National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hodgkin Lymphoma

Version 2.2014

NCCN.org

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Hodgkin Lymphoma

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NCCN Guidelines Panel Disclosures

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Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

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Summary of the changes in the 2.2014 version of the NCCN Guidelines for Hodgkin Lymphoma from the 1.2014 version include:

HODG-E (1 of 2)

- The title was changed to "Principles of Systemic Therapy for Relapsed or Refractory Disease." (Also for HODG-E 2 of 2)
- Third bullet was added with corresponding reference, " Brentuximab vedotin is a treatment option for patients with classical Hodgkin lymphoma (CHL) who have failed HDT/ASCR or at least 2 prior multi-agent chemotherapy regimens."
- Fourth bullet was revised, "Rituximab should be considered with *all second-line chemotherapy* regimens for relapsed *or refractory* NLPHL."

HODG-E (2 of 2)

- "Only for CHL" was added to brentuximab vedotin and everolimus.
- Bendamustine and lenalidomide were each moved to a new section, "Third-Line Therapy (only for CHL)".
- Footnote was added: "Brentuximab vedotin is a treatment option for patients who have failed HDT/ASCR or at least 2 prior multi-agent chemotherapy regimens."

MS-1

- The discussion section was updated to reflect the algorithm changes.

Summary of the changes in the 1.2014 version of the NCCN Guidelines for Hodgkin Lymphoma from the 2.2013 version include:

General

- Pathways were added for positive and negative results after each biopsy.
- Pathways were updated to include separate options for Deauville 5a (Markedly > liver) and Deauville 5b (New sites).
- All Deauville 5a (Markedly > liver), biopsy positive: See Refractory Disease (HODG-14)
- "ISRT" replaced "RT."
- "Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)" replaced "lymphocyte-predominant Hodgkin lymphoma (LPHL)."
- Footnote "o" was revised: See Deauville PET Criteria (HODG-D) *and see Discussion*.

HODG-1

Workup

- Essential, 8th bullet was modified, "Diagnostic ~~chest/abdominal/ pelvic~~ CT *(contrast enhanced)."*

Footnotes

- Added reference to footnote "b": Swerdlow SH, Campo E, Harris NL, et al; WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC; 2008.
- Footnote "c" was modified: "*Although the diagnostic CT will often be neck/chest/abdomen/pelvis, at minimum it should include the areas identified as abnormal on PET-CT.* A separate diagnostic CT does not need to be done if it was part of the integrated PET-CT scan."
- Footnote "h" was modified: "~~Excludes the~~ NCCN Unfavorable Factors for stage I-II disease..." (Also for HODG-2)

HODG-2

Primary Treatment

- Combined modality therapy [ABVD x 2-4 cycles ~~+ involved-site RT (ISRT)~~ (category 1) or Stanford V x 8 weeks].

HODG-2 (continued)

- Definitions were added below each of the Deauville criteria.
  - Deauville 1-3 *(Uptake ≤ liver);* Deauville 4 *(Moderately increased uptake > liver);* Deauville 5a *(Markedly increased uptake > liver at initial site);* Deauville 5b *(New sites)*
- Following restaging after chemotherapy, Deauville 5a: follows same pathway as Deauville 4 after biopsy.
- Deauville 5b is followed by a biopsy, then:
  - Negative: Observe with short interval follow-up (see HODG-13).
  - Positive: See Refractory Disease (HODG-14).
- After ISRT and restaging, Deauville 4-5, biopsy negative: "Observe with short interval follow-up (see HODG-13)" was added.

Footnotes

- Footnote "m" was modified: *"ISRT fields are generally smaller than IFRT fields.* See Principles of Radiation Therapy (HODG-C)."
- Footnote "r" was modified: "~~Biopsy to confirm histology.~~ *Additional medical management may be required.* Clinical circumstances may warrant additional treatment even in face of negative biopsy."
- Footnote "s" was modified: "Deauville 3 should have short interval follow-up including PET-CT, *potentially repeated every 3-6 months until stable (up to 1 year)."*
- Footnote "t" was added: "Repeat PET-CT every 3-6 months until Deauville 1-2 or until no progression for 12 months or more." (Also for HODG-3-HODG-16)

HODG-3

- After primary treatment with ABVD x 2 cycles:
  - "Restage with PET-CT" was modified to, " Restage with PET-CT *including diagnostic CT of areas of initial disease."*
  - After Deauville 1-2, two options were added: "Complete response (CR) or unconfirmed complete response (CRu) on CT," and "Partial response (PR) on CT."

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Summary of the changes in the 1.2014 version of the NCCN Guidelines for Hodgkin Lymphoma from the 2.2013 version include:

HODG-3 (continued)

- Following Deauville 3-4:
  - Treatment was modified: ABVD x ~~4~~ 2 cycles (total ~~6~~ 4).
  - After treatment with ABVD, and restaging:
    - ◊ Deauville 1-2: ABVD x 2 (total 6) or ISRT, then See Follow-up (HODG-13).
    - ◊ Deauville 3-4: ABVD x 2 (total 6) + ISRT or ISRT alone, then See Follow-up (HODG-13).
    - ◊ Deauville 5a, biopsy negative: ISRT then, observe with short interval follow-up (see HODG-13).
    - ◊ Deauville 5b is followed by a biopsy, then:
      - – For negative biopsy: Observe with short interval follow-up (see HODG-13).
      - – For positive biopsy: See Refractory Disease (HODG-14).
- Deauville 5a after negative biopsy: follows the same pathway as Deauville 3-4.
- Deauville 5b is followed by a biopsy, then:
  - For negative biopsy: Observe with short interval follow-up (see HODG-13).
  - For positive biopsy: See Refractory Disease (HODG-14).

HODG-4

- Primary treatment with ABVD was modified: ABVD x ~~2~~-4 cycles (category 1).
- "Escalated" was added to Primary treatment with BEACOPP.
- Deauville 1-3: ABVD x 2-~~4~~ cycles (total ~~4~~-6) + *ISRT or ISRT* alone.
- Deauville 4 or Deauville 5a, biopsy negative: ABVD x 2-~~4~~ cycles (total 6).
- Deauville 5b is followed by a biopsy, then:
  - For negative biopsy: *ISRT to initially bulky sites*, then Observe with short interval follow-up (see HODG-13).
  - For positive biopsy: See Refractory Disease (HODG-14).

Footnotes

- Footnote "x" was added: "In the GHSG trial on which this therapy is based, patients with both bulky disease and B symptoms were excluded and treated according to the algorithm for stage III-IV disease (HODG-11)." (Also for HODG-7)

HODG-5

- Significant revisions were made to this page based on the changes to HODG-4.

HODG-6

- Deauville 1-3: ISRT to initial sites >5 cm (~~36~~ *30* Gy begins optimally within 3 weeks).
- Following Deauville 4 and ISRT: Restage after 3 mo with ~~CT (or~~ PET-CT ~~if last PET scan was Deauville 3-4)~~.
- Deauville 5a follows the Deauville 4 biopsy pathway.
- Deauville 5b is followed by a biopsy, then:
  - For negative biopsy: Observe with short interval follow-up (see HODG-13).
  - For positive biopsy: See Refractory Disease (HODG-14).

Footnotes

- Footnote "y" was modified: "...Patients with elevated ESR, *and/or* >3 sites in absence of bulky disease..."

HODG-7

- Significant revisions were made to this page.
- "Escalated" was added to "BEACOPP x 2."
- "Restage with PET-CT" was moved after the completion of all recommended chemotherapy.
- Deauville 1-4 follows the same updated pathway.
- Deauville 5a,b is followed by a biopsy, then:
  - For negative biopsy: ISRT, then Observe with short interval follow-up (see HODG-13).
- For positive biopsy: See Refractory Disease (HODG-14)
- Based on the revisions to HODG-7, the page that followed was eliminated.

HODG-8

- Primary treatment with ABVD was modified: ABVD x 2-~~4~~ cycles.
- Deauville 1-2: ABVD x 2-4 cycles (total 4-6) + ISRT or ABVD x ~~2~~-4 cycles (total ~~4~~-6)(if stage I-IIA).
- Deauville 3-4: ABVD x ~~2~~-4 cycles (total 6) + ISRT.
- Deauville 5a, biopsy negative: follows the pathway for Deauville 3-4.
- Deauville 5b:
  - For negative biopsy: ABVD x 4 cycles (total 6), then Observe with short interval follow-up (see HODG-13).
  - For positive biopsy: See Refractory Disease (HODG-14)

Footnotes

- Footnote was removed: "If observation, total 6 cycles of ABVD recommended.
- Based on the revisions to HODG-8, the page that followed was eliminated.

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Summary of the changes in the 1.2014 version of the NCCN Guidelines for Hodgkin Lymphoma from the 2.2013 version include:

HODG-9

- Primary treatment with ABVD was modified: ABVD x 2~~-4~~ cycles.
- Deauville 1-~~2~~3: ABVD x ~~2-~~4 cycles (total 6)
- Deauville ~~3-~~4-5a: ~~ABVD x 2-4 cycles (total 6) or~~ Biopsy
  - For negative biopsy: ABVD x 4 cycles (total 6)
  - For positive biopsy: See Refractory Disease (HODG-14)
  - Following Deauville 4-5a, biopsy negative, ABVD x 4 cycles (total 6), restage with PET-CT:
    - ◊ Deauville 1-~~2~~3: Observe or ISRT ~~selectively~~ to initially bulky *or PET+* sites.
    - ◊ Deauville ~~3~~4-5a: *Biopsy*
    - ◊ For negative biopsy: Observe *with short interval follow-up (see HODG-13)* ± ISRT ~~selectively~~ to initially bulky *or PET+ sites*.
    - ◊ For positive biopsy: See Refractory Disease (HODG-14)
- Deauville 5b: *Biopsy*
  - For negative biopsy: *ABVD x 4 cycles (total 6),* then Observe *with short interval follow-up (see HODG-13)* ± ISRT ~~selectively~~ to initially bulky *or PET+ sites*.

HODG-10

- Deauville 1-3: ISRT to initial sites >5 cm, involved spleen (~~36~~ *30* Gy begins optimally within 3 wks).
- Deauville 4, following ISRT: Restage after 3 mo with ~~CT (or~~ PET-CT ~~if last PET scan was Deauville 3-4)~~.
- Following Deauville 1-~~4~~: Follow-up (HODG-13) ~~Progressive disease (HODG-16).~~
- Deauville 5b: biopsy negative, Observe *with short interval follow-up (see HODG-13).*

HODG-11

- Deauville 1-3 treated with 2 cycles of BEACOPP, restaged with PET-CT, then:
  - *Deauville 1-2*: See Follow-up (HODG-13)
  - *Deauville* ~~1-~~*3-4*: ~~Observe or~~ ISRT to residual sites >2.5 cm PET positive.
  - Deauville ~~4-~~5a: Biopsy added.
    - ◊ *For negative biopsy*: *Observe* with *short interval follow-up (see HODG-13) or ISRT ~~selectively~~ to initially bulky* or PET+ *sites.*
    - ◊ *For positive biopsy*: See Refractory Disease (HODG-14)
  - *Deauville 5b*: biopsy, then:
    - ◊ For negative biopsy*: Observe* with *short interval follow-up (see HODG-13).*
    - ◊ For positive biopsy*:* See Refractory Disease (HODG-14).
- Deauville 4-5a,b: biopsy negative follows the same pathway as Deauville 1-3.
- Footnote was removed: "Deauville 3 should have short interval follow-up including PET-CT."

HODG-12

Clinical Presentation

- CS IA, IIA *(non-bulky)*
- CS IB, IIB *or CS IA, IIA (bulky)*

Primary Treatment

- "Preferred" added to "ISRT" for CS IA, IIA (non-bulky).
- Primary treatment for CS IB, IIB or CS IA, II A (bulky) was revised: Chemotherapy + *ISRT* ± Rituximab.
- Restage after Primary Treatment:
  - Deauville 1-~~3~~4: Observe, *if asymptomatic or ISRT (if no prior RT)*
  - Deauville ~~4-~~5a: *Biopsy*
    - ◊ For negative biopsy: follow pathway for Deauville 1-4.
    - ◊ For positive biopsy: Observe, if asymptomatic or Second-line therapy (See HODG-16) or ISRT (if no prior RT)
  - *Deauville 5b*: biopsy, then:
    - ◊ For negative biopsy*: Observe, if asymptomatic.*
    - ◊ For positive biopsy*:* See Refractory Disease (HODG-16).

Footnotes

- Footnote "r" was added: "Additional medical management may be required. Clinical circumstances may warrant additional treatment even in face of negative biopsy."
- Footnote "cc" was added: "Generally a brief course of chemotherapy (3-4 months) would be given with radiation therapy."

HODG-13

Follow-up After Completion of Treatment up to 5 years

- Interim H&P was modified: Every ~~2-4~~ *3-6* mo for 1-2 y, then every ~~3-6~~ *6-12* mo ~~*for next 3-5 y*~~ *until year 3, then annually*.
- Laboratory studies, first sub-bullet modified: CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile ~~every 2-4 mo for 1-2 y, then every 3-6 mo for next 3-5 y~~ with each clinic visit.
- 4th bullet was revised: Abdominal/pelvic CT every 6-12 mo for first 2~~-3~~ y.

Monitoring Late Effects After 5 years

- "Cardiovascular symptoms may emerge at a young age" was moved to 2nd bullet. The following 2 bullets were revised and moved to sub-bullets under it:
  - Consider ~~baseline~~ stress test/echocardiogram at 10-y *intervals* after treatment is complete, especially if chest cardiac irradiation.
  - Consider carotid ultrasound~~, especially~~ *at 10-y intervals* if neck irradiation.
- Last bullet was added: "Consider a referral to a survivorship clinic."

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Summary of the changes in the 1.2014 version of the NCCN Guidelines for Hodgkin Lymphoma from the 2.2013 version include:

HODG-14

- Second-line therapy was modified: Second-line chemotherapy ~~± RT~~.
- Additional therapy for Deauville 1-3 was modified: HDT/ASCR ± *ISRT* or Observe ± *ISRT* (if HDT/ASCR contraindicated).
- Deauville 4 and 5: After additional therapy and restaging, therapy for Deauville 1-4 was modified: HDT/ASCR ± *ISRT* or Observe ± *ISRT* only (if CR and HDT/ASCR contraindicated).`

HODG-15

- Following negative rebiopsy, revised: ~~Observation~~ *Observe with short interval follow-up (see HODG-13)*
- Second-line therapy:
  - Modified after Intitial stage IA-IIA: Second-line chemotherapy ± *IS*RT (*preferred)* or RT *in selected cases.*
  - Modified after "all others": Second-line chemotherapy ~~± RT.~~
  - Following Deauville 1-3, "*± ISRT"* was added to HDT/ASCR.

Footnotes

- Footnote "t" was added: "Repeat PET-CT every 3-6 months until Deauville 1-2 or until no regression for 12 months or more."
- Footnote "oo" was added: If radiation is being used alone as a salvage therapy, conventional involved field or extended field treatment is indicated.

HODG-16

- Refractory disease: Following Deauville 1-3, "if asymptomatic" was added to "Observe."
- Suspected Relapsed disease
  - Biopsy was added.
  - "LPHL" was revised to "NLPHL."
  - Following biopsy negative, "Observe" was modified to "Observe with short interval follow-up (see HODG-13)."

HODG-A

- Footnote "**" was modified: "The EORTC definition of nodal sites differs from the Ann Arbor System in that the infraclavicular region is included with the ipsilateral axilla. ~~and the bilateral hila is included with the mediastinum.~~"

HODG-B 1 of 2

- "Escalated BEACOPP" replaced "BEACOPP."
- References were updated.

HODG-B 2 of 2

Regimen was removed: EPOCH (cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) ± rituximab

HODG-C

- Fields:
  - The first line was revised: Radiation oncologists ~~have begun to~~ endorse the concept of "involved site" radiation therapy (ISRT) as an alternative to "involved field" radiation therapy (IFRT). *Involved site fields are generally smaller than classical involved fields.*
  - The 3rd bullet was modified: "The pre-chemotherapy or pre-biopsy gross tumor volume (GTV) provides the basis for determining the clinical target volume (CTV). Concerns for questionable subclinical disease and uncertainties in original imaging accuracy or localization may lead to expansion of the CTV and are determined individually based upon clinical judgment. *For example, the CTV definition for treating NLPHL with radiation therapy alone will be greater than that employed for classical Hodgkin lymphoma with similar disease distribution being treated with combined modality therapy.* Possible movement..."
- Dose of combined modality therapy for non-bulky disease (stage IB-IIB) was modified: 30~~-36~~ Gy.
- Reference was added: Specht L, Yahalom J, Illidge T, et al; Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)International Journal of Radiation Oncology, Biology, Physics 2013.

HODG-D

- Footnote was added: For definitions of 5a and 5b as used in the NCCN Guidelines, see MS-4.
- Below the table a text box was added: Copyright permission is pending for the updated version of the Deauville PET Criteria, which can be found in Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8 9 April 2010. Leuk Lymphoma 2010;51:2171 2180. See discussion.

HODG-E 2 of 2

- Regimens were added: Everolimus and Lenalidomide
- Regimens were removed: ChlVPP (chlorambucil, vinblastine, procarbazine, prednisone) and VIM-D (etoposide, ifosfamide, mitoxantrone, and dexamethasone).
- C-MOPP became a category 2B recommendation.
- References were updated.

MS-1

- The discussion section was updated to reflect the changes in the algorithm.

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DIAGNOSIS

- Excisional biopsy (recommended)
- Core needle biopsy may be adequate if diagnostic[a]
- Immunohisto-chemistry evaluation[b]

WORKUP

Essential:

- H&P including: B symptoms, alcohol intolerance, pruritus, fatigue, performance status, exam lymphoid regions, spleen, liver
- CBC, differential, platelets
- Erythrocyte sedimentation rate (ESR)
- Lactate dehydrogenase (LDH), liver function test (LFT), albumin
- BUN, creatinine
- Pregnancy test for women of childbearing age
- Chest x-ray
- Diagnostic CT[c] (contrast enhanced)
- PET-CT scan[d]
- Adequate bone marrow biopsy in stage IB, IIB and stage III-IV
- Evaluation of ejection fraction for doxorubicin-containing regimens
- Counseling: Fertility, smoking cessation, psychosocial (see NCCN Guidelines for Distress Management)

Useful in selected cases:

- Fertility preservation[e]
- Neck CT, if neck RT contemplated
- Pulmonary function tests (PFTs incl. DLCO) if ABVD or escalated BEACOPP are being used
- Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated
- HIV test (encouraged)

CLINICAL STAGING

- Classical Hodgkin lymphoma (CHL)[f]
  - Stage IA, IIA Favorable[h] → See Primary Treatment (HODG-2)[i]
  - Stage I-II Unfavorable[h] (Bulky disease) → See Primary Treatment (HODG-4)[i]
  - Stage I-II Unfavorable[h] (Non-bulky disease) → See Primary Treatment (HODG-8)[i]
  - Stage III-IV → See Primary Treatment (HODG-9)[i]
- Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)[g] → See Primary Treatment (HODG-12)[i]

[a] FNA alone is to be avoided and only considered to be adequate if called diagnostic of Hodgkin lymphoma by a hematopathologist or cytopathologist.

