some studies suggest that interim PET/CT can predict outcome and thus allow for modifications of therapy (de-escalation or escalation); however, until further confirmatory studies become available, interim PET/CT should not influence clinical decisions. End of Treatment End-of-therapy assessment is to be performed using PET/CT, and the current recommendation is to grade the PET/CT using the 5-point Deauville scale.	NR

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
American College of Radiology Appropriateness Criteria: Localized Nodal Indolent Lymphoma (2013)	Literature Review (46 references total) and Expert Consensus At least Two studies (type NR), other guidelines	**Localized Nodal Indolent Lymphoma** Initial Staging FDG-PET/CT scans can demonstrate more disseminated disease and upstage patients thought to have localized involvement. Additionally, they can be useful in RT treatment planning.	NR
Other Guidelines			
Alberta Health Services Clinical Practice Guideline 2018 - Adult Lymphomas	Expert Consensus and Literature Review Overview Staging: 12 references (type NR) Post-transplant lymphoproliferative disease (PTLD): 6 small case series HL Staging: 6 citations type NR, 4 RCTs	**Overview** Initial Staging FDG-PET and Diagnostic Neck/Chest/Abdomen/Pelvis CT for FDG-avid, nodal lymphomas, which includes all histologies except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma, mycosis fungoides, and marginal zone NHLs (unless there is a suspicion of aggressive transformation). Nodal lymphomas that are not FDG avid should have a staging diagnostic CT scan of NCAP. PET-CT is especially important for patients who otherwise have non-bulky, stage IIIA lymphoma, and are being considered for involved field radiation (IFRT) following abbreviated (or no) chemotherapy. Restaging: Assessment of residual radiographic or clinical abnormalities of uncertain significance at the time of re-staging following completion of therapy. If a residual mass is seen on the CT after completion of all therapy, then repeat a PET/CT for aggressive lymphoma to determine partial or complete remission. **Follicular Lymphoma** Initial Staging PET/CT is not necessarily required for Follicular Lymphoma if the results will not change management, particularly for a patient who will likely undergo watchful waiting. **Primary Cutaneous B-Cell Lymphoma** Initial Staging	NR

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
		PET/CT or CT is recommended for primary cutaneous anaplastic large cell lymphoma (pcALCL), Subcutaneous panniculitis-like T-cell lymphoma (SPTCL), primary cutaneous follicle center cell lymphoma (pcFCL), and pc diffuse large B-cell lymphoma **post-transplant lymphoproliferative disease** Initial Staging PET-CT is an effective imaging modality for staging in post-transplant lymphoproliferative disease (PTLD). However, some subtypes of PTLD, such as early lesions and T-cell lymphomas, may not be FDG-avid, necessitating CT as an alternate staging modality **Mycosis Fungiodes/Sezary Syndrome** Initial Staging For patients with MF stage II or higher imaging including CT scan of chest, abdomen, and pelvis and/or FDG-PET scan are recommended. **Hodgkin Lymphomas** Initial Staging For HL, a PET scan with body CT is preferred as initial staging and after 2 cycles of ABVD. If a PET/CT is not done, then perform a bone marrow aspiration and biopsy (2cm core preferable) for patients with stage IIB-IV or cytopenias (note: flow cytometry on the marrow aspirate does not add useful information and should not be done). Interim PET Based upon recent clinical trial data, Alberta Health Services finds it reasonable to adopt a PET-guided therapy approach for early and advanced staged Hodgkin lymphoma, which will minimize the long-terms risks of cytotoxic chemotherapy and radiotherapy for PET- patients after ABVD x2, while maintaining PFS rates <5% inferior to conventional combined modality treatments. This approach is the current preferred approach in Alberta, especially at centres where PET scans are more easily available. Follow-up If a residual mass is seen on the CT after completion of all therapy, then consider PET/CT scan or consider a repeat CT scan 6 months later. Otherwise, no further routine CT scans are required.	