[b] Typical immunophenotype for classical Hodgkin lymphoma: CD15+, CD30+, PAX-5+ (weak); CD3-, CD20- (majority), CD45-, CD79a-. Typical immunophenotype for nodular lymphocyte-predominant Hodgkin lymphoma: CD20+, CD45+, CD79a+, BCL6+, PAX-5+; CD3-, CD15-, CD30- (Swerdlow SH, Campo E, Harris NL, et al; WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC; 2008). An expanded panel of markers may be required especially if equivocal diagnosis. See NHL Guidelines.

[c] Although the diagnostic CT will often be neck/chest/abdomen/pelvis, at minimum it should include the areas identified as abnormal on PET-CT. A separate diagnostic CT does not need to be done if it was part of the integrated PET-CT scan.

[d] In cases of PET positivity where sites of disease are inconsistent with usual presentation of Hodgkin lymphoma or if an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage patient. See (ST-1).

[e] Fertility preservation options include: Semen cryopreservation, if chemotherapy or pelvic RT contemplated; IVF or ovarian tissue or oocyte cryopreservation and oophoropexy in pre-menopausal women if pelvic RT is contemplated.

[f] Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.

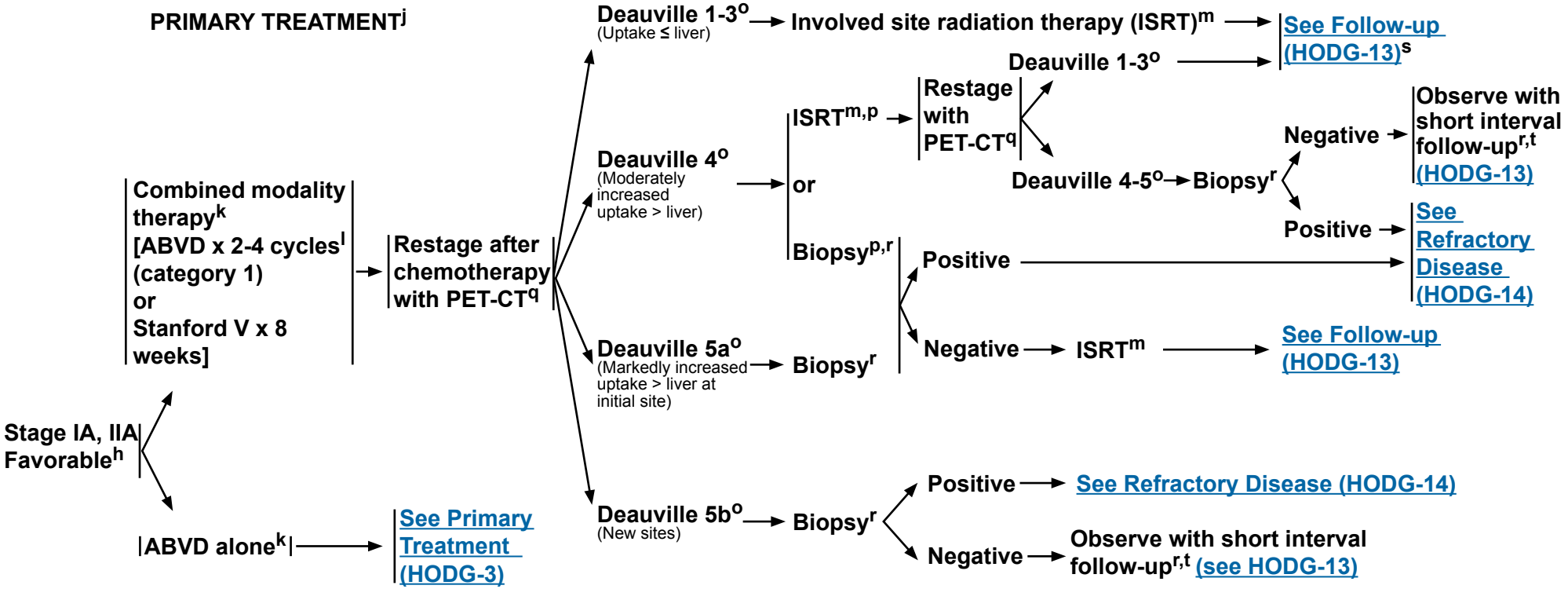
[g] Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) has a different natural history and response to therapy than classical Hodgkin lymphoma, especially stages I-II. For that reason, separate guidelines are presented for NLPHL.

[h] NCCN Unfavorable Factors for stage I-II disease: bulky mediastinal or >10 cm disease, B symptoms, ESR >50, >3 sites of disease (see Unfavorable Factors HODG-A).

[i] Treatment recommendations for postadolescent Hodgkin lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

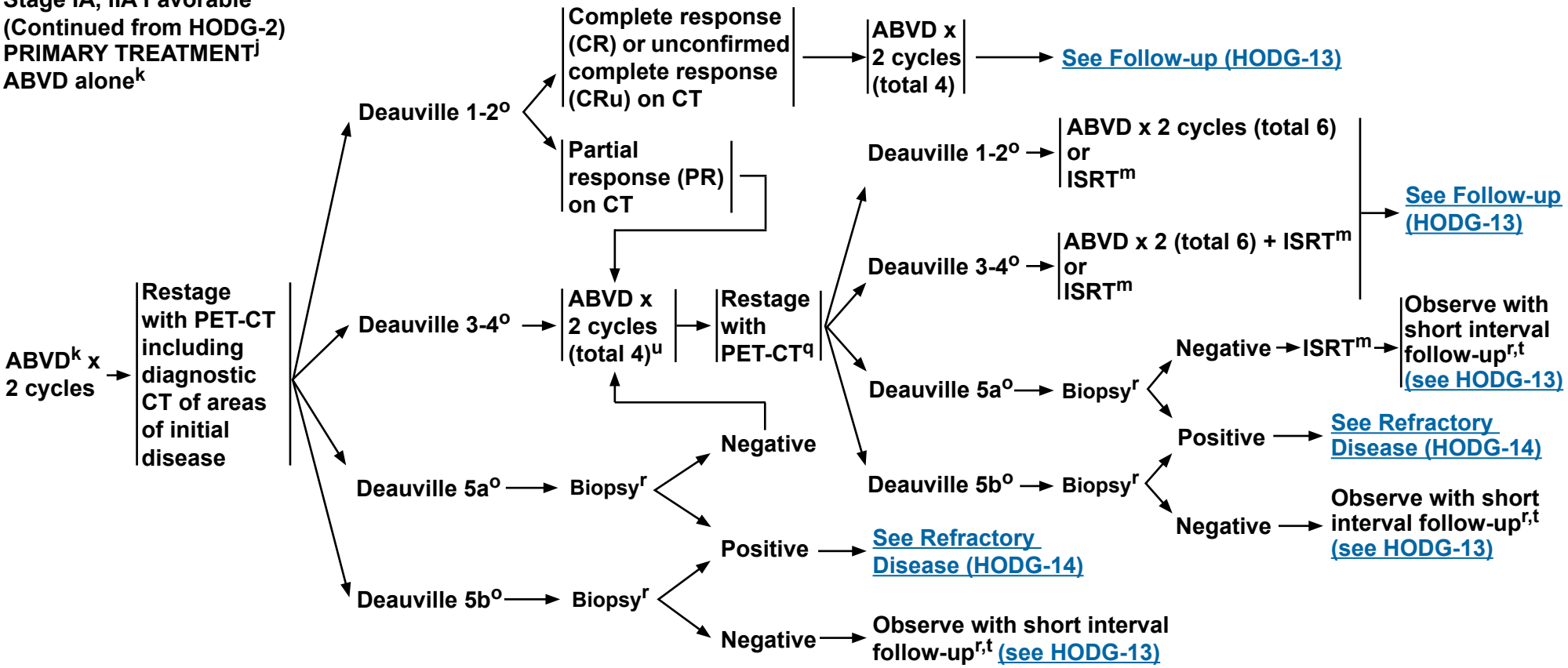
CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage IA, IIA Favorable



[f]Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.
[h]NCCN Unfavorable Factors for stage I-II disease: bulky mediastinal or >10 cm disease, B symptoms, ESR >50, >3 sites of disease. (see Unfavorable Factors HODG-A).
[j]Individualized treatment may be necessary for older patients and patients with concomitant disease.
[k]See Principles of Systemic Therapy (HODG-B).
[l]4 cycles of ABVD unless patient fulfills strict criteria of the GHSG with only 2 sites of disease and no extralymphatic lesions in which case 2 cycles is sufficient.
[m]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
[o]See Deauville PET Criteria (HODG-D) and Discussion (MS-4).
[p]If ABVD, recommend 4 cycles (total) before proceeding to ISRT or biopsy.
[q]An integrated PET-CT or a PET with a diagnostic CT is recommended.
[r]Additional medical management may be required. Clinical circumstances may warrant additional treatment even in face of negative biopsy.
[s]Deauville 3 should have short interval follow-up including PET-CT, potentially repeated every 3-6 months until stable (up to 1 year).
[t]Repeat PET-CT every 3-6 months until Deauville 1-2 or until no progression for 12 months or more.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage IA, IIA Favorable
(Continued from HODG-2)
PRIMARY TREATMENT[j]
ABVD alone[k]

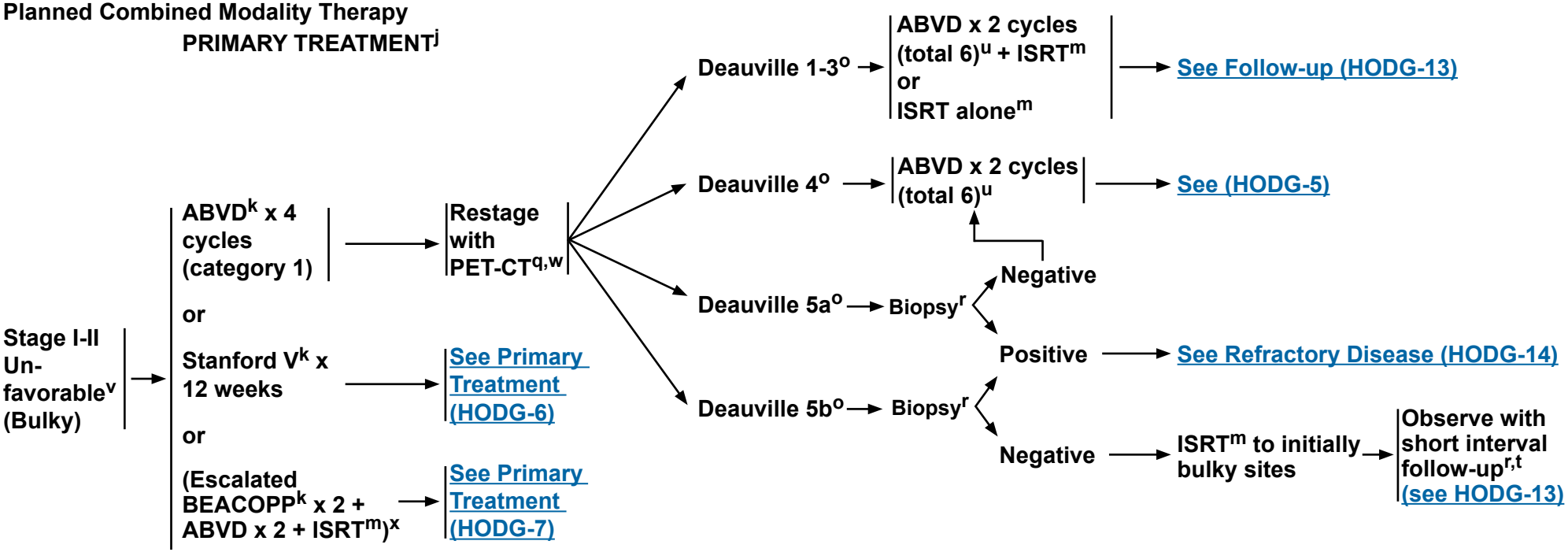


[f]Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.
[j]Individualized treatment may be necessary for older patients and patients with concomitant disease.
[k]See Principles of Systemic Therapy (HODG-B).
[m]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
[o]See Deauville PET Criteria (HODG-D) and Discussion (MS-4).
[r]Additional medical management may be required. Clinical circumstances may warrant additional treatment even in face of negative biopsy.
[t]Repeat PET-CT every 3-6 months until Deauville 1-2 or until no progression for 12 months or more.
[u]Consider PFTs after 4 cycles of ABVD.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage I-II Unfavorable[u] (Bulky)
Planned Combined Modality Therapy

PRIMARY TREATMENT[j]



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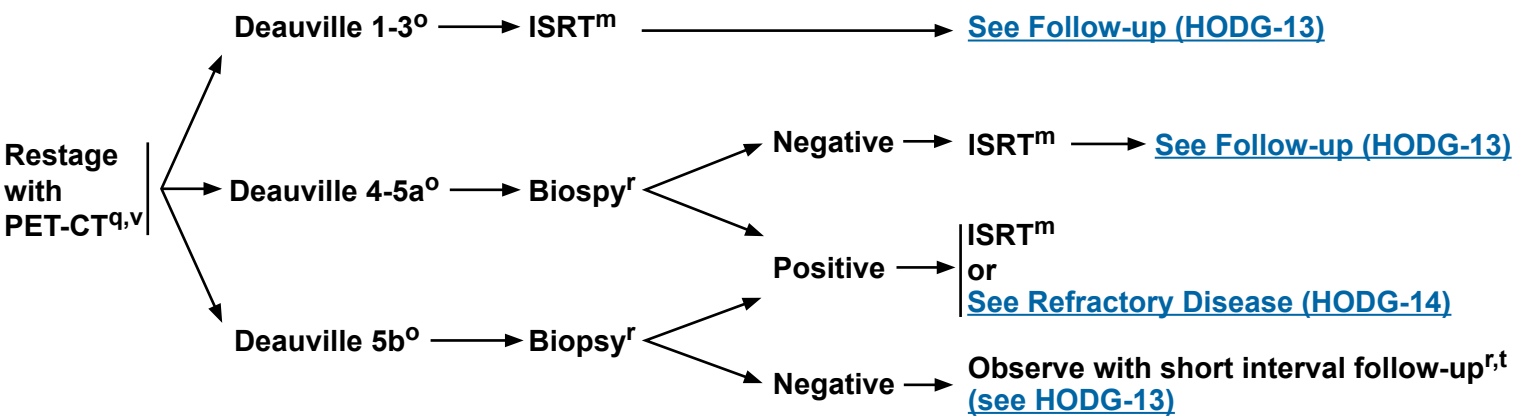
[v]NCCN Unfavorable Factors for stage I-II disease: bulky mediastinal or >10 cm disease, B symptoms, ESR >50, >3 sites of disease (see Unfavorable Factors HODG-A).
[w]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.
[x]In the GHSG trial on which this therapy is based, patients with both bulky disease and B symptoms were excluded and treated according to the algorithm for stage III-IV disease (HODG-11).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage I-II Unfavorable[v] (Bulky)
Planned Combined Modality Therapy
PRIMARY TREATMENT[j]
(continued from HODG-4)



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Note: All recommendations are category 2A unless otherwise indicated.
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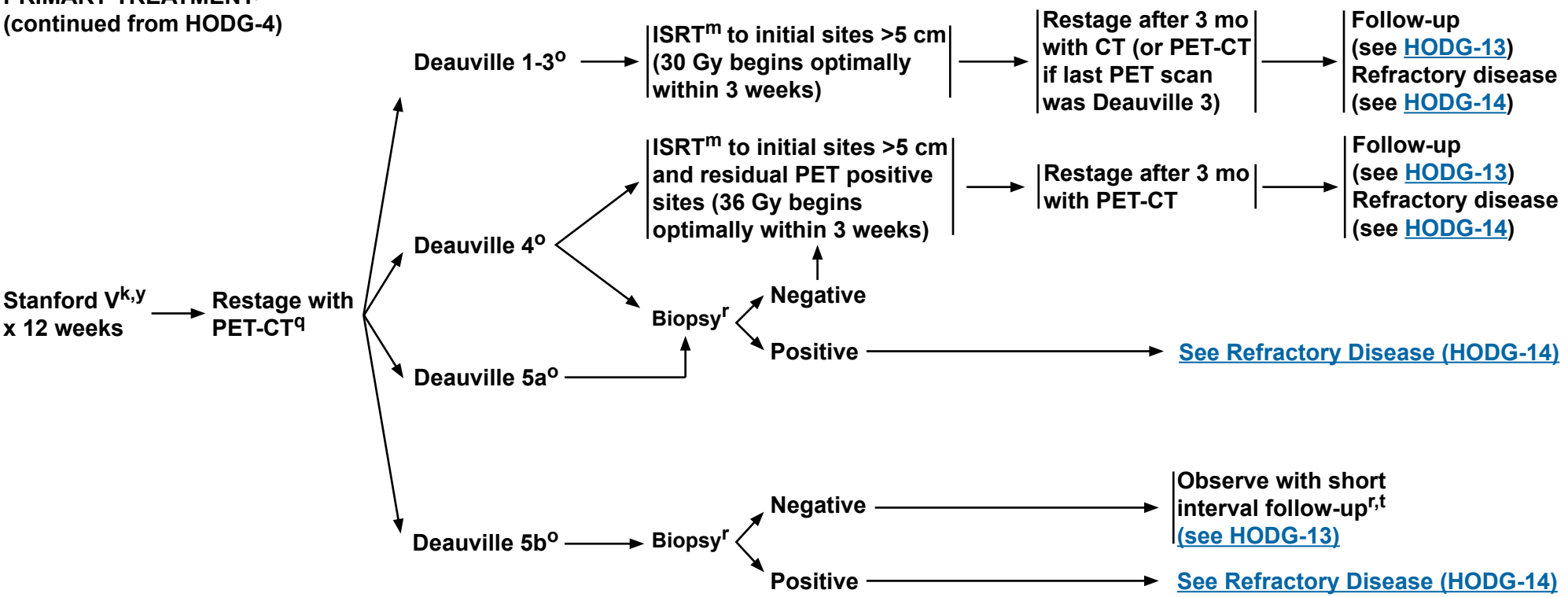
CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage I-II Unfavorable[v] (Bulky or Non-bulky)
PRIMARY TREATMENT[j]
(continued from HODG-4)



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[k]See Principles of Systemic Therapy (HODG-B).
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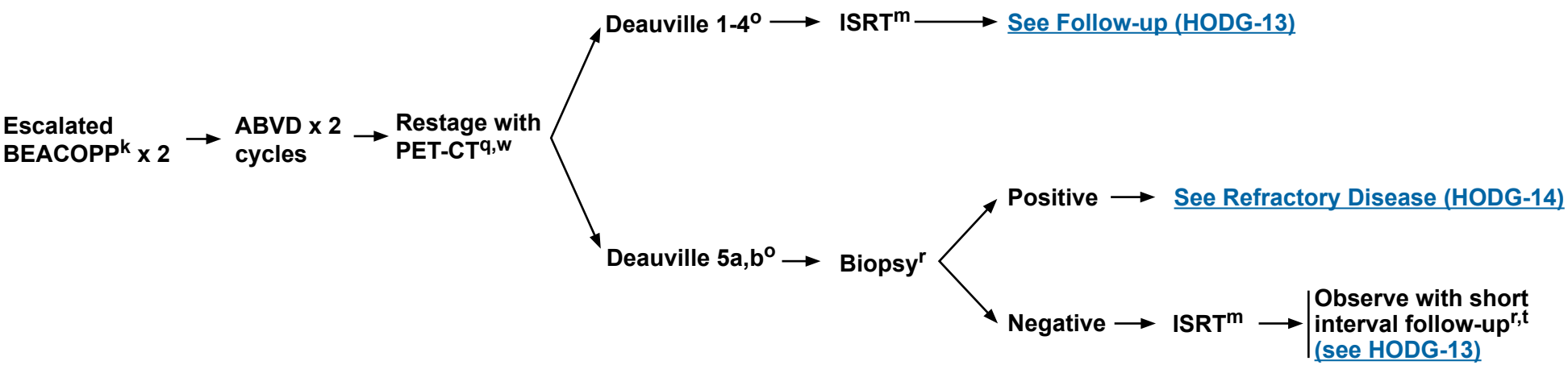
[r]Additional medical management may be required. Clinical circumstances may warrant additional treatment even in face of negative biopsy.
[t]Repeat PET-CT every 3-6 months until Deauville 1-2 or until no progression for 12 months or more.
[v]NCCN Unfavorable Factors for stage I-II disease: bulky mediastinal or >10 cm disease, B symptoms, ESR >50, >3 sites of disease (see Unfavorable Factors HODG-A).
[y]The Stanford V regimen is used in this fashion for patients with bulky mediastinal disease or >10 cm disease and/or B symptoms. Patients with elevated ESR, and/or >3 sites in absence of bulky disease are treated according to the Stanford V algorithm on HODG-2.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage I-II Unfavorable[v,x]
PRIMARY TREATMENT[j]
(continued from HODG-4 and HODG-9)



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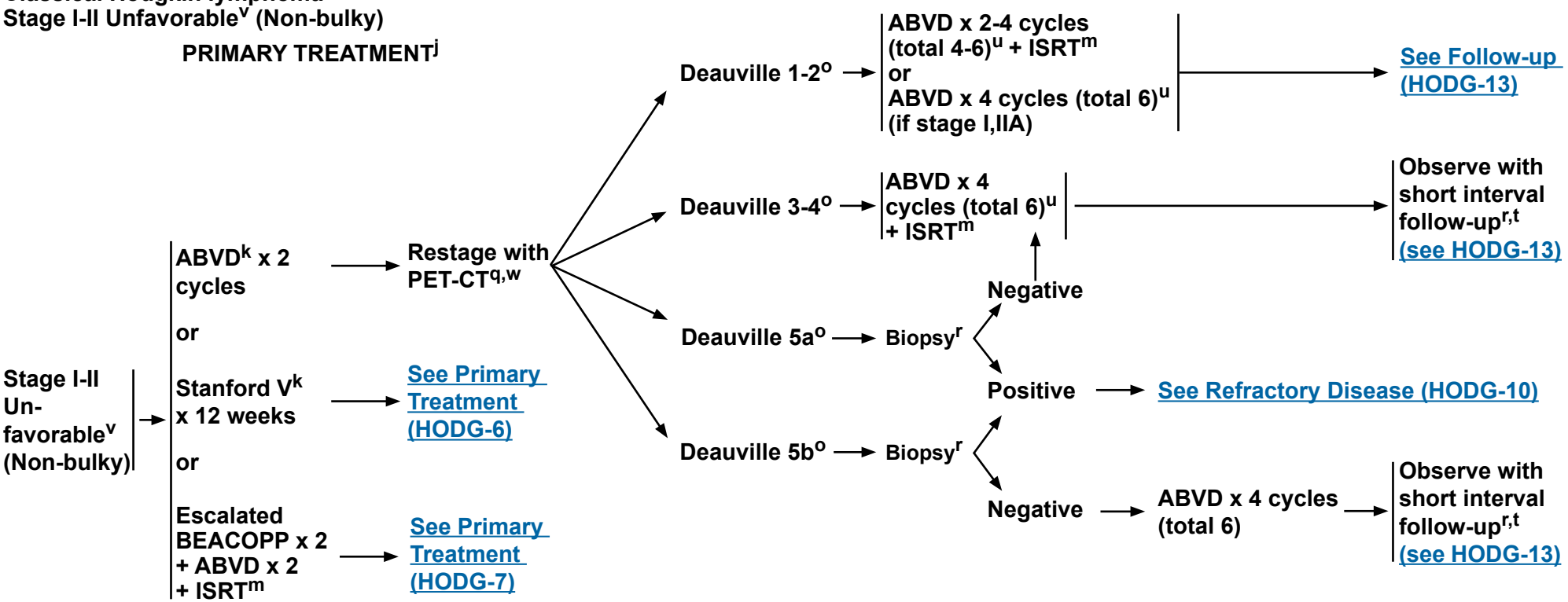
CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage I-II Unfavorable[v] (Non-bulky)

PRIMARY TREATMENT[j]



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[w]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.

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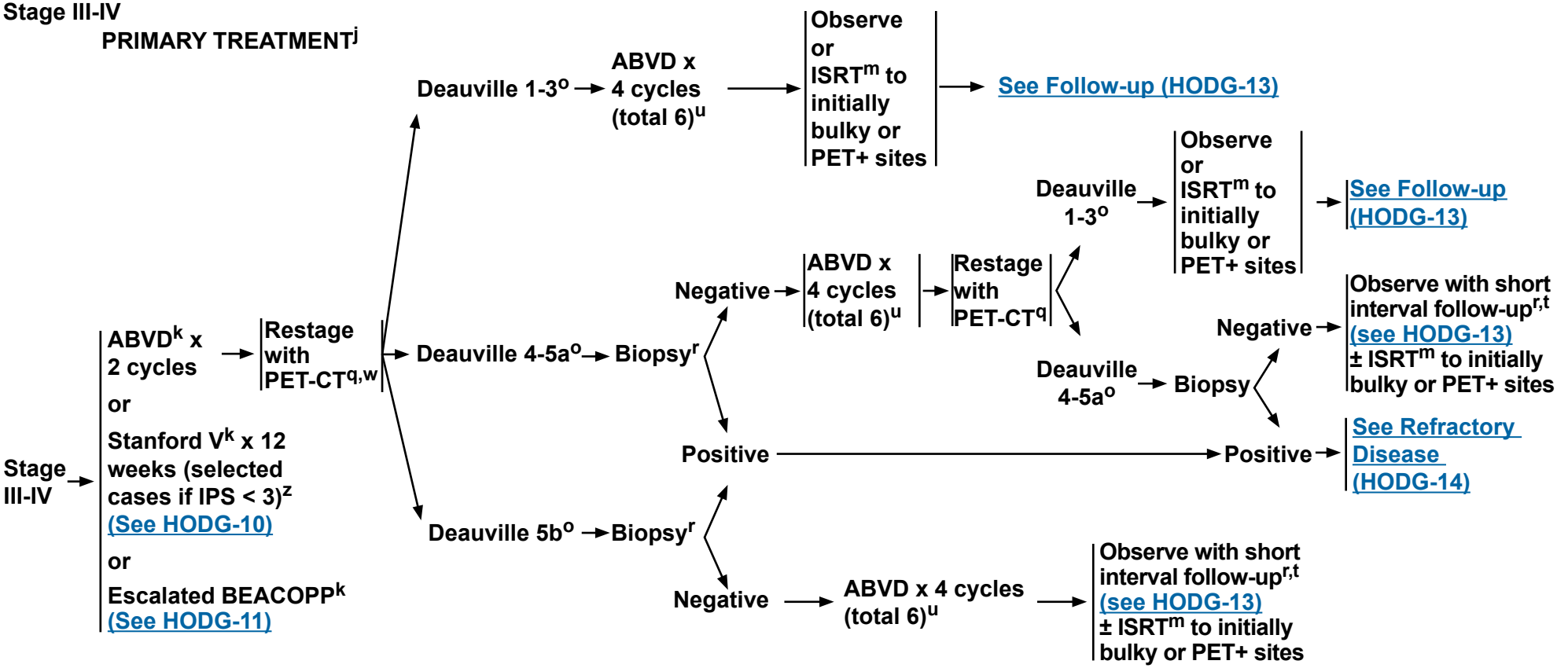
CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage III-IV

PRIMARY TREATMENT[j]



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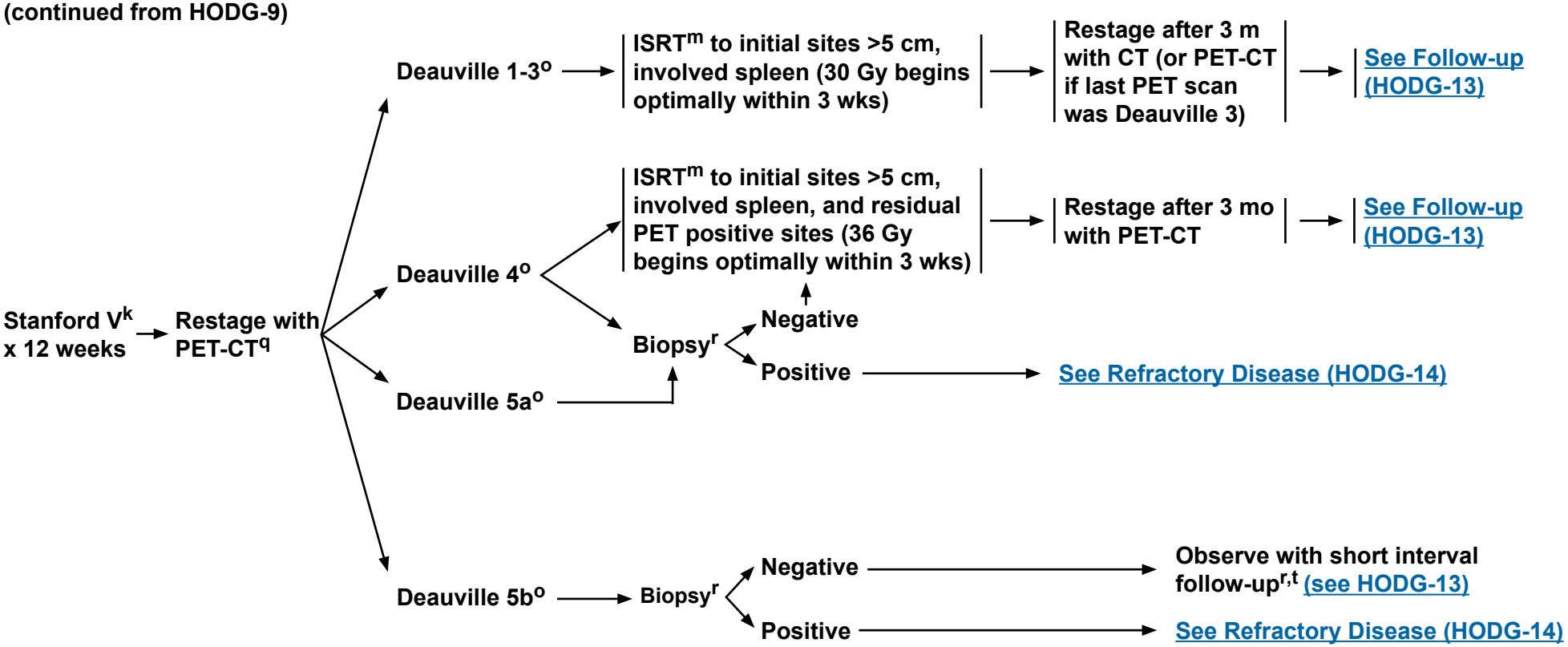
[u]Consider PFTs after 4 cycles of ABVD.
[w]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.
[z]See International Prognostic Score (IPS) (HODG-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage III-IV
PRIMARY TREATMENT[j]
(continued from HODG-9)



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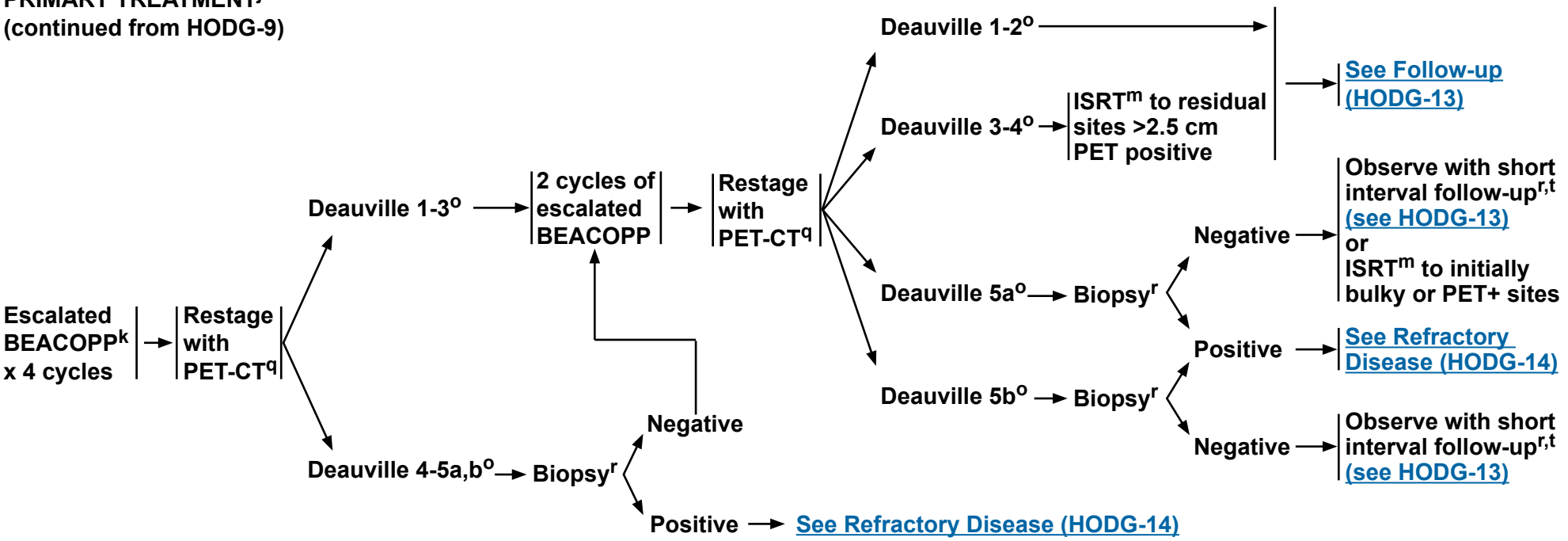
CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage III-IV
PRIMARY TREATMENT[j]
(continued from HODG-9)



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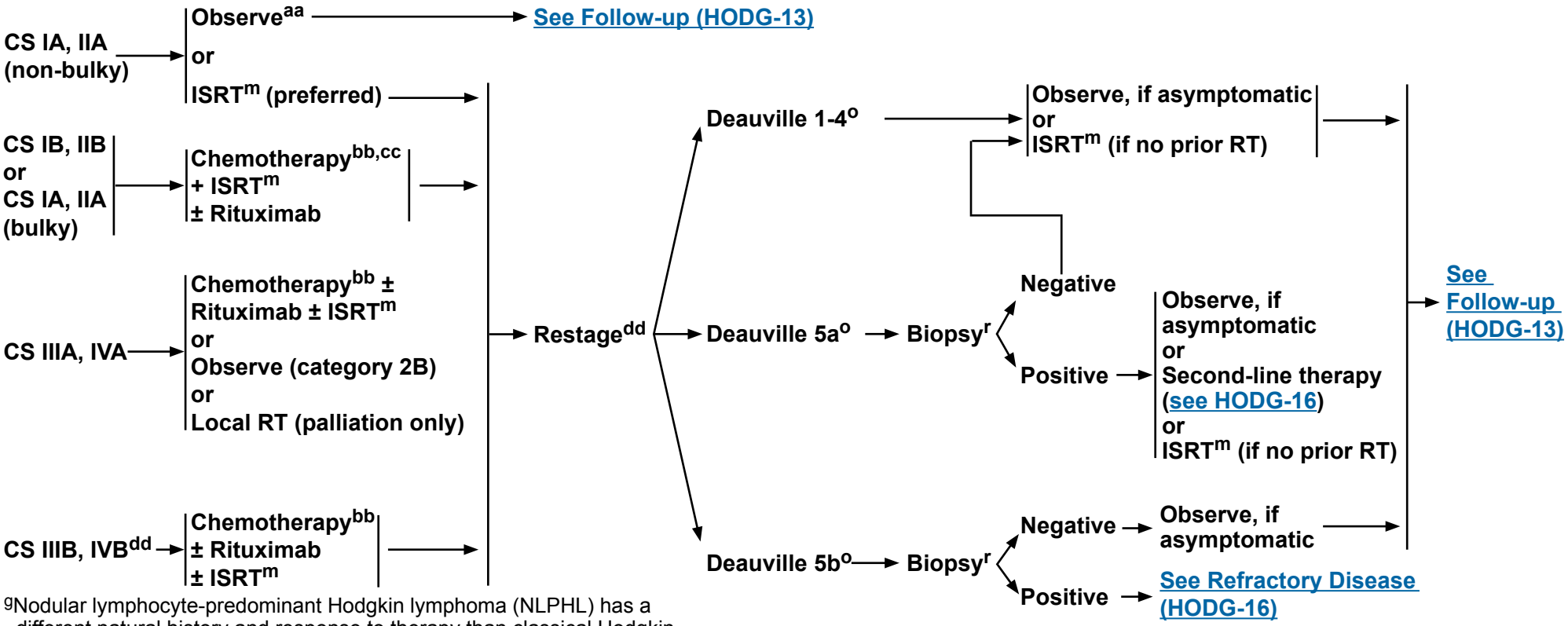
CLINICAL PRESENTATION:
Nodular Lymphocyte-predominant Hodgkin lymphoma[g]

PRIMARY TREATMENT



[g]Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) has a different natural history and response to therapy than classical Hodgkin lymphoma, especially stages I-II. For that reason, separate guidelines are presented for NLPHL.

[m]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

[o]See Deauville PET Criteria (HODG-D) and Discussion (MS-4).