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
Australian Government Medical Services Advisory Committee (MSAC) - Public Summary Document Application No. 1406 – 18F-FDG PET for indolent non-Hodgkin's lymphoma (2016)	Literature Review 1 comparative prognostic study, 1 prospective study, 6 studies type NR; 1 economic analysis	**Indolent NHL** <u>Initial Staging</u> FDG PET/CT is supported in place of CT for staging of all newly diagnosed and relapsed indolent non-Hodgkin's lymphoma **(very low)** <u>End of Treatment</u> FDG PET/CT is supported in place of CT for indolent non-Hodgkin's lymphoma **(very low)** <u>Restaging</u> FDG PET/CT is supported in place of CT for indolent non-Hodgkin's lymphoma after confirmation of recurrence **(very low)**	Evidence based described as weak due to a lack of direct evidence, supported only by linked evidence, although this was found to be acceptable on the basis of the rareness of indolent NHL overall. Evidence rated as **very low quality** using The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature to evaluate levels of evidence and to assess the strength of recommendations.
Clinical Oncology Working Group: Herst, J., et al. (2017). "Management of Early-stage Hodgkin Lymphoma: A Practice Guideline." Clin Oncol	Systematic Literature Review and Expert Consensus 3 RCTs	**Early Hodgkin Lymphoma** <u>Interim PET</u> The Working Group does not recommend the use of a negative interim PET scan to identify patients with early-stage Hodgkin lymphoma for whom radiotherapy can be omitted without a reduction in PFS (**HIGH**)	GRADE methodology; evidence certainty rated as HIGH
AIM Specialty Health Clinical Appropriateness Guidelines: Positron Emission Testing, Other PET Applications, including Oncologic Tumor Imaging 2018	Citations provided but lymphoma specific evidence not characterized References include at least 1 systematic review and NCCN guidelines for CLL/SLL and HL	**Hodgkin's Lymphoma** <u>Initial Staging</u> PET is indicated for initial staging <u>Interim</u> PET is indicated for evaluation of response after 2-4 cycles of treatment <u>End of Treatment</u> PET is indicated for post-treatment evaluation <u>Restaging (Relapsed/Refractory)</u>	NR

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
		PET is indicated for evaluation of suspected recurrence or disease progression based on standard imaging or objective signs/symptoms. <u>Surveillance</u> PET not indicated. **Intermediate or High Grade (Aggressive) NHL and other subtypes** <u>Initial Staging</u> PET is indicated for initial staging <u>Interim</u> PET is indicated for evaluation of response after 2-4 cycles of treatment when standard imaging has not clearly demonstrated progression or regression <u>End of Treatment</u> PET is indicated for post-treatment evaluation <u>Restaging (Relapsed/Refractory)</u> PET is indicated for evaluation of suspected recurrence or disease progression <u>Surveillance</u> PET not indicated for surveillance. **Low Grade Indolent NHL or lymphoproliferative disorders (other than CLL/SLL)** <u>Initial Staging</u> PET is indicated for evaluation of suspected transformation to aggressive lymphoma based on clinical signs or symptoms, and prior to initiation of therapy. <u>End of Treatment</u> PET is indicated for post-treatment response evaluation <u>Restaging (Relapsed/Refractory)</u>	

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
		PET is indicated for evaluation of suspected recurrence, disease progression based on standard imaging, or transformation to more aggressive lymphoma based on clinical signs or symptoms <u>Surveillance</u> PET not indicated for surveillance. **CNS Lymphoma** <u>Initial Staging</u> PET is indicated to evaluate possible systemic disease in proven CNS lymphoma <u>Restaging (Relapsed/Refractory)</u> PET not indicated. <u>Surveillance</u> PET not indicated. **Chronic lymphocytic leukemia (CLL) or Small lymphocytic lymphoma (SLL)** PET is indicated when there is suspicion of Richter's transformation when PET is utilized to direct biopsy	
Spanish Lymphoma Group - Guidelines for diagnosis, prevention and management of central nervous system involvement in diffuse large B-cell lymphoma patients by the Spanish Lymphoma Group (GELTAMO) (2017)	NA	**DLBCL** <u>No PET-specific recommendations</u>	NA

Guideline	Evidence Base	Recommendations*	Rating/Strength of Recommendation
Recommendations of the SFH (French Society of Haematology) for the diagnosis, treatment and follow-up of hairy cell leukemia (2014)	NA	**Hairy Cell Leukemia** No PET-specific recommendations	NA