[r]Additional medical management may be required. Clinical circumstances may warrant additional treatment even in face of negative biopsy.

[aa]Observation may be an option for stage IA patients with a completely excised solitary lymph node.

[bb]See Principles of Systemic Therapy (HODG-B 2 of 2).

[cc]Generally a brief course of chemotherapy (3-4 months) would be given with radiation therapy.

[dd]Consider biopsy of persistent or new subdiaphragmatic sites to rule out transformation.

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FOLLOW-UP AFTER COMPLETION OF TREATMENT AND MONITORING FOR LATE EFFECTS

- **It is recommended that the patient be provided with a treatment summary at the completion of his/her therapy.**
- **Follow-up with an oncologist is recommended, especially during the first 5-y interval to detect recurrence, and then annually due to the risk of late complications including second cancers and cardiovascular disease.[ee,ff] Late relapse or transformation to large cell lymphoma may occur in NLPHL.**
- **The frequency and types of tests may vary depending on clinical circumstances: age and stage at diagnosis, social habits, treatment modality, etc. There are few data to support specific recommendations; these represent the range of practice at NCCN Member Institutions.**

Follow-up After Completion of Treatment up to 5 Years

- **Interim H&P:**
  Every 3-6 mo for 1-2 y, then every 6-12 mo until year 3, then annually.
  - **Annual influenza vaccine**
- **Laboratory studies:**
  - **CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile with each clinic visit**
  - **Thyroid-stimulating hormone (TSH) at least annually if RT to neck**
- **Chest x-ray or CT every 6-12 mo during first 2 y, then chest x-ray optional**
- **Abdominal/pelvic CT every 6-12 mo for first 2 y**
- **Counseling:**
  Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion.
- **Surveillance PET should not be done routinely due to risk for false positives. Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed.**

Suspected Relapse CHL (HODG-15) or NLPHL (HODG-16)

Monitoring for Late Effects After 5 Years[ee,ff]

- **Interim H&P: Annually**
  - **Annual blood pressure, aggressive management of cardiovascular risk factors**
  - **Pneumococcal, meningococcal, and H-flu revaccination after 5-7 y, if patient treated with splenic RT or previous splenectomy**
  - **Annual influenza vaccine**
- **Cardiovascular symptoms may emerge at a young age.**
  - **Consider stress test/echocardiogram at 10-y intervals after treatment is completed, especially if chest cardiac irradiation.**
  - **Consider carotid ultrasound at 10-y intervals if neck irradiation.**
- **Laboratory studies:**
  - **CBC, platelets, chemistry profile annually**
  - **TSH at least annually if RT to neck**
  - **Annual lipids**
- **Consider chest imaging for patients at increased risk for lung cancer[gg]**
- **Annual breast screening:**
  Initiate 8-10 y post-therapy, or at age 40, whichever comes first, if chest or axillary radiation. The NCCN Hodgkin Lymphoma Guidelines Panel recommends breast MRI in addition to mammography for women who received irradiation to the chest between ages 10 and 30 y, which is consistent with the American Cancer Society Guidelines.
- **Counseling:**
  Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, and skin cancer risk.
- **Treatment summary and consideration of transfer to PCP.**
- **Consider a referral to a survivorship clinic.**

[ee]Mauch P, Ng A, Aleman B, et al. Report from the Rockefeller Foundation sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9-16, 2003, Bellagio, Italy. Eur J Haematol 2005;75(s66).
[ff]Appropriate medical management should be instituted for any abnormalities.
[gg]Chest imaging optional after 5 y if patient treated with a non-alkylating agent, no RT to the chest, and no other risk factors are present.

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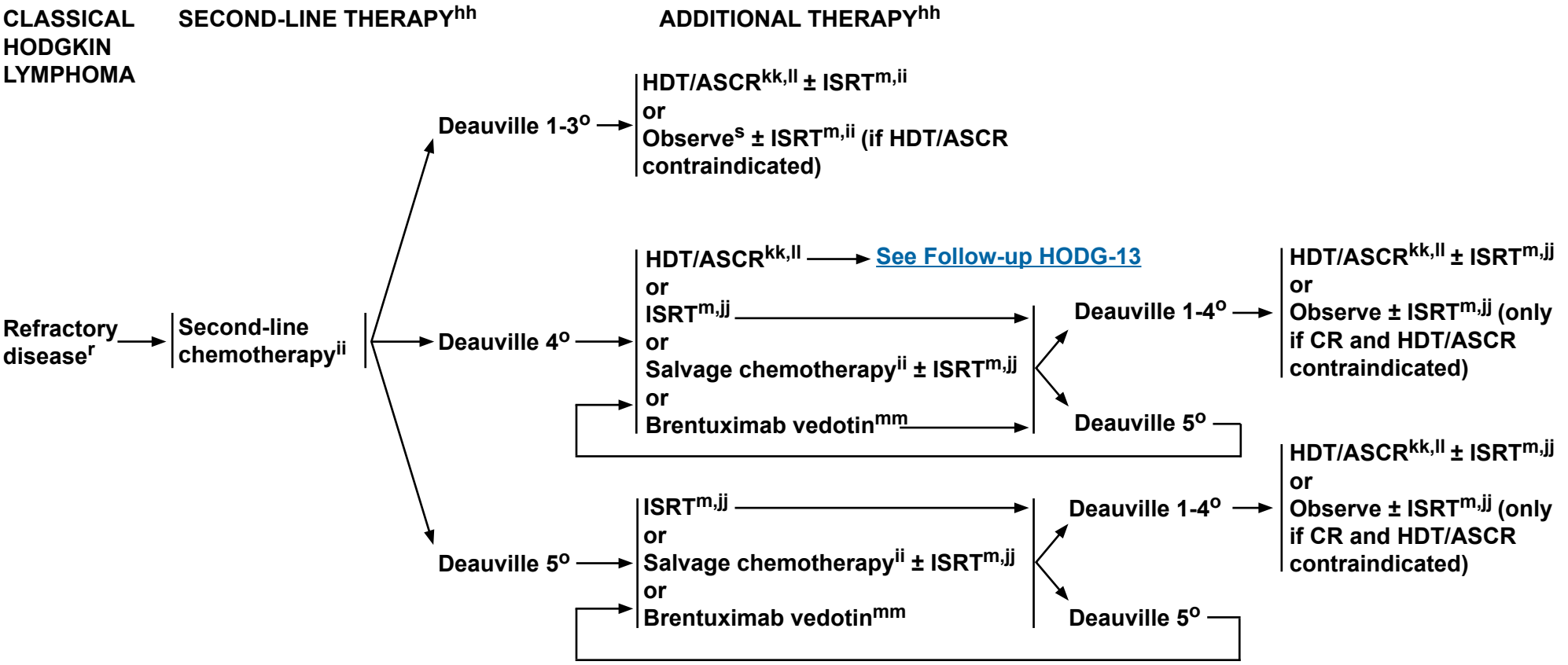

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[o]See Deauville PET Criteria (HODG-D) and Discussion (MS-4).
[s]Deauville 3 should have short interval follow-up including PET-CT, potentially repeated every 3-6 months until stable (up to 1 year).
[hh]There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.
[ii]See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-E).
[jj]Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.
[kk]Radiation therapy recommended when sites have not been previously irradiated. In a radiation-naive patient, TLI may be an appropriate component of HDT.
[ll]Allotransplant is an option in select patients as a category 3 recommendation.
[mm]Brentuximab vedotin is a treatment option for patients who have failed HDT/ASCR or at least 2 prior multi-agent chemotherapy regimens.

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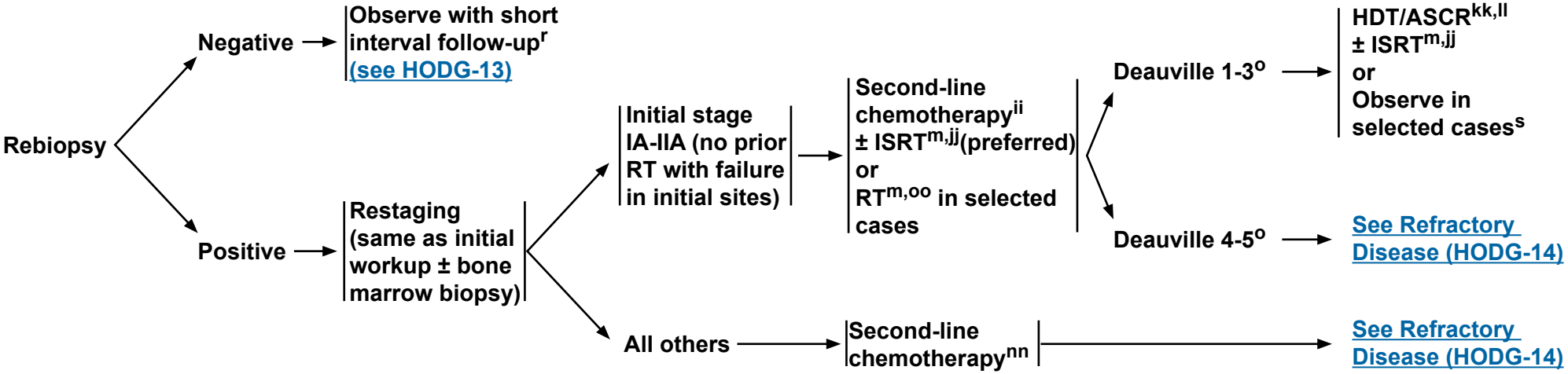
CLASSICAL HODGKIN LYMPHOMA
SUSPECTED RELAPSE

SECOND-LINE THERAPY[hh]



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[hh]There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.
[ii]See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-E).
[jj]Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.
[kk]Radiation therapy recommended when sites have not been previously irradiated. In a radiation-naive patient, TLI may be an appropriate component of HDT.
[ll]Allotransplant is an option in select patients as a category 3 recommendation.
[nn]For select patients with long disease-free interval and other favorable features; selection of chemotherapy should be individualized.
[oo]If radiation therapy is being used alone as a salvage therapy, conventional involved field or extended field treatment is indicated.

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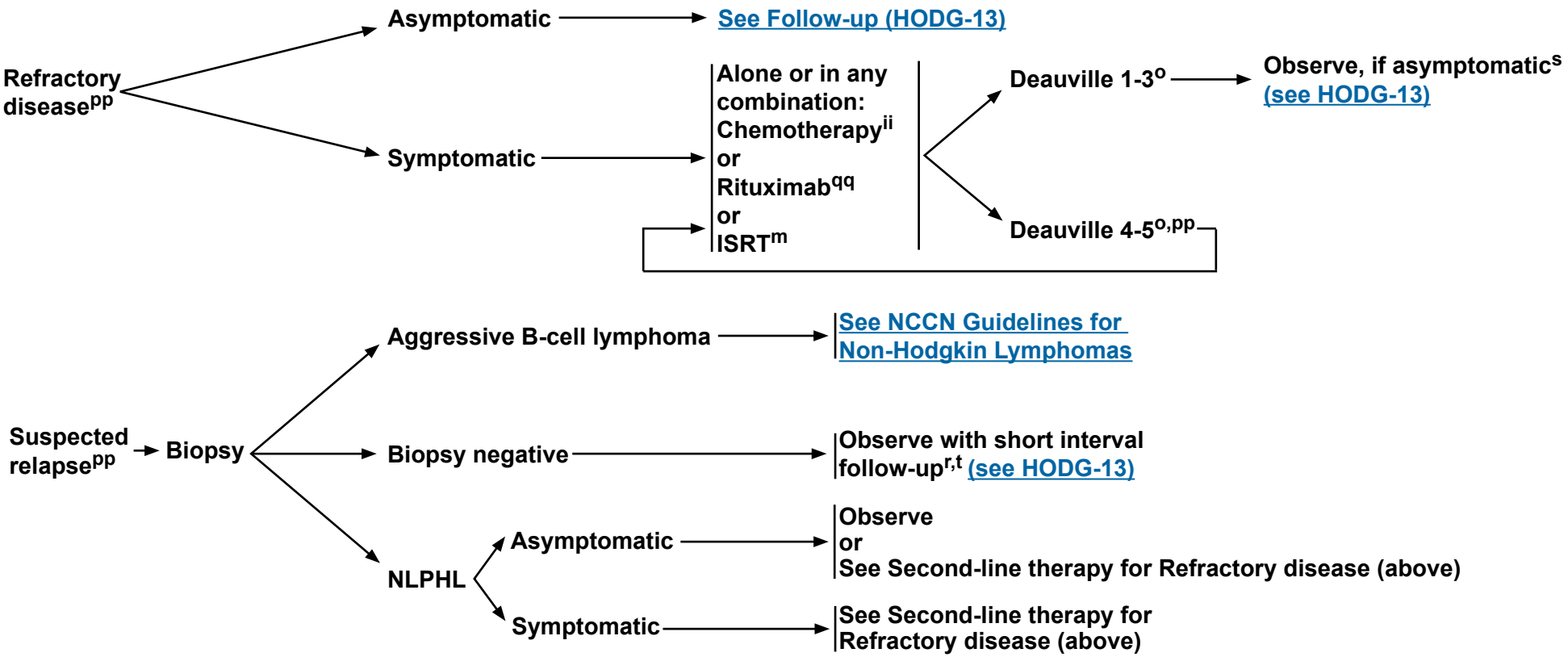
NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA REFRACTORY OR SUSPECTED RELAPSE

SECOND-LINE THERAPY[hh]



[m]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

[o]See Deauville PET Criteria (HODG-D) and Discussion (MS-4).

[r]Additional medical management may be required. Clinical circumstances may warrant additional treatment even in face of negative biopsy.

[s]Deauville 3 should have short interval follow-up including PET-CT, potentially repeated every 3-6 months until stable (up to 1 year).

[t]Repeat PET-CT every 3-6 months until Deauville 1-2 or until no progression for 12 months or more.

[hh]There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.

[ii]See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-E).

[pp]Some patients with NLPHL have a chronic indolent course that may not require aggressive re-treatment. These asymptomatic patients may be observed. At relapse, patient should be considered for re-biopsy because of risk for transformation.

[qq]In some patients treated with rituximab alone, maintenance rituximab may be considered for 2 years.

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Examples of Unfavorable Risk Factors for Stage I-II Hodgkin Disease

Risk Factor	GHSG	EORTC	NCIC	NCCN
Age		≥50	≥40	
Histology			MC or LD	
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	>50 or any B sx	>50 or any B sx
Mediastinal mass	MMR > .33	MTR > .35	MMR > .33 or > 10 cm	MMR > .33
# Nodal sites	>2*	>3**	>3	>3
E lesion	any			
Bulky				>10 cm

GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer
NCIC = National Cancer Institute, Canada
MC = Mixed cellularity
LD = Lymphocyte depleted
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

*The GHSG definition of nodal sites differs from the Ann Arbor System in that the infraclavicular region is included with the ipsilateral cervical/supraclavicular, the bilateral hila are included with the mediastinum, and the abdomen is divided into 2 regions, upper (spleen hilum, liver hilum, celiac) and lower.
**The EORTC definition of nodal sites differs from the Ann Arbor System in that the infraclavicular region is included with the ipsilateral axilla.

International Prognostic Score (IPS) 1 point per factor (advanced disease)[1]

- **Albumin < 4 g/dL**
- **Hemoglobin < 10.5 g/dL**
- **Male**
- **Age ≥ 45 years**
- **Stage IV disease**
- **Leukocytosis (white blood cell count at least 15,000/mm^3)**
- **Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm^3)**

[1]Derived from Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease: International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998;339:1506-1514.

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PRINCIPLES OF SYSTEMIC THERAPY (1 of 2)

Classical Hodgkin Lymphoma

- **The most common variants of chemotherapy used at NCCN Member Institutions include ABVD and Stanford V. Routine use of growth factors is not recommended. Leukopenia is not a factor for delay of treatment or reduction of dose intensity (except for escalated BEACOPP).**

Regimens and References

ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) ± RT

Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD 11 trial. J Clin Oncol 2010;28:4199-4206.
Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 2010;363:640-652.
Meyer R, Gospodarowicz M, Connors J, et al. ABVD Alone versus Radiation Based Therapy in Limited Stage Hodgkin's Lymphoma. N Engl J Med 2012;366:399-408.
Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: Long-Term Results. J Clin Oncol 2004;22(14):2835-2841.

Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone)*

Gordon LI, Hong F, Fisher RI, et al. Randomized Phase III Trial of ABVD Versus Stanford V With or Without Radiation Therapy in Locally Extensive and Advanced-Stage Hodgkin Lymphoma: An Intergroup Study Coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol 2013;31:684-691.
Advani RH, Hoppe RT, Baer D, et al. Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: mature results of the G4 trial. Ann Oncol 2013;24:1044-1048.
Edwards-Bennett SM, Jacks LM, Moskowitz CH, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. Ann Oncol 2010;21:574-581.

Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone)

Engert A, Haverkamp H, Cobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. The Lancet 2012; 379(9828):1791-1799.

Escalated BEACOPP followed by ABVD with RT

von Tresckow B, Plutschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD14 Trial. J Clin Oncol 2012:30:907-913.

*Cyclophosphamide may be used as an alternate to nitrogen mustard.

See Principles of Chemotherapy for NLPHL (HODG-B 2 of 2)

See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-E)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY (2 of 2)

Nodular Lymphocyte-Predominant Hodgkin Lymphoma[1]

• The most common chemotherapies used at NCCN Member Institutions for NLPHL are listed below.

Regimens and References

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) ± rituximab

Savage KJ, Skinnider B, Al-Mansour M, et al. Treating limited stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. Blood 2011;118:4585-4590.

Canellos GP, Mauch P. What is the appropriate systemic chemotherapy for lymphocyte-predominant Hodgkin's Lymphoma? J Clin Oncol 2010;28:e8.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab

Fanale MA, Lai C-M, McLaughlin P, et al. Outcomes of Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL) Patients Treated with R-CHOP. ASH Annual Meeting Abstracts 2010;116:2812.

CVP (cyclophosphamide, vincristine, prednisone) ± rituximab

Rituximab

Ekstrand BC, Lucas JB, Horwitz SM, et al. Rituximab in lymphocyte-predominant Hodgkin disease: results of a phase 2 trial. Blood. 2003;101(11):4285-4289.

Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). Blood 2008;111(1):109-111.

Horning SJ, Bartlett NL, Breslin S, et al. Results of a Prospective Phase II Trial of Limited and Extended Rituximab Treatment in Nodular Lymphocyte Predominant Hodgkin's Disease (NLPHD). ASH Annual Meeting Abstracts. 2007;110:644.

Eichenauer DA, Fuchs M, Pluetschow A, et al. Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group. Blood 2011;118:4363-4365.

[1]Ongoing clinical trials will help to clarify the role of a watch-and-wait strategy or systemic therapy, including anthracycline (epirubicin or doxorubicin), bleomycin, and vinblastine-based chemotherapy or antibody-based approaches, in the treatment of these patients.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF RADIATION THERAPY[a]

Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.

Fields: Radiation oncologists endorse the concept of "involved site" radiation therapy (ISRT) as an alternative to "involved field" radiation therapy (IFRT). Involved site fields are generally smaller than classical involved fields.

- **Planning for ISRT requires modern CT-based simulation and planning capabilities. The incorporation of other additional imaging techniques, such as PET and MRI, often enhances treatment planning.**
- **ISRT targets the site of the originally involved lymph node(s) and possible extranodal extension. The field encompasses the pre-chemotherapy and/or surgical site, yet it spares adjacent uninvolved organs (such as lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy.**
- **The pre-chemotherapy or pre-biopsy gross tumor volume (GTV) provides the basis for determining the clinical target volume (CTV). Concerns for questionable subclinical disease and uncertainties in original imaging accuracy or localization may lead to expansion of the CTV and are determined individually based upon clinical judgment. For example, the CTV definition for treating NLPHL with radiation therapy alone will be greater than that employed for classical Hodgkin lymphoma with similar disease distribution being treated with combined modality therapy. Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy (internal target volume, ITV) should also influence the final CTV.**
- **The planning target volume (PTV) is an additional expansion of the CTV that accounts only for setup variations (see ICRU definitions).**
- **Organs at risk (OARs) should be outlined for optimizing treatment plan decisions.**
- **The treatment plan is designed using conventional, 3-D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR.**

Dose:

Combined Modality Therapy

Non-bulky disease (stage I-II): 20*-30 Gy (if treated with ABVD), 30 Gy (if treated with Stanford V)
Non-bulky disease (stage IB-IIB): 30 Gy
Bulky disease sites (all stages): 30-36 Gy

RT Alone (uncommon, except for NLPHL):
Involved regions: 30-36 Gy (the dose of 30 Gy is mainly used for NLPHL)
Uninvolved regions: 25-30 Gy

***A dose of 20 Gy following ABVD x 2 is sufficient if the patient has non-bulky stage I-IIA disease with an ESR < 50, no extralymphatic lesions, and only one or two lymph node regions involved. See HODG-A for definition of nodal sites according to GHSG.**

[a]Specht L, Yahalom J, Illidge T, et al; Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG) International Journal of Radiation Oncology, Biology, Physics 2013.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

DEAUVILLE PET CRITERIA*

Score	PET/CT scan result
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately increased compared to the liver at any site
5	Uptake markedly increased compared to the liver at any site
X	New areas of uptake unlikely to be related to lymphoma

*For definitions of 5a and 5b as used in the NCCN Guidelines, see MS-4.

Copyright permission is pending for the updated version of the Deauville PET Criteria, which can be found in: Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. Leuk Lymphoma 2010;51:2171 2180. See discussion.

With kind permission from Springer Science + Business Media: Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 2010:37:1824-1833.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE (1 OF 2)

- **The selection of second-line chemotherapy regimens depends on the pattern of relapse and the agents previously used.**
- **Some studies have suggested that patients with minimal disease burden at relapse (not refractory) may not need additional treatment prior to high-dose chemotherapy with stem-cell rescue.[1-3] However, patients tend to have an improved outcome when transplanted in a minimal disease state.[4] Thus, cytoreduction with chemotherapy before high-dose chemotherapy with stem-cell rescue may be beneficial. In addition, second-line chemotherapy serves as a test for drug sensitivity and to facilitate the harvest of stem cells.**
  - **Nitrogen mustard, procarbazine, carmustine, and melphalan may adversely affect both quality and quantity of stem-cell collection.**
- **Brentuximab vedotin is a treatment option for patients with classical Hodgkin lymphoma (CHL) who have failed HDT/ASCR or at least 2 prior multi-agent chemotherapy regimens.[5]**
- **Rituximab should be considered with all second-line chemotherapy regimens for relapsed or refractory NLPHL.**

See Regimens and References (HODG-E 2 of 2)

[1]Sweetenham JW, Taghipour G, Milligan D, et al. High-dose therapy and autologous stem cell rescue for patients with Hodgkin's disease in first relapse after chemotherapy: results from the EBMT. Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. 1997;20(9):745-52.
[2]Bierman PJ, Anderson JR, Freeman MB, et al. High-dose chemotherapy followed by autologous hematopoietic rescue for Hodgkin's disease patients following first relapse after chemotherapy. Ann Oncol 1996;7(2):151-6.
[3]Chopra R, McMillan AK, Linch DC, et al. The place of high-dose BEAM therapy and autologous bone marrow transplantation in poor-risk Hodgkin's disease. A single-center eight-year study of 155 patients. Blood 1993;81:1137-45.
[4]Stewart DA, Guo D, Gluck S, et al. Double high-dose therapy for Hodgkin's disease with dose-intensive cyclophosphamide, etoposide, and cisplatin (DICEP) prior to high-dose melphalan and autologous stem cell transplantation. Bone Marrow Transplant 2000;26(4):383-8.
[5]Younes A, Gopal AK, Smith SE, et al. Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma. J Clin Oncol 2012;30:2183-2189.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE (2 OF 2)
Regimens and References
(listed in alphabetical order)

Second-Line Therapy:

Brentuximab vedotin* (only for CHL)
Younes A, Gopal AK, Smith SE, et al. Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma. J Clin Oncol 2012;30:2183-2189.

C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) (category 2B)

DHAP (dexamethasone, cisplatin, high-dose cytarabine)
Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Ann Oncol 2002;13(10):1628-1635.
Abali H, Urün Y, Oksüzoğlu B, Budakoğlu B, et al. Comparison of ICE (ifosfamide-carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. Cancer Invest 2008;26(4):401-406.

ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)
Aparicio J, Segura A, Garcera S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. Ann Oncol 1999;10(5):593-595.
Fernández de Larrea C, Martínez C, et al. Salvage chemotherapy with alternating MINE-ESHAP regimen in relapsed or refractory Hodgkin's lymphoma followed by autologous stem cell transplantation. Ann Oncol 2010;21(6):1211-1216.

Everolimus (only for CHL)
Johnston PB, Inwards DJ, Colgan JP, et al; A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. Am J Hematol. 2010;85(5):320-4.

GCD (gemcitabine, carboplatin, dexamethasone)
Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemicitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by Puget Sound Oncology Consortium. Leuk Lymphoma 2010;51:1523-1529.

GVD (gemcitabine, vinorelbine, liposomal doxorubicin)
Bartlett N, Niedzwiecki D, Johnson J, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Ann Oncol 2007;18(6):1071-1079.

ICE (ifosfamide, carboplatin, etoposide)
Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001;97(3):616-623.
Abali H, Urün Y, Oksüzoğlu B, Budakoğlu B, et al. Comparison of ICE (ifosfamide-carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. Cancer Invest 2008;26(4):401-406.

IGEV (ifosfamide, gemcitabine, vinorelbine)
Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica 2007;92(1):35-41.

Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)
Colwill R, Crump M, Couture F, et al. Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease before intensive therapy and autologous bone marrow transplantation. J Clin Oncol 1995;13:396-402.
Martín A, Fernández-Jiménez MC, Caballero MD, et al. Long-term follow-up in patients treated with Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease. Br J Haematol 2001;113(1):161-171.

MINE (etoposide, ifosfamide, mesna, mitoxantrone)
Rodriguez MA, Cabanillas FC, Hagemeister FB, et al. A phase II trial of mesna/ifosfamide, mitoxantrone and etoposide for refractory lymphoms. Ann Oncol 1995;6(6):609-611.

Third-Line Therapy (only for CHL):

Bendamustine
Moskowitz AJ, Hamlin PA, Perales M-A, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol 2013;31:456-460.

Lenalidomide
Fehniger TA, Larson S, Trinkaus K, et al; A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood 2011;118(19):5119-25.

*Brentuximab vedotin is a treatment option for patients who have failed HDT/ASCR or at least 2 prior multi-agent chemotherapy regimens.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Table 1

Definitions of Stages in Hodgkin's Disease[1]

Stage I Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (I_E).

Stage II Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s), with or without involvement of other lymph node regions on the same side of the diaphragm (II_E).

Note: The number of lymph node regions involved may be indicated by a subscript (eg, II_3).

Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), by involvement of the spleen (III_S), or by both (III_{E+S}).

Stage IV Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

A No systemic symptoms present

B Unexplained fevers >38°C; drenching night sweats; or weight loss >10% of body weight (within 6 months prior to diagnosis)

Adapted from **Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31(11):1860-1**.

[1]PET scans are useful for upstaging in Stage I-II disease. If there is PET positivity outside of disease already identified, further clinical investigation is recommended to confirm or refute the observation. PET scans are usually positive in patients with HIV infection, even in the absence of Hodgkin lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Discussion

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.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged 55 years or older. In 2014, an estimated 9,190 people will be diagnosed with HL in the United States and 1,180 people will die from the disease.[1]

The WHO classification divides HL into 2 main types: nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (CHL).[2] CHL is divided into 4 subtypes: nodular sclerosis CHL (NSCHL); mixed cellularity CHL (MCCHL); lymphocyte-depleted CHL (LDCHL); and lymphocyte-rich CHL (LRCHL). In Western countries, CHL accounts for 95% and NLPHL accounts for 5% of all HL.

CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas NLPHL lacks Reed-Sternberg cells but is characterized by the presence of lymphocyte-predominant cells, sometimes termed *popcorn cells*.

The past few decades have seen significant progress in the management of patients with HL; it is now curable in at least 80% of patients. The advent of more effective treatment options has improved the 5-year survival rates that are unmatched in any other cancer over the past 4 decades. Every patient with newly diagnosed HL has an overwhelming likelihood of being cured with the appropriate treatment. In fact, cure rates for HL have increased so markedly that overriding of treatment considerations often relate to long-term toxicity, especially for patients with early- or intermediate-stage disease. Clinical trials still emphasize improvement in cure rates for patients with advanced disease, but the potential long-term effects of treatment remain an important consideration.

The NCCN Guidelines discuss the clinical management of patients with CHL and NLPHL, focusing exclusively on patients from post adolescence through the seventh decade of life who do not have serious intercurrent disease. The guidelines do not address HL in pediatric or older patients or those with unusual situations, such as HIV positivity or pregnancy. Individualized treatment may be necessary for older patients and those with concomitant disease. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

Staging and Prognosis

Staging for HL is based on the Ann Arbor staging system. Patients with HL are usually classified into 3 groups: early-stage favorable (stage I-II with no unfavorable factors); early-stage unfavorable (stage I-II with any of the unfavorable factors such as large mediastinal adenopathy; B symptoms; numerous sites of disease; or significantly elevated erythrocyte sedimentation rate [ESR]), and advanced-stage disease (stage III-IV). Each stage is subdivided into A and B categories. “A” indicates that no systemic symptoms are present and “B” is assigned to patients with unexplained weight loss of more than 10% of their body weight, unexplained fevers, or drenching night sweats.[3]

Mediastinal bulk is an unfavorable prognostic factor in patients with early-stage HL. Mediastinal bulk on chest radiograph is measured most commonly using the mediastinal mass ratio (MMR).[4] The MMR is the ratio of the maximum width of the mass and the maximum intrathoracic diameter. Any mass with MMR greater than 0.33 is defined as bulky disease. Another definition of bulk is any single node or nodal mass that is 10 cm or greater in diameter. According to the Cotswolds modification of the Ann Arbor staging system, bulky disease is defined

as a mediastinal mass exceeding one third of the internal transverse diameter of the thorax at the T5-T6 interspace on a posteroanterior chest radiograph.[5]

Other unfavorable prognostic factors for patients with stage I and stage II disease include the presence of B symptoms, more than 2 to 3 nodal sites of disease, or an ESR of 50 or more. These factors are based largely on the definition of unfavorable prognostic groups from the clinical trials conducted by the EORTC, German Hodgkin Study Group (GHSG), and the National Cancer Institute of Canada (NCIC).[6,7] The NCCN unfavorable factors for stage I-II disease include bulky mediastinal disease (MMR greater than 0.33) or bulky disease greater than 10 cm, B symptoms, ESR greater than 50, and more than 3 nodal sites of disease.

An international collaborative effort evaluating more than 5000 patients with advanced CHL (stage III-IV) identified 7 adverse prognostic factors, each of which reduced survival rates by 7% to 8% per year:[8]

- Age 45 years or older
- Male gender
- Stage IV disease
- Albumin level below 4 g/dL
- Hemoglobin level below 10.5 g/dL
- Leucocytosis (white blood cell count more than 15,000/mm^3)
- Lymphocytopenia (lymphocyte count less than 8% of the white blood count and/or lymphocyte count less than 600/mm^3)

The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis.[8] IPS helps to determine the clinical management and predict prognosis for patients with stage III-IV disease. For instance, selected patients with IPS <3 and advanced disease could be treated with Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone) while escalated-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), or ABVD (doxorubicin bleomycin, vinblastine, and dacarbazine) may be more appropriate for all other patients with stage III-IV disease.

Response Criteria

Clinical management of patients with CHL involves initial treatment with chemotherapy or combined modality therapy, followed by restaging at the completion of chemotherapy to assess treatment response. Assessment of response to initial treatment is essential because the need for additional treatment is based on the treatment response.

The International Working Group published the guidelines for response criteria in 1999.[9] These criteria are based on the size reduction of enlarged lymph nodes as measured on CT scan, and the extent of bone marrow involvement determined using bone marrow aspirate and biopsy. The original response criteria included CRu (complete response uncertain), indicating that it was not possible to determine whether residual masses identified on CT scan represented residual HL, scarring, or some other nonmalignant process.

In 2007, the IWG guidelines were revised by the International Harmonization Project (IHP) to incorporate immunohistochemistry, flow cytometry, and PET scans in the definition of response.[10,11] The revised guidelines eliminated CRu based partly on the ability of PET scans to further characterize residual masses detected with CT. Using the revised system, response is categorized as complete response (CR), partial response (PR), stable disease, relapsed disease, or progressive disease.[10] The IHP response criteria were initially developed for the

interpretation of PET scans at the completion of treatment. In recent years, these criteria have also been used for interim response assessment.[12]

In 2009, the Deauville criteria were defined for the interpretation of interim and end-of-treatment PET scans based on the visual assessment of FDG uptake in the involved sites. These criteria use a 5-point scale to determine the FDG uptake in the involved sites relative to that of the mediastinum and the liver.[13,14] PET scans with a score of 1 or 2 are considered "negative" and PET scans with a score of 4 and 5 are considered "positive."[15] In some situations, a score of 3 may be considered negative; however, for de-escalation of therapy based on interim PET scans, a threshold for positivity that includes Deauville 3 using the mediastinal blood pool uptake as the reference is appropriate (ie, PET scans with a score of Deauville 1-2 are considered negative and PET scans with a score of Deauville 3-5 are considered positive).[16] The Deauville 5-point criteria are being validated in international multicenter trials for PET-guided interim response assessment and risk-adapted therapy in patients with HL.[16,17]

In the Deauville criteria, scores 1-4 refer to initially involved sites and score 5 refers to an initially involved site and/or new lesions related to lymphoma.[13,14] In the NCCN modification to Deauville criteria, scores 1-5a refer to initially involved sites (score 5a refers to uptake markedly increased > liver at any initially involved site) and score 5b refers to any new sites of disease possibly related to lymphoma.

Role of PET Scans

PET imaging and, more recently, integrated PET and CT (PET/CT, hereafter referred to as PET) has become an important tool for initial staging and response assessment at the completion of treatment in patients with HL.[12] In a recent meta-analysis, PET scans showed high positivity and specificity when used to stage and restage patients with lymphoma.[18] PET positivity at the end of treatment has been shown to be a significant adverse risk factor in patients with early-stage as well as advanced-stage disease.[19-21] In a study of 73 patients (the majority of whom had stage I-IIA disease), Sher et al reported that the actuarial 2-year failure-free survival (FFS) rate was 95% for those who were PET-negative at the end of chemotherapy, and 69% for the PET-positive group.[21] In the HD15 trial, positive PET after chemotherapy with BEACOPP was associated with a higher risk of subsequent treatment failure. The progression-free survival (PFS) at 48 months was 92.6% and 82.6%, respectively, for PET-negative and PET-positive patients (P = .022).[22] In this study, PET-positive patients received radiation therapy (RT) to the PET-positive sites.

The NCCN PET Task Force and the NCCN Guidelines recommend PET scans for initial staging and for evaluating residual masses at the end of treatment.[23] An integrated PET scan plus a diagnostic CT is recommended, although a separate diagnostic CT is not needed if it was part of the integrated PET scan.

The role of PET in post-therapy surveillance remains controversial, and further studies are needed to determine its role. Until those studies are completed, PET scans are not recommended for routine surveillance due to the risk of false positive findings.[24-26]

Interim PET Scans

PET scans are increasingly being used to assess treatment response during therapy. Interim PET scans may be useful to identify a subgroup of patients with early-stage disease that can be treated with chemotherapy alone.[27] The NCCN Guidelines emphasize that the value of interim PET scans remains unclear for many clinical scenarios

and all measures of response should be considered in the context of management decisions.

The guidelines recommend biopsy for all patients with a score of Deauville 5a (uptake markedly increased > liver at any initially involved site) and 5b (new sites of disease possibly related to lymphoma) on interim PET scan. In general, patients with a positive biopsy should be managed as described for refractory disease, and those with a negative biopsy could be observed with short-interval follow-up (PET scans every 3-6 months, until the score Deauville 1-2 or no disease progression for 12 months or more). However, in some clinical circumstances, additional treatment may be warranted even if the biopsy is negative.

Stage IA-IIA (Favorable Disease)

Available evidence, primarily from retrospective studies, suggests only a limited value for interim PET imaging among patients with early-stage disease.

Hutchings et al reported that five of seven (71%) patients with stage I-II disease who had a positive interim PET scan remained in remission at a median follow-up of 3 years, whereas all patients with advanced disease (stage III-IV) with a positive PET scan had relapsed within 2 years.[28]

In another study that included a majority of patients with stage I-IIA disease (43 out of 73), the actuarial 2-year FFS rate was 95% for those who were PET-negative at the end of chemotherapy, and was 69% for the PET-positive group.[21] However, among the 46 patients who underwent interim PET imaging after 2 or 3 cycles of chemotherapy, 20 patients had positive interim PET scans and 13 of these 20 patients (65%) had negative PET scans at the completion of chemotherapy. The actuarial 2-year FFS rate was 92% for this group compared to 96% for patients with negative PET scans during and after completion of chemotherapy.