ASCT = autologous stem cell transplant; ceCT = contrast-enhanced Computerized Tomography; C/A/P= chest / abdomen / pelvis; CT = computerized tomography; FDG = flurodeoxyglucose; HDCT = high dose chemotherapy; NA = not applicable; NCCN = National Comprehensive Cancer Network; NR = not reported; PET = positron emission tomography; PET/CT = positron emission tomography and computerized tomography**;** RT = radiation therapy

*For a full list of abbreviations and definitions including chemotherapy regimens and lymphomas refer to Appendix M. Definitions and abbreviations

Appendix Table L3. Bibliography of Guidelines of PET for Lymphoma

	Citation
1.	NICE Guidelines: Non-Hodgkin's lymphoma: diagnosis and management: NICE; 2016 07/20/16.
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8.	Clemens MW, Horwitz SM. NCCN Consensus Guidelines for the Diagnosis and Management of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Aesthetic surgery journal 2017;37:285-9.
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APPENDIX M. Definitions and Abbreviations

Appendix Table M1. List of Lymphoma and Chemotherapy Abbreviations, Acronyms and Definitions

Abbreviations	Description
ABVD	adriamycin + bleomycin + vinblastine + dacarbazine
AITL	Angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALL	acute lymphoblastic leukemia
alloSCT	Allogenic Stem Cell Transplant
AML	acute myeloid leukemia
aNHL	Aggressive Non-Hodgkin Lymphoma
ASCT	Autologous Stem Cell Transplant
ATCL	adult T-cell lymphoma
AVG	doxorubicin, vinblastine, and gemcitabine
BCNU	carmustine
BEACOPP	bleomycin + etoposide + adriamycin + cyclophosphamide + vincristine + procarbazine + prednisone
BEAM	BCNU + etoposide + cytarabine + melphalan
BIA-ALCL	Breast Implant Associated Anaplastic Large Cell Lymphomas
BL	Burkitt lymphoma
BMT	bone marrow transplant
B-R	Bendamustine-rituximab
BV	Brentuximab vedotin
Burkitt Protocol	HD-MTX + cytarabine, high dose cyclophosphamide and ifosfamide, split-dose doxorubicin and etoposide, vincristine, vindesine, and dexamethasone
C-ALCL	Cutaneous Anaplastic Large Cell Lymphoma
CAP	cyclophosphamide + adriamycin + prednisone
CBV	cyclophosphamide + BCNU + etoposide
CEC	cyclophosphamide + lomustine + vindesine + melphalan + prednisone + epidoxirubicin + vincristine + procarbazine + vinblastine + bleomycin
CEPP	cyclophosphamide + etoposide + procarbazine + prednisone
ChlVPP	chlorambucil + vinblastine + procarbazine + prednisone
cHL	Classical Hodgkin Lymphoma
ChT	Chemotherapy
CHOP	cyclophosphamide + adriamycin + vincristine + prednisone
CHOEP	cyclophosphamide + adriamycin + vincristine + etoposide + prednisone
CLL	chronic lymphocytic leukemia
CMED	cyclophosphamide + etoposide + methotrexate + dexamethasone + leucovorin + G-CSF
CNS	central nervous system
CR	complete remission (response)
CT	computed tomography scan

Abbreviations	Description
CTCL	cutaneous T-cell lymphoma
DA-EPOCH-R	Dose-Adjusted Etoposide, Prednisone, Oncovin (vincristine), Cyclophosphamide, Hydroxydaunorubicin (doxorubicin) with R (Rituximab)
DFS	Disease Free Survival
DHAP	dexamethasone + cytarabine + cisplatin
DICE	dexamethasone + ifosfamide + cisplatin + etoposide + mesna
DICEP	dexamethasone + cyclophosphamide + etoposide + cisplatin + mesna + Septra
DLBCL	diffuse large B-cell lymphoma
EATL	Enteropathy-associated intestinal T-cell lymphoma
eBEACOPP	Escalated bleomycin + etoposide + adriamycin + cyclophosphamide + vincristine + procarbazine + prednisone
EBV	Epstein-Barr virus
EFS	Event Free Survival
ENKTCL or ENKL	Extranodal Natural Killer/T-Cell Lymphoma
ESHAP	etoposide + methylprednisolone + cytarabine + cisplatin
FDG-PET	Positron emission tomography using 18F fluorodeoxyglucose
FFTF	Freedom from treatment failure
FL	Follicular Lymphoma
FND	fludarabine + mitoxantrone + dexamethasone
GCB	Germinal center B-Cell
G-CSF	granulocyte-colony stimulating factor
GDP	gemcitabine + dexamethasone + cisplatin
GVD	Gemcitabine, Vinorelbine, Doxil
HCL	Hairy Cell Leukemia/Lymphoma
HDCT/HDT	high dose chemotherapy
HD-MTX	High Dose Methotrexate
HL	Hodgkin lymphoma
HR	Hazard Ratio
HSCT	hematopoietic stem cell transplantation
HSTL	Hepatosplenic T-cell lymphoma
ICE	ifosfamide + carboplatin + etoposide
IELSG	International Extranodal Lymphoma Study Group
IFRT	involved field radiation therapy
IGEV	Ifosfamide, Gemcitabine and Vinorelbine
IMRT	intensity-modulated radiation therapy
INRT	Involved Node Radiation Therapy
iNHL	Indolent Non-Hodgkin Lymphoma
ISRT	Involved-Site Radiation Therapy
IVE	ifosfamide + vincristine + etoposide