Barnes et al also showed that interim PET scans did not predict outcome in patients with non-bulky stage I-II disease. The 4-year PFS rate was 91% for those with a negative interim PET scan and 87% for those with a positive interim PET scan (P = .57).[29]

In a recent prospective study (CALGB 50203), Straus et al reported that although both interim and end-of-treatment PET scans were predictive of outcome in patients with stage I-II non-bulky disease treated with doxorubicin, vinblastine and gemcitabine (AVG), the difference in the 2-year PFS was greater between the PET-positive and PET-negative patients after 6 cycles of AVG chemotherapy (27% and 89%, respectively) than after 2 cycles (50% and 90%, respectively).[30]

More recent reports have confirmed the prognostic significance of interim PET scans after 2 or 3 cycles of chemotherapy in patients with early-stage disease.[31,32]

In a retrospective analysis that included 147 patients with early-stage disease, Zinzani et al recently reported the best predictive value for interim PET scans after 2 cycles of ABVD (PET-2) in patients with early-stage favorable disease.[31] At a median follow-up of 45 months, 97.6% of patients with a negative PET-2 scan remained in CR, whereas only 21% of patients with a positive PET-2 scan remained in CR at a median follow-up of 28 months. The 9-year PFS rate was also significantly higher for patients with a negative PET-2 scan than for those with a positive PET-2 scan (94.7% and 31.3%, respectively). The corresponding 9-year overall survival (OS) rates were 100% and 85.2%, respectively (P = .0001) for the 2 groups.

In the recent update from the CALGB 50203 study, interim PET scan after 2 cycles of AVG chemotherapy (PET-2) based on IHP and the Deauville criteria was predictive of PFS in patients with stage I-II non-bulky disease.[32] After a median follow-up of 3.3 years, the 2-year PFS rates were significantly different between the PET-2–negative and PET-2–positive groups. By the IHP criteria, the 2-year PFS rates were 88% and 54%, respectively, for the PET-2–negative and PET-2–positve groups (*P* = .0009). The corresponding PFS rates were 85% and 50%, respectively, for the 2 groups using the Deauville criteria. This study also showed that the combined PET/CT scans after 2 cycles had a better predictive value for PFS compared to either test alone.

NCCN Recommendations

Initial results from retrospective analyses failed to demonstrate the prognostic significance of interim PET scans in patients with stage I-II favorable disease.[21,28-30] More recent reports suggest that interim response assessment with PET/CT after 2 or 3 cycles of chemotherapy based on the Deauville criteria is a good prognostic indicator in patients with early-stage disease.[31,32]

Based on these recent findings, the panel consensus was to incorporate the Deauville criteria for interim response assessment with PET scans after 2 to 4 cycles of ABVD for patients receiving combined modality therapy and after 2 cycles of ABVD for patients receiving chemotherapy alone. In patients receiving the Stanford V regimen, interim response assessment is usually performed after completion of chemotherapy (8 weeks) prior to the initiation of involved-site RT (ISRT).

Stage I-II (Unfavorable Disease) and Stage III-IV Disease

Early interim PET imaging after chemotherapy has been shown to be a sensitive prognostic indicator of treatment outcome in patients with advanced-stage disease (stage II disease with unfavorable risk factors [with or without bulky disease] or stage III-IV disease).[33,34]

In two prospective studies, the PET scan after 2 cycles of standard ABVD chemotherapy was a strong and independent prognostic factor of PFS in patients with advanced-stage and extranodal disease.[35,36] In a combined report from these two prospective studies (190 patients with stage IIB-IVB; 70 patients with stage IIA with adverse prognostic factors), the 2-year PFS was significantly better for patients with negative PET after 2 cycles of ABVD than for those with positive PET (95% vs.13%).[37]

Cerci et al reported similar findings in a recent prospective study of 102 patients with stage II-IV disease (35% had stage IV disease; 58% had bulky disease; and 63.5% had B symptoms). The 3-year event-free survival (EFS) rate was 53% for patients with positive PET after 2 cycles of ABVD and 90.5% for those with negative PET (*P* < .001).[38]

A retrospective international validation study in HL confirmed that interim response assessment (based on the Deauville criteria) after 2 cycles of ABVD was predictive of FFS in patients with stage IIB–IVB disease.[39] Among 260 of 440 enrolled patients with an interim PET scan of diagnostic quality, the 3-year FFS was 95% for patients with a negative PET scan (Deauville 1-3) and 28% for those with a positive PET scan (Deauville 4-5).

In a retrospective analysis of 81 patients with stage I/II (non-bulky or bulky mediastinal disease) and stage III/IV disease treated with the Stanford V regimen, Advani and colleagues showed that PET positivity after 8 and 12 weeks of chemotherapy was a significant predictor of PFS even after controlling for bulky disease and IPS > 2. At a median follow-up of 4 years, the freedom from progression (FFP) was 96% in

those with negative PET scans compared with 33% in those with positive PET scans at the completion of chemotherapy.[40]

Markova and colleagues demonstrated that interim PET scans after 4 cycles of BEACOPP (PET-4) is a strong prognostic marker for PFS in patients with early-stage unfavorable (stages IIB with large mediastinal mass or extranodal disease) or advanced-stage (stages III and IV) disease.[41] At a median follow-up of 55 months, the 4-year PFS for PET-4 negative (n = 51) and PET-4 positive (n = 18) patients was 96% and 78%, respectively (*P* = .016). PET scans at 3 months after the completion of chemotherapy was of limited value when the interim PET-4 was negative.

The Israeli Study Group has evaluated the utility of interim PET scans to develop risk-adapted and/or response-adapted treatment in small cohorts of patients with early-stage unfavorable and advanced-stage disease.[42-44] Avigdor and colleagues evaluated response-adapted de-escalation of therapy (escalated-dose BEACOPP followed by ABVD) in patients with advanced-stage disease and IPS ≥3.[42] Forty-five patients were initially treated with 2 cycles of escalated-dose BEACOPP followed by interim PET scan. Patients with a negative interim PET scan received 4 cycles of ABVD, and those with a positive interim PET scan were removed from the study and considered for salvage therapy. After a median follow-up of 48 months, the PFS and OS rates were 78% and 95%, respectively, for patients who completed 4 cycles of ABVD. The 4-year PFS for PET-negative patients (n = 31) and PET-positive patients (n = 13) were 87% and 53%, respectively (*P* = .01). Dann and colleagues evaluated a risk-adapted approach with BEACOPP based on the results of interim PET scan for patients with early-stage unfavorable and advanced-stage disease (n = 124).[43,44] Patients with advanced disease (stage I-II bulky with B symptoms and stage III-IV) with an IPS ≥ 3 were treated with 2 cycles of escalated-dose BEACOPP, and those with an IPS ≤ 2 received 2 cycles of standard-dose BEACOPP followed by restaging. Those with a positive interim PET scan received 4 additional cycles of escalated-dose BEACOPP, whereas 4 cycles of standard-dose BEACOPP were given to patients with a negative interim PET scan. The 10-year PFS rate was 83% for patients with a positive interim PET scan and 93% for those with a negative interim PET scan.[44]

Risk- and/or response-adapted approach based on interim PET scans is being investigated in several large ongoing studies.[16]

NCCN Recommendations

Although the prognostic significance of interim PET scans has been established in patients with advanced disease, the timing of the interim PET scans is still unclear. In one of the prospective studies, there was no significant difference between the prognostic value of interim PET scans after 2 and 4 cycles of chemotherapy.[36] In a recent prospective study, interim PET imaging after 2 cycles of ABVD was highly predictive of treatment success in patients with stage I-II unfavorable disease and stage III-IV disease; the difference in 3-year EFS was significant for patients with stage III-IV disease (*P* < .001) and for those with stage I-II disease (*P* = .002).[38]

Based on the recent findings, the panel consensus was to incorporate the Deauville criteria for interim response assessment with PET scans for patients with stage I-II (unfavorable, bulky, or non-bulky disease) and patients with stage III-IV disease. The guidelines recommend interim response assessment with PET after 2 or 4 cycles of ABVD or after 4 cycles of escalated-dose BEACOPP. In patients receiving Stanford V regimen, interim response assessment is usually performed after completion of chemotherapy (8 or 12 weeks) prior to the initiation of RT. The panel also acknowledges that guiding therapy based on the

results of interim PET scans is considered investigational and is not recommended outside the context of a clinical trial.

Principles of Radiation Therapy

RT can be delivered with photons or protons. Preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (OAR; eg, lung, heart, breasts) can be achieved with proton beam RT, which can reduce the risk of late effects.[45,46] Long-term follow-up is needed to confirm the efficacy of proton beam RT.

Involved-field RT (IFRT) refers to treatment of the involved lymph node regions only.[47] ISRT and involved-node RT are being used as alternatives to IFRT, in an effort to restrict the size of the RT fields and to further minimize the radiation exposure to adjacent uninvolved organs and the potential long-term toxicities associated with radiation exposure.[48]

ISRT targets the originally involved nodal sites and possible extranodal extensions (based on a modified involved field that is smaller than the one used in IFRT).[49] The field encompasses the pre-chemotherapy and/or surgical site, yet it spares the adjacent uninvolved organs (such as lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy. The treatment planning for ISRT requires the use of modern CT-based simulation. The incorporation of additional imaging techniques such as PET and MRI often enhances the treatment planning. The optimized treatment plan for ISRT is designed using conventional, 3-D conformal RT or intensity-modulated RT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR. The gross tumor volume (GTV) defined by PET-CT imaging prior to chemotherapy or surgery provides the basis for determining the clinical target volume (CTV). The planning target volume (PTV) is an additional expansion of the CTV to account for any setup variations and internal organ motion. PTV margins should be defined individually for each disease site.

In combined modality therapy, the panel recommends an RT dose of 30 to 36 Gy when combined with ABVD or 36 Gy with Stanford V for patients with bulky disease (all stages).[50,51] In patients with stage I-II non-bulky disease, the recommended RT dose is 20 to 30 Gy following ABVD and 30 Gy after Stanford V. [52,51] The recommended RT dose with BEACOPP is 30 to 36 Gy. For patients with NLPHL treated with RT alone, the recommended dose is 30-36 Gy.

The panel recommends that high cervical regions in all patients and axillae in women always be excluded from RT fields, if those regions are uninvolved.

Treatment Guidelines

Diagnosis

Core needle biopsy may be adequate for diagnosis, but the panel recommends excisional lymph node biopsy generally be performed. Although fine-needle aspiration (FNA) biopsy is widely used in the diagnosis of malignant neoplasms, its role in the diagnosis of lymphoma is still controversial and a diagnosis of lymphoma cannot be ruled out by a negative FNA biopsy.[53-55] FNA biopsy should be avoided and is considered to be adequate only when it is called diagnostic of HL by an expert hematopathologist or cytopathologist.

Immunohistochemistry evaluation is recommended. The Reed-Sternberg cells of CHL express CD15 and CD30 in the majority of patients and are usually negative for CD3 and CD45. CD20 may be detectable in less than 40% of patients. Immunostaining for CD3, CD15, CD20, CD30, and CD45 is recommended for CHL. NLPHL cells

are usually CD45+ and CD20+, do not express CD3 or CD15, and rarely express CD30. In addition, NLPHL cells also express epithelial membrane antigen, which is usually not present in CHL. For NLPHL, the guidelines recommend staining for CD3, CD15, CD20, CD21, CD30, and CD57. An expanded panel of markers may be required, especially for equivocal diagnosis.

Workup

Workup should include a thorough history and physical examination (including determination of B symptoms, alcohol intolerance, pruritus, fatigue, and performance status, and examination of the lymphoid regions, spleen, and liver); standard laboratory tests (complete blood count, differential, platelets, ESR, serum lactate dehydrogenase, albumin, and liver and renal function tests); chest radiograph; PET/CT; and diagnostic contrast-enhanced CT. Although diagnostic CT scans will often include neck, chest, abdomen or pelvis, it should at minimum also include other involved areas identified as abnormal on PET scan. The NCCN Guidelines recommend using PET scans to define the extent of disease. However, it should be noted that PET scans may be positive in sites of infection or inflammation, even in the absence of HL. In patients with PET-positive sites outside of the disease already identified, or if the PET-positive sites are inconsistent with the usual presentation of HL, additional clinical or pathologic evaluation is recommended.

An adequate bone marrow biopsy should be performed for patients with B symptoms or stage III-IV disease. Evaluation of ejection fraction is recommended for most patients undergoing doxorubicin-based chemotherapy. HIV testing should be encouraged for patients with risk factors for HIV or unusual disease presentations. Pulmonary function tests (PFTs) including the test of the diffusion capacity of the lungs for carbon monoxide (DLCO) are recommended for patients receiving bleomycin-based chemotherapy. H-flu, pneumococcal, and meningococcal vaccines are recommended if splenic RT is contemplated. A neck CT scan is also recommended for patients in whom RT to the neck is planned.

A pregnancy test should be performed before women of childbearing age undergo treatment. Chemotherapy with alkylating agents is associated with a higher risk of premature ovarian failure than chemotherapy with non-alkylating agents.[56] The guidelines recommend fertility preservation (semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients) prior to the initiation of chemotherapy with alkylating agents or pelvic RT.[57,58] Oophoropexy should be considered to preserve ovarian function in pre-menopausal women if pelvic RT is contemplated.[59]

Classical Hodgkin Lymphoma

Patients are divided into the following groups after initial diagnosis and workup:

- Stage I-II
- Stage III-IV

Patients with stage I-II are further classified into the following subgroups depending on the presence or absence of NCCN unfavorable factors:

- Stage IA-IIA (favorable)
- Stage I-II (unfavorable with bulky disease)
- Stage I-II (unfavorable with non-bulky disease)

Stage I-II Favorable Disease

RT alone was a standard treatment option for patients with early-stage HL for many decades.[60] However, the potential long-term toxicity of high-dose, large-field irradiation includes an increased risk for heart disease, pulmonary dysfunction, and secondary cancers.[61] With the incorporation of chemotherapy regimens routinely used in advanced disease (ABVD and Stanford V) into the management of patients with early-stage disease, combined modality therapy (chemotherapy and RT) has replaced RT alone as the treatment of choice for patients with early-stage, favorable disease.

The ABVD regimen was developed as an alternative to MOPP (mechlorethamine, vincristine, prednisone, and procarbazine) and is associated with lower rates of sterility and leukemia.[50] The Stanford V regimen is a brief but dose-intensive regimen with significantly fewer cumulative doses of doxorubicin and bleomycin than those used in ABVD, alternating MOPP/ABVD, BEACOPP, or other hybrid regimens, thereby reducing the risks for chemotherapy-related infertility, secondary neoplasms, and cardiac and pulmonary toxicity.[62,63] RT is an integral part of the Stanford V regimen.[64]

Bonadonna and colleagues initially established the safety and efficacy of ABVD (4 cycles) followed by 36 Gy IFRT as the standard treatment for patients with early-stage disease.[50] The HD10 trial from the GHSG investigated the reduction of the number of cycles of ABVD as well as the IFRT dose in patients with stage I-II disease with no risk factors.[52] Patients were not eligible if they had 3 or more sites of disease, any E-lesions, bulky mediastinal adenopathy, ESR > 50, or ESR > 30 in conjunction with B symptoms. In this trial, 1370 patients were randomized to one of the 4 treatment groups: 4 cycles of ABVD followed by 30 Gy or 20 Gy of IFRT; 2 cycles of ABVD followed by 30 Gy or 20 Gy of IFRT.[52] The final analysis of this trial showed that (with a median follow-up of 79–91 months), there was no significant differences between 4 and 2 cycles of ABVD in terms of 5-year OS (97.1% and 96.6%), freedom from treatment failure (FFTF) (93.0% vs. 91.1%), and PFS (93.5% vs. 91.2%). With respect to the dose of IFRT, the OS (97.7% vs. 97.5%), FFTF (93.4% vs. 92.9%), and PFS (93.7% vs. 93.2%) were also not significantly different between 30 Gy and 20 Gy IFRT.[52] More importantly there were also no significant differences in OS, PFS, and FFTF among the four treatment arms. The results of the HD10 study confirm that 2 cycles of ABVD with 20 Gy of IFRT is an effective primary treatment for patients with a very favorable presentation of early-stage disease with no risk factors, thereby minimizing the risk of late effects.

The G4 study conducted by the Stanford Group evaluated the efficacy of the abbreviated Stanford V chemotherapy (8 weeks or 2 cycles) followed by IFRT (30 Gy) in patients with non-bulky stage IA or IIA disease.[51] Among the 87 patients included in the study, unfavorable risk factors according to GHSG criteria (more than 2 nodal sites, ESR ≥ 50, or extranodal involvement) were present in 42 patients (48%) and 33 patients (38%) had unfavorable characters defined by EORTC criteria (more than 3 nodal sites, ESR ≥ 50, mixed cellularity, and age 50 years or older). At a median follow-up of 10.6 years, the estimated 10-year FFP, disease-specific survival, and OS rates were 94%, 99%, and 94%, respectively. Among patients with GHSG criteria, FFP was 100% for patients with favorable disease and 88% for those with unfavorable non-bulky disease. The FFP was 98% and 88%, respectively, for patients with favorable and unfavorable disease according to EORTC criteria. No patient developed secondary acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). No late cardiac or pulmonary toxicities have been observed.

Chemotherapy with ABVD alone has also been investigated as a treatment option for patients with early-stage non-bulky disease (stage I-II or IIIA).[65-68]

In the Memorial Sloan-Kettering Cancer Center (MSKCC) study, 152 patients with stages I, II, and IIIA non-bulky disease were prospectively randomized to ABVD (6 cycles) followed by RT (36 Gy) or ABVD (6 cycles) alone. At 60-month follow-up, there were no significant differences in CR duration (91% vs. 87%, respectively; *P* = .61), FFP (86% vs. 81%, respectively; *P* = .61), and OS (97% vs. 90%, respectively, *P* = .08) among patients treated with ABVD plus radiation and those treated with ABVD alone.[66]

In the multicenter study conducted by the NCIC Clinical Trials Group (HD.6), 405 patients with stage IA or IIA HL were randomized to receive ABVD (4–6 cycles) or subtotal nodal RT with or without ABVD.[67] In patients assigned to RT, those who had a favorable risk profile received subtotal nodal RT alone, and those with any of the adverse prognostic factors (high ESR, age >39, mixed cellularity or lymphocyte depleted histology, or ≥4 nodal sites) were treated with 2 cycles of ABVD followed by subtotal nodal RT. At a median follow-up of 12 years, OS rate was higher among patients treated with ABVD alone than those treated with subtotal nodal RT with or without ABVD (94% vs. 87%; *P* = .04).[68] However, ABVD alone was associated with a lower rate of FFP than subtotal nodal RT with or without ABVD (87% vs. 92%; *P* = .05), and there were no significant differences in the EFS rates between the two groups (85% and 80%, respectively; *P* = .60). In the subset analysis of patients with a favorable disease, there were no significant differences between any outcome for patients randomly assigned to subtotal nodal RT alone and those assigned to ABVD alone.[68] Among patients with unfavorable risk factors, the 12-year estimated OS rate was higher among patients in the ABVD-only group than among the patients who received subtotal nodal RT plus ABVD (92% vs. 81%, respectively; *P* =.04), whereas the rate of FFP was lower in the ABVD-only group (86% vs. 94%; *P* = .006) and there was no significant difference in the 12-year EFS rate (83% vs. 78%; *P* = .74) between the groups.[68] Among patients randomized to ABVD alone the FFP was significantly higher among those who achieved a CR or CRu after 2 cycles of ABVD than among those who did not achieve CR (12-year estimated rate of FFP 94% and 81%, respectively, P = .02). This study, however, was closed prematurely since the results of the EORTC H8-F study demonstrated excellent outcomes for patients with stage I-II favorable disease treated with chemotherapy and IFRT.[69]

Combined modality therapy (ABVD or Stanford V chemotherapy plus IFRT) is the preferred treatment for patients with stage I-II favorable disease. ABVD alone could be a reasonable choice of treatment, especially for younger patients who are in CR after 2 cycles of ABVD (as documented by CT scan), in order to avoid the long-term risks of RT.

NCCN Recommendations

Combined modality therapy (ABVD plus ISRT [category 1] [52] or Stanford V chemotherapy)[51] or chemotherapy (ABVD alone)[67,68] are included as treatment options for patients with stage IA to IIA favorable disease.

In combined modality therapy, ABVD is generally administered for 4 cycles followed by 30 Gy ISRT. In patients who fulfill the GHSG criteria for favorable disease (ESR less than 50, no extralymphatic lesions, and only two lymph node regions involved), 2 cycles of ABVD followed by 20 Gy ISRT may be sufficient.[52] Stanford V regimen is administered for 8 weeks followed by 30 Gy ISRT.[51] ISRT is optimally instituted within 3 weeks of completion of chemotherapy.

There are two studies from Europe evaluating the value of interim PET scans in defining the need for RT in patients with stage I-II favorable disease (the UK RAPID trial and the EORTC H10 trial).[27,70] However, these trials come to somewhat different conclusions and both have been published only as abstracts. Therefore, the panel members feel that longer follow-up data are needed and that the omission of RT is not recommended at this time for patients with stage IA-IIA disease based on the results of interim PET scans.

The guidelines recommend interim restaging with PET after 4 cycles of ABVD (after 2 cycles for patients who fulfill the GHSG criteria for favorable disease) or after 8 weeks of Stanford V chemotherapy. Completion of planned course of ISRT followed by observation is recommended for patients with a Deauville score 1-3. For patients with a Deauville score 4, a biopsy or ISRT followed by another restaging is recommended. No further treatment is necessary if the final PET is Deauville 1-3. For patients undergoing a biopsy, ISRT is administered if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Biopsy is recommended for all patients with a score of Deauville 5 after chemotherapy and for those with a score of Deauville 4-5 after completion of ISRT. Clinical circumstances may warrant additional treatment even if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

In the NCIC study (HD.6), patients assigned to ABVD alone were restaged with CT after 2 cycles [67,68] The FFP was superior for patients who achieved a CR or CRu after 2 cycles of ABVD (compared to those who did not, based on CT criteria) and these patients went on to receive 2 more cycles of ABVD alone (4 total); patients who did not achieve a CR or CRu received a total of 6 cycles of ABVD.

The results of a recent exploratory subset analysis involving patients treated in the HD10 and HD.6 trials showed that combined modality therapy provides better disease control than ABVD alone in patients with stage IA-IIA disease not achieving CR after 2 cycles of ABVD.[71]

Among patients treated with chemotherapy alone, ABVD is initially administered for 2 cycles followed by interim restaging with PET including CT scan of areas of initial disease. Consistent with the results of the NCIC study (HD.6), the guidelines recommend 2 additional cycles of ABVD (total of 4) followed by observation for patients with a score of Deauville 1-2 on interim PET scan and a CR or CRu on CT after 2 cycles of ABVD.[27,28] However, given the inferior outcome of patients who are not in CR after 2 cycles of ABVD, the panel agreed that patients with a score of Deauville 1-2 on interim PET scan and PR on CT after 2 cycles of ABVD should have the option of receiving additional cycles of ABVD followed by ISRT. These patients should be managed as described below for patients with a score of Deauville 3-4 on interim PET scan.

Patients with a score of Deauville 3-4 on interim PET scan are treated with 2 additional cycles (total of 4) of ABVD followed by another restaging. ISRT is recommended for patients with a score of Deauville 1-2 or Deauville 3-4 after 4 cycles of ABVD. Alternatively, patients with a score of Deauville 1-2 can be treated with 2 additional cycles of ABVD alone (total of 6), and those with a score of Deauville 3-4 can be treated with 2 additional cycles of ABVD (total of 6) with ISRT.

Biopsy is recommended for all patients with a score of Deauville 5 after 2 or 4 cycles of ABVD. Clinical circumstances may warrant additional treatment even if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Stage I-II Unfavorable Disease

The HD8 trial from the GHSG is the largest that investigated the efficacy of IFRT vs. extended-field RT (EFRT) in the context of combined modality therapy for patients with early-stage unfavorable HL with one or more risk factors (large mediastinal mass; extranodal disease; splenic involvement; elevated ESR with or without B symptoms; and more than two lymph node areas of involvement).[72] This trial randomized 1204 patients to 4 cycles of chemotherapy (COPP [cyclophosphamide, vincristine, procarbazine, and prednisone] plus ABVD) followed by EFRT or IFRT. RT (30 Gy plus 10 Gy to bulky sites in both arms) was initiated after chemotherapy for all patients without progressive disease. At 5 years of follow-up, FFTF (85.8% for EFRT and 84.2% for IFRT) and OS (90.8% vs. 92.4%) were similar for the two groups. In contrast, acute side effects, including thrombocytopenia, leukopenias, and gastrointestinal toxicity, were more frequent in the EFRT group. The 10-year follow-up results confirmed the non-inferiority of IFRT in terms of FFTF (79.8% vs. 79.7%), PFS (79.8% vs. 80.0%), and OS (86.4% vs. 87.3%).[73] IFRT was also associated with less acute toxicity and fewer secondary malignancies.

The HD11 multicenter trial from the GHSG demonstrated that 4 cycles of ABVD followed by 30 Gy IFRT is an effective treatment option for patients with early-stage unfavorable disease.[74] In this study, 1395 patients with stage I-II unfavorable disease (stage IA, IB, or IIA with at least one of the following risk factors: bulky mediastinal mass; extranodal involvement; ESR ≥ 50 or ESR ≥ 30 with B symptoms; or 3 or more involved lymph nodes and stage IIB disease with no bulky mediastinal mass or extranodal involvement) were randomized to either ABVD (4 cycles followed by 30 Gy or 20 Gy IFRT) or standard-dose BEACOPP (4 cycles followed by 30 Gy or 20 Gy IFRT). BEACOPP was more effective than ABVD when followed by 20 Gy IFRT (5-year FFTF and PFS rates were 86.8% and 87%, respectively, for BEACOPP. The corresponding rates were 81% and 82%, respectively, for ABVD). However, there was no difference between the 2 regimens when followed by 30 Gy of IFRT (5-year FFTF and PFS were 87% and 88%, respectively, for BEACOPP. The corresponding rates were 85% and 87%, respectively, for ABVD). BEACOPP was also associated with more toxicity than ABVD.

The results of the prospective study conducted by the Stanford group demonstrated the efficacy of Stanford V regimen followed by RT to initially bulky sites for patients with locally extensive and advanced-stage disease.[75] In this study, 142 patients with locally extensive mediastinal stage I or II disease or stage III or IV disease were treated with Stanford V chemotherapy (12 weeks) followed by RT (36 Gy) to initial bulky sites (≥5 cm) or macroscopic splenic disease. With a median follow-up of 5.4 years, the 5-year FFP and OS rates were 89% and 96%, respectively. No patient progressed during treatment and there were no treatment-related deaths or secondary leukemia. Among 16 patients who relapsed, the freedom from second relapse was 69% at 5 years.

A randomized Italian study reported that ABVD and MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) were superior to the Stanford V regimen in response rate, FFS, and PFS in patients with intermediate-stage and advanced-stage HL.[76] However, interpretation of these results was difficult because the timing of response evaluation was different among the arms (8 and 12 weeks for Stanford V, 16 weeks for ABVD, and 24 weeks for MOPPEBVCAD). In addition, modifications of the RT protocol in the Stanford V arm were substantial, including limitation of the number of sites irradiated (no more than 2) and a different definition of bulky disease.

Other investigators, however, have confirmed that the Stanford V regimen is highly effective for locally extensive and advanced HL with a low toxicity profile, when RT is administered according to Stanford V protocol guidelines.[77-79] In the MSKCC study, 126 patients with either locally extensive or advanced disease were treated with the 12-week Stanford V chemotherapy regimen followed by 36 Gy IFRT to bulky sites (5 cm or larger) and/or to macroscopic splenic disease.[78] The 5- and 7-year OS rates were 90% and 88%, respectively. Fifty-eight percent of the patients for whom the Stanford V regimen failed underwent successful second-line therapy with high-dose therapy with autologous stem cell rescue (HDT/ASCR). Aversa and colleagues from another Italian study group also reported similar findings in patients with bulky or advanced disease.[77] The randomized trial conducted by the United Kingdom National Cancer Research Institute Lymphoma Group (Study ISRCTN 64141244) also showed that the efficacies of Stanford V and ABVD were comparable in terms of overall response rate, the 5-year PFS and OS rates in patients with stage I to IIA with bulky disease, or other adverse features, stage IIB, III, or IV disease. RT was administered in both arms to sites of previous bulky sites (> 5 cm) and to splenic deposits.[79] At the median follow-up of 4.3 years, the ORR, 5-year PFS, and 5-year OS rates were 91%, 76%, and 90%, respectively, for ABVD. The corresponding rates were 92%, 74%, and 92%, respectively, for Stanford V.

The phase III intergroup trial (E2496) also confirmed that there were no significant differences between ABVD and Stanford V in terms of response rates, FFS, OS, and toxicity in patients with locally extensive (stage I-IIA/B and bulky mediastinal disease) and stage III-IV disease.[80] In this trial, 854 patients were randomized to ABVD (n = 428; 6–8 cycles plus 36 Gy RT only for patients with bulky mediastinal disease) or Stanford V (n = 426; 12 weeks of chemotherapy plus 36 Gy RT for sites larger than 5 cm or for macroscopic splenic disease). The primary endpoint was FFS, defined as the time from randomization to progression, relapse, or death, whichever occurred first. With a median follow-up of 6.4 years, there was no difference in ORR (clinical CR rates were 72.7% for ABVD and 68.7% for Stanford V), OS (88% at 5 years for both ABVD and Stanford V; $P = .86$), or FFS (74% for ABVD and 71% for Stanford V at 5 years; $P = .32$) between the two arms. Toxicity was also similar in both groups. The planned subgroup analysis showed that the outcome of patients with locally extensive disease was significantly better than that of patients with stage III-IV disease.[80] The 3-year and 5-year FFS rates were 82% for patients with locally extensive disease. The corresponding survival rates were 71% and 67%, respectively, for patients with stage III-IV disease ($P = .001$). The 5-year OS rates were 94% and 85%, respectively ($P < .001$).

The HD14 trial of the GHSG demonstrated that BEACOPP followed by ABVD and IFRT significantly improved tumor control and PFS in patients with early-stage unfavorable disease (stage IA, IB, or IIA with at least one of the following risk factors: bulky mediastinal mass; extranodal involvement; ESR ≥ 50 or ESR ≥ 30 with B symptoms; or 3 or more involved lymph nodes) and stage IIB disease with either of the latter two risk factors.[81] In this trial, 1528 patients were randomized to 4 cycles of ABVD (n = 765) or 2 cycles of escalated-dose BEACOPP followed by 2 cycles of ABVD (n = 763). Chemotherapy was followed by 30 Gy of IFRT in both arms. At a median follow-up of 43 months, the 5-year FFTF rate was 94.8% compared to 87.7% for ABVD ($P < .001$). The 5-year PFS rate was 95.4% and 89.1%, respectively ($P < .001$). The 5-year OS rate was not significantly different between the 2 arms (97.2% and 96.8%, respectively; $P = .731$). The rate of progression or relapse was also lower in patients treated with BEACOPP followed by ABVD (2.5% vs. 8.4%; $P < .001$).

These results suggest that ABVD plus 30 Gy IFRT remains the standard of care for patients with early-stage unfavorable disease. Stanford V (when given as described with RT) or BEACOPP followed by ABVD are acceptable alternatives for some patients.

NCCN Recommendations

Stage I-II (Unfavorable Bulky Disease)

ABVD followed by ISRT (category1) [74] or Stanford V[75,80] or escalated BEACOPP (2 cycles) followed by ABVD (2 cycles) and ISRT[81] are included as options for patients with stage I-II unfavorable bulky disease. In the HD14 trial that evaluated escalated BEACOPP followed by ABVD and ISRT, patients with bulky disease and B symptoms were excluded.[81] These patients are managed as described for stage III-IV disease.

ABVD is initially administered for 4 cycles followed by interim restaging with PET. Patients with a score of Deauville 1-3 are treated with ISRT alone or in combination with 2 additional cycles of ABVD (total of 6), and those with a score of Deauville 4 are treated with 2 additional cycles of ABVD (total of 6) followed by another restaging. ISRT followed by observation is recommended if the repeat PET scan is Deauville 1-3.

Biopsy is recommended for all patients with a score of Deauville 5 after 4 cycles of ABVD and for those with a score of Deauville 4-5 after 6 cycles of ABVD. Clinical circumstances may warrant additional treatment even if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Stanford V is administered for 12 weeks (3 cycles) followed by ISRT (36 Gy) to patients with stage I-II bulky mediastinal disease or bulky disease more than 10 cm with or without B symptoms.[75,80] Patients are restaged with PET at the completion of chemotherapy. ISRT for initial sites larger than 5 cm as well as for residual PET-positive sites is recommended for all patients with a score of Deauville 1-3 or Deauville 4. ISRT should be instituted within 3 weeks of completion of chemotherapy. Restaging with CT or PET/CT after 3 months is recommended for patients whose interim PET scan was Deauville 3 or 4. Biopsy is included as an option for patients with a score of Deauville 4 prior to the initiation of ISRT which is recommended only if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Biopsy is recommended for all patients with a score of Deauville 5 after completion of therapy. Clinical circumstances may warrant additional treatment even if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Patients receiving escalated BEACOPP (2 cycles) and ABVD (2 cycles) are restaged after completion of chemotherapy. ISRT is recommended for all patients except for those with a score of Deauville 5a or 5b. Biopsy is recommended for these patients. Patients with a positive biopsy should be managed as described for refractory disease. ISRT followed by observation with short-interval follow-up is recommended for those with a negative biopsy.

Stage I-II (Unfavorable Non-bulky Disease)

ABVD is initially administered for 2 cycles followed by interim restaging with PET. ISRT following additional cycles of ABVD is recommended for patients with a score of Deauville 1-2 (2 to 4 cycles to a total of 4–6) or Deauville 3-4 (4 cycles to a total of 6). Alternatively, patients with stage I-IIA disease and a score of Deauville 1-2 can be treated with 4 additional cycles of ABVD alone (total of 6). Biopsy is recommended for all patients with a score of Deauville 5. Clinical circumstances may

warrant additional treatment even if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Stanford V is administered for 12 weeks (3 cycles) followed by IFRT (30 Gy) for patients with stage I-II unfavorable non-bulky disease based upon presence of B symptoms.[80] Patients are restaged with PET at the completion of chemotherapy as described above for patients with stage I to II unfavorable bulky disease. Patients with other criteria for unfavorable disease (elevated ESR or more than 3 sites of disease) are treated with 8 weeks of Stanford V plus 30 Gy IFRT followed by restaging as described for stage IA-IIA favorable disease.[51]

Restaging and additional treatment for patients treated with BEACOPP followed by ABVD are similar to that described above for patients with stage I to II (unfavorable bulky disease).

Stage III-IV

While chemotherapy is always used for patients with advanced-stage disease, combined modality therapy is the management approach for some treatment regimens, especially for patients with bulky disease, and is used for poor responders to chemotherapy in other treatment regimens.[22,75,80]

MOPP was the first successful regimen for patients with advanced HL, with a response rate of 84% and a 66% disease-free survival of more than 10 years from end of treatment.[82] However, in addition to other long-term toxicities, MOPP is associated with loss of fertility (mostly in men) and myelodysplasia.

The landmark randomized trial by the CALGB showed that ABVD alone or alternating with MOPP was superior to MOPP alone in patients with newly diagnosed advanced HL (stage III-IV).[83] ABVD also was less myelotoxic than MOPP, or ABVD alternating with MOPP. These results were confirmed in a large Intergroup study, which compared ABVD with a MOPP/ABV hybrid regimen in 856 patients with advanced HL.[84] The rates of complete remission (76% vs. 80%), 5-year FFS (63% vs. 66%), and OS (82% vs. 81%) rates were similar for ABVD and MOPP/ABV, respectively. However, MOPP/ABV was associated with a greater risk for acute pulmonary and hematologic toxicity, MDS, and leukemia.

Another randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) also confirmed that there was no significant difference in EFS and OS between ABVD and other multidrug regimens in patients with advanced HL. Multidrug regimens were more toxic than ABVD and were associated with poorer outcomes in older patients.[85] Updated results with a median follow-up of 83 months were consistent with the early results.[86]

ABVD has since been the standard treatment for patients with stage III-IV disease. Stanford V and BEACOPP are the other two regimens developed to improve the outcome of patients with advanced disease.

The results from prospective studies conducted by the Stanford group and other investigators have demonstrated the efficacy of Stanford V and IFRT in patients with advanced-stage disease.[75,77-79] The recently completed phase III intergroup trial (E2496) also showed that there was no significant difference between ABVD and Stanford V (with RT, when indicated, according to Stanford V protocol guidelines) in ORR, FFS, OS, and toxicity in patients with stage III-IV disease.[80] However, among patients with high-risk disease (IPS ≥ 3), the 5-year FFS rate was significantly better for ABVD than Stanford V (67% vs. 57%; $P = .02$), but there was no significant difference in 5-year OS rate (84% vs. 77%; $P = .15$).