Abbreviations	Description
KPS	Karnofsky Performance Status Scale
LDcHL	Lymphocyte-Depleted classical Hodgkin Lymphoma
LPL	lymphoplasmacytic lymphoma
LRcHL	Lymphocyte-Rich classic Hodgkin Lymphoma
MACOP-B	methotrexate + adriamycin + cyclophosphamide + vincristine + bleomycin + prednisone
MALT	Mucosa-Associated Lymphoid Tissue Lymphoma
MCL	Mantle Cell Lymphoma
MCcHL	Mixed Cellularity classical Hodgkin Lymphoma
MF/SS	Mycosis Fungoides / Sezary Syndrome
MGZL	Mediastinal Gray-Zone Lymphoma
MINE	mesna, ifosfamide, mitoxantrone, etoposide
Mini-BEAM	low dose BEAM
MRI	Magnetic resonance imaging
MTX	methotrexate
NHL	non-Hodgkin lymphoma
NK	natural killer
NLPHL	nodular lymphocyte predominant Hodgkin Lymphoma
NScHL	Nodular Sclerosis classical Hodgkin's Lymphoma
NPV	Negative predictive value
ORR	Overall response rate
OS	Overall Survival
PBL	Primary Breast Lymphoma
PBoL	Primary Bone Lymphoma
pcFCL	Primary Cutaneous Follicle Center Lymphoma
pcGD-TCL	Primary cutaneous Gamma-Delta T-Cell Lymphoma
pcMZBCL	Primary Cutaneous Marginal Zone B-Cell Lymphoma
PCNSL	primary central nervous system lymphoma
PD	Progressive Disease
PDG	cisplatin, gemcitabine, and dexamethasone
PET	positron emission tomography
PET/CT or PET-CT	positron emission tomography / computed tomography
PFS	progression-free survival
PMBCL	Primary Mediastinal B-cell Lymphoma
PPV	Positive predictive value
PR	partial response
PTCL	Peripheral T-Cell Lymphoma
PTCL-NOS	Peripheral T-Cell Lymphoma, Not Otherwise Specified
PTL	Primary Testicular Lymphoma
PTLL	Peripheral T-lymphoblastic Lymphoma/Leukemia

Abbreviations	Description
PTLD	post-transplant lymphoproliferative disorder
R	rituximab
R-ACVBP	rituximab with doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone
R-CHOP	rituximab + cyclophosphamide + adriamycin + vincristine + prednisone
R-CHOEP	rituximab + cyclophosphamide + adriamycin + vincristine + etoposide + prednisone
RT	radiotherapy
SCT	stem cell transplant
SD	stable disease
SLL	small lymphocytic lymphoma
Stanford V	doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone
STNI	subtotal nodal irradiation
TBuC	thiotepa + busulfan + cyclophosphamide
TBI	total body irradiation
TRM	Treatment-related mortality
VABEM	vindesine, doxorubicin, carmustine, etoposide and methylprednisolone;
VIPD	etoposide + ifosfamide + cisplatin + dexamethasone
WHO	World Health Organization
Z-BEAM	Zevalin with BCNU + etoposide + cytarabine + melphalan

APPENDIX N. Clinical Expert Peer Review

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