The efficacy of BEACOPP in patients with advanced disease was demonstrated in two phase III randomized trials conducted by the GHSG.[87,88] In the HD9 study, 1196 patients with stage IIB and IIIA disease with risk factors or stage IIIB and IV disease were randomized to undergo 8 cycles of COPP-ABVD, 8 cycles of standard-dose BEACOPP, or 8 cycles of escalated-dose BEACOPP.[87] Each regimen was followed by RT to initial sites of disease greater than 5 cm. The majority of patients in each treatment arm had stage III-IV disease. At 5-year analysis, escalated-dose BEACOPP showed better tumor control and OS than COPP-ABVD and significantly lower rates of early progression than COPP-ABVD or standard-dose BEACOPP. The 10-year analysis confirmed that escalated-dose BEACOPP was significantly better than standard-dose BEACOPP or COPP-ABVD in terms of FFTF (82%, 70%, and 64%, respectively) and OS rates (86%, 80%, and 75%, respectively). Escalated-dose BEACOPP was significantly better than standard-dose BEACOPP in terms of FFTF ($P < .0001$) and OS ($P = .0053$).[88]

The final results of the HD12 study (n = 1670) that compared escalated-dose BEACOPP (8 cycles) with 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP, with or without RT, also confirmed the efficiency of escalated-dose BEACOPP for patients with advanced-stage HL who have risk factors, as reported in the HD9 trial.[89] In this study, at 5 years, the FFTF (86.4% and 84.8%, respectively) and PFS (87.5% and 85%, respectively) were better (although the difference was not significant) for 8 cycles of escalated-dose BEACOPP compared to 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP. The 5-year OS rate, however, was not different (92% and 90.3%, respectively).[89]

Results from two Italian studies that have compared escalated-dose BEACOPP with standard-dose BEACOPP or ABVD failed to show an OS advantage for escalated-dose BEACOPP, although it resulted in better tumor control in patients with advanced disease.[90,91] However, these studies were not sufficiently powered to determine differences in OS due to small patient numbers.

The final analysis of the HD15 trial recently reported by Engert et al showed that 6 cycles of escalated-dose BEACOPP followed by PET-guided RT resulted in significantly superior OS and tumour control than 8 cycles of escalated-dose BEACOPP in patients with advanced-stage disease (stage IIB with large mediastinal mass or stage III-IV).[22] In this study, 2182 patients were randomly assigned to one of the 3 treatment groups: 8 cycles of escalated-dose BEACOPP (n = 728), 6 cycles of escalated-dose BEACOPP (n = 726), or 8 cycles of a time-intensified standard-dose BEACOPP (n = 728). RT (30 Gy) was restricted to patients with PET-positive residual sites (2.5 cm or more) after chemotherapy. The 5-year FFTF rates were 84.4%, 89.3%, and 85.4%, respectively, for the 3 groups. The corresponding OS rates were 91.9%, 95.3%, and 94.5%, respectively, and were significantly better with 6 cycles of escalated-dose BEACOPP than with 8 cycles of escalated-dose BEACOPP ($P = .019$). Escalated-dose BEACOPP was also associated with less treatment-related mortality (TRM) (4.6% vs. 7.5% for 8 cycles of escalated-dose BEACOPP and 5.2% for 8 cycles of time-intensified standard-dose BEACOPP) and fewer secondary cancers (2.4% compared to 4.7% and 3.1%, respectively, for 8 cycles of escalated-dose BEACOPP and 8 cycles of time-intensified standard-dose BEACOPP). These results confirm that 6 cycles of escalated-dose BEACOPP followed by PET-guided RT is an acceptable treatment for patients with advanced-stage disease.

The ongoing EORTC 20012 trial is evaluating BEACOPP (4 cycles of escalated-dose and 4 cycles of standard-dose) and ABVD (8 cycles) in high-risk patients with stage III-IV disease. The preliminary results showed that there was no improvement in OS (86.7% and 90.3, respectively, at 4 years; *P* = .208) or EFS (63.7% and 69.3%, respectively, at 4 years; *P* = .312), although the PFS was significantly better with BEACOPP (83.4% vs. 72.8% for ABVD; *P* = .005). The median follow-up was 3.8 years.[92] Long-term follow-up is necessary to confirm these preliminary findings.

Several trials have addressed the role of consolidative RT after completion of chemotherapy in patients with stage III to IV disease.

The Southwest Oncology Group multicenter study showed no improvement in OS rates for patients who underwent low-dose IFRT after MOP-BAP (mechlorethamine, vincristine, prednisone plus bleomycin, doxorubicin, and procarbazine), but the remission duration was prolonged in several subgroups, especially patients with bulky nodular sclerosis.[93] In the randomized trial (EORTC 20884 trial) that assessed the role of consolidation RT following MOPP-ABV chemotherapy in patients with advanced disease, 739 patients with untreated stage III to IV disease received 6 to 8 cycles of MOPP-ABV. Patients with a CR on CT imaging after chemotherapy were randomized to no further treatment or IFRT, and those with a PR received IFRT to involved nodal areas and extranodal sites.[94] The 8-year OS and EFS rates in the PR group were 76% and 84%, respectively. These outcomes were not significantly different in patients with a CR (with or without IFRT), suggesting that consolidative IFRT is beneficial for patients experiencing PR after chemotherapy.

In the randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) that compared ABVD with two other multidrug regimens, IFRT was recommended for incomplete response to chemotherapy or bulk disease at presentation.[86] PFS was superior for patients who received RT (5-year PFS was 71% without RT and 86% with RT) and a similar advantage was also seen for OS. The final results of the HD12 trial also showed that consolidation RT was beneficial for patients with residual disease after escalated-dose BEACOPP (FFTF was 90.4% and 87%, respectively), whereas this effect was not seen in patients with initial bulk disease who were in CR after chemotherapy.[89] In contrast, Laskar and colleagues reported a survival advantage for consolidative RT in patients experiencing CR after initial chemotherapy, particularly in patients younger than 15 years and in patients with B symptoms and bulky and advanced disease.[95] However, this study included patients with a different distribution of histologic subtypes of HL than those included in Western studies, and most patients had early-stage HL. Of note, none of these studies incorporated PET scan for the evaluation of response.

In the HD15 trial, RT (30 Gy) after BEACOPP chemotherapy was restricted to those patients in PR with PET-positive residual disease (2.5 cm or more). PET-negative patients received no additional RT.[22] Of the 739 qualified patients with residual disease (2.5 cm or more) after 6 to 8 cycles of BEACOPP, 548 patients (74%) were PET-negative; 191 patients (26%) were PET-positive and received consolidative RT. The final analysis showed that the prognosis of patients in PR with a PET-negative persistent residual disease after chemotherapy was similar to those who were in CR as measured by conventional CT (4-year PFS was 92.1%), suggesting that consolidative RT could be omitted in patients with a PET-negative PR.[22]

Two recent European trials evaluated the role of HDT/ASCR as a consolidative therapy for patients with advanced-stage and unfavorable HL that responded to initial chemotherapy.[96,97] Neither trial showed an advantage for HDT/ASCR over conventional chemotherapy for patients with unfavorable and advanced HL experiencing complete or partial remission after an initial course of doxorubicin-based chemotherapy. Instead, additional courses of the same conventional chemotherapy used as initial treatment produced equivalent or better outcomes than HDT/ASCR.

NCCN Recommendations

ABVD, Stanford V (selected patients with IPS < 3), or escalated-dose BEACOPP are included as options for primary treatment for patients with stage III-IV disease.[22,78,80,84]

ABVD is initially administered for 2 cycles followed by restaging with PET. Patients with a score of Deauville 1-3 are treated with an additional 4 cycles (total of 6). Biopsy is recommended for all patients with a score of Deauville 4-5. Patients with a negative biopsy are treated with an additional 4 cycles of ABVD (total of 6) followed by another restaging (if the interim PET scan was Deauville 4 or 5a), and those with a positive biopsy managed as described for refractory disease. Consistent with the results of the E2496 study, observation or ISRT to the mediastinum (if bulky mediastinal disease was initially present) are included as options for patients with a PET score of Deauville 1-3 after 6 cycles of ABVD.[80]

Biopsy is recommended for all patients with a score of Deauville 4-5 after 6 cycles of ABVD. Clinical circumstances may warrant additional treatment even if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Stanford V is administered for 12 weeks (3 cycles). Consolidative irradiation is instituted within 3 weeks (30 Gy to initial sites for stage IB-IIB; 36 Gy to initial bulky sites of 5 cm or larger and spleen if focal nodules are present initially for stage III-IV).[78,79] Restaging and additional treatment for patients treated with the Stanford V regimen are similar to stage I-II unfavorable disease.

Escalated-dose BEACOPP is administered for 4 cycles followed by restaging with PET. Two more cycles of escalated-dose BEACOPP followed by another restaging is recommended for patients with a score of Deauville 1-3. Biopsy is recommended for patients with a score of Deauville 4-5. Patients with a negative biopsy are treated with 2 more cycles of escalated-dose BEACOPP followed by another restaging as described above, whereas those with a positive biopsy should be managed as described for refractory disease. No further treatment is necessary if the repeat PET is Deauville 1-2 after completion of 6 cycles of BEACOPP. Based on the final results of the HD 12 and HD 15 trials, ISRT to residual PET-positive sites greater than 2.5 cm is recommended for patients with a score of Deauville 3-4 after 6 cycles of BEACOPP.[89,22]

Biopsy is recommended for all patients with a score of Deauville 5 after 6 cycles of BEACOPP. Clinical circumstances may warrant additional treatment even if the biopsy is negative. Patients with a positive biopsy should be managed as described for refractory disease.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

NLPHL is characterized by an indolent course and occasional late relapse. It has a different natural history and response to therapy compared with CHL.[98] The majority of patients has early-stage disease and very rarely present with B symptoms, mediastinal or extranodal involvement, and bulky disease.[99-101] In the retrospective analysis from

the GHSG that included 394 patients with NLPHL, 63% had early-stage favorable, 16% had early-stage unfavorable, and 21% had advanced-stage disease. At a median follow-up of 50 months, FFTF (88% vs. 82%) and OS (96% vs. 92%) were better for NLPHL compared with CHL.[100] Among patients with NLPHL, FFTF was better for early-stage favorable disease (93%) compared with early-stage unfavorable (87%) and advanced-stage disease (77%). The European Task Force on Lymphoma also reported favorable FFTF for early-stage disease (85% for stage I; 71% for stage II) compared with those with stage III (62%) or stage IV (24%) disease.[99] Advanced stage at presentation, age (≥45 years), low hemoglobin, and the presence of B symptoms are associated with worse OS.[100,101]

Several retrospective studies have reported favorable clinical outcomes for patients with stage I to II disease treated with RT alone [102-106] or in combination with chemotherapy.[101,107,108] RT alone is an effective treatment option for patients with stage IA-IIA disease.[102,104] In a retrospective analysis, Schlembach and colleagues reported favorable 5-year relapse-free survival (RFS; 95%) and OS (100%) for patients with stage IA disease treated with IFRT and regional RT alone.[102] There was no evidence of secondary solid tumors even after long-term follow-up (11.6 years for IFRT and 5.5 years for regional RT). Longer follow-up is needed to define the risks for cardiac toxicity; however, mediastinal treatment is infrequently required for patients with NLPHL. Another retrospective study from the Australasian Radiation Oncology Lymphoma Group reported longer follow-up of 202 patients with stage I to II NLPHL treated with RT alone, including mantle and total lymphoid irradiation (TLI).[104] At 15 years, FFP was 84% for patients with stage I disease and 73% for those with stage II disease.

Among the studies that have evaluated the outcomes of patients treated with RT alone or combine modality treatment, the subgroup analysis of 64 patients with NLPHL included in the GHSG HD7 trial, showed a non-significant trend toward better 7-year FFTF for the combined modality group (96%) compared with the EFRT group (83%; P = .07).[108] However, other retrospective studies have shown no difference in outcome between patients treated with RT alone or in combination with chemotherapy.[103,105,106] The MD Anderson study that evaluated RFS, OS, and patterns of first recurrence in patients with stage I-II NLPHL treated with RT alone or with chemotherapy followed by RT showed that the RFS (77% and 68%, respectively) and OS (90% and 100%, respectively) were similar in the 2 treatment groups at 9.3 years and that chemotherapy did not reduce the recurrence outside the RT field.[103] The GHSG retrospectively compared 3 treatment options, including EFRT, IFRT, and combined modality treatment in patients with stage IA NLPHL.[105] Median follow-up was 78 months for EFRT, 40 months for combined modality, and 17 months for IFRT. Complete remissions were observed in 98% after EFRT, 95% after combined modality, and 100% after IFRT, and no significant differences were seen in FFTF, suggesting that IFRT is equally as effective as EFRT and combined modality treatment. Recently, Chen and colleagues reported the long-term outcome of 113 patients with NLPHL treated at the author's institution with a median follow-up of 136 months.[106] Ninety-three patients received RT alone, 13 received RT with chemotherapy, and 7 received chemotherapy alone. The 10-year PFS rates were 85% (stage I) and 61% (stage II); OS rates were 94% and 97% for stages I and II, respectively. The addition of chemotherapy to RT did not improve PFS or OS compared with RT alone and six of seven patients who received chemotherapy alone developed early disease progression.

A recent report from the French Adult Lymphoma Study group that analyzed the long-term outcome of 164 patients with NLPHL (82% of

patients had stage IA-IIA disease) included 58 patients who were observed following diagnosis and lymph node biopsy.[109] The 10-year PFS rate for this group of patients was 41% compared to 66% for patients who received specific treatment. However, the 10-year OS rate was not different between the two groups (91% and 93% respectively) and 50% of patients treated with a watch and wait approach were in CR at a median follow-up of 3 years. Watchful waiting has also been shown to be an appropriate treatment options in pediatric patients with early stage NLPHL who are in CR following lymph node excision.[110,111]

Patients with advanced-stage NLPHL have a worse prognosis than those with early-stage favorable disease, and can be treated with chemotherapy. In the European Task Force on Lymphomas study, the 8-year disease-specific survival and FFTF were 94% and 62%, respectively, for stage III disease and 41% and 24%, respectively, for stage IV disease.[99] Most of these patients (80%–95%) were treated with chemotherapy (MOPP- or ABVD-like regimens) with or without RT.

In the absence of randomized trials comparing different chemotherapy regimens, no preferred chemotherapy regimen exists for NLPHL, although ABVD is often used based on the data for patients with CHL. Savage et al from British Columbia Cancer Agency have reported that ABVD chemotherapy with (n = 89) or without (n =11) RT was associated with superior outcomes compared to a historical cohort of patients treated with RT alone for stage IA, IB or IIA NLPHL.[112] With a median follow-up of 6.4 years, patients treated with ABVD-like chemotherapy with or without RT had a superior 10-year TTP (98% vs. 76%), PFS (91% vs. 65%), and OS (93% vs. 84%) compared to those treated with RT alone. On the other hand, an analysis of the combined data from the CALGB trials and Dana-Farber Cancer Institute trials that included patients with stage III-IV NLPHL treated with chemotherapy alone, showed that the failure rate was 75% for the 12 patients treated with ABVD or EVA (etoposide, vinblastine, and doxorubicin) while it was only 32% for the 25 patients treated with alkylating agent-containing regimens (MOPP or MOPP/ABVD).[113] Some investigators have also reported good response rates with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus rituximab [114,115] or CVP (cyclophosphamide, vincristine, and prednisone) in patients with early-stage or advanced disease.[116]

Because NLPHL cells consistently express CD20 antigen, several clinical studies have explored the efficacy of rituximab, an anti-CD20 antibody for patients with newly diagnosed and relapsed or refractory NLPHL.[117-122]

In a prospective phase II trial conducted by the Stanford group, previously treated (n =10) and untreated (n =12) patients with stage I to IV NLPHL received 4 weekly doses of rituximab at 375 mg/m^2. The ORR was 100% (41% CR, 54% PR, and 5% CRu). At a median follow-up of 13 months, 9 patients had relapsed and the estimated median FFP was 10.2 months.[117] The estimated probability of disease progression at 10.2 months was 52%. The protocol was later modified to repeat 4 weekly 375 mg/m^2 doses at 6-month intervals for 2 years.[118] Rituximab was well tolerated, with few adverse side effects. At a median follow-up of 60 months, extended rituximab treatment was associated with better CR rates and median FFP than limited rituximab. The rate of CR and CRu was 88% and 56%, respectively, for patients treated with extended rituximab and limited rituximab (P = .08). The estimated FFP at 30 months was 88% and 52%, respectively.

In a GHSG phase II study that investigated rituximab in patients with newly diagnosed stage IA NLPHL (n=28), the ORR was 100% (complete and partial remission were achieved in 86% and 14% of patients, respectively). At a median follow-up of 43 months, the OS rate

was 100%; the PFS rate at 12, 24, and 36 months was 96%, 85%, and 81%, respectively.[121] However, the relapse rate was 25%. In the GHSG phase II study that evaluated rituximab in patients with relapsed or refractory CD20-positive NLPHL (n = 15), the ORR was 94% (8 patients with CR and 6 patients with PR). At a median follow-up of 63 months, median time to progression was 33 months and the median OS was not reached.[119]

Rituximab followed by rituximab maintenance has also been evaluated in patients with newly diagnosed and relapsed or refractory NLPHL.[120] In a study conducted by the Stanford group in newly diagnosed patients (n =19), Advani et al reported an ORR of 100% (10 patients achieved CR/Cru and 7 patients had PR) at the end of initial therapy with rituximab alone.[120] The estimated PFS rates at 5 and 10 years were 51.7% and 35.4%, respectively. The corresponding estimated OS rates were 93.3% and 76%, respectively. Rituximab as initial treatment was also associated with a pattern of late relapse with transformation to aggressive diffuse large B-cell lymphoma (DLBCL) at a median of 4.2 years. Rituximab maintenance for 2 years was associated with a non-significant increase in median PFS compared to rituximab alone (67 months and 50 months, respectively; *P* = .7).

Collectively, the above data suggest that rituximab alone or in combination with chemotherapy has activity in the management of patients with newly diagnosed as well as those with relapsed NLPHL. However, single-agent rituximab was associated with higher relapse rates when used as initial therapy for newly diagnosed patients.[117,120,121] At the present time, single-agent rituximab or rituximab maintenance is not recommended as initial therapy for newly diagnosed patients.

NCCN Recommendations

Available evidence from retrospective studies supports the use of ISRT alone as a treatment option for patients with early-stage disease.[102-106]

The panel recommends that ISRT (30–36 Gy) be the preferred treatment for all patients with stage IA or IIA non-bulky disease. Observation may be an option for highly selected patients with stage IA disease with a completely excised solitary node. A brief course of chemotherapy plus ISRT with or without rituximab is recommended for patients with stage IB or IIB disease and for very rare patients presenting with stage IA or IIA bulky disease. Chemotherapy with or without ISRT or rituximab is recommended for all patients with stage III-IV disease. Alternatively, asymptomatic patients with stage IIIA-IVA disease can either be observed (category 2B) or treated with local RT for palliation. Abdominal involvement has been associated with the risk of transformation to an aggressive B-cell lymphoma.[120] Biopsy of persistent or new subdiaphragmatic sites should be considered to rule out transformation for patients with stage III or IV disease.

Restaging with PET occurs after completion of initial therapy. Although patients who fail to achieve a score of Deauville 1-4 may require additional therapy, some have a chronic indolent course that may not require aggressive retreatment. Observation is recommended for all asymptomatic patients with a score of Deauville 1-4 or Deauville 5 with a negative biopsy. Alternatively, patients with a score of Deauville 1-4 or Deauville 5a with a negative biopsy can be treated with ISRT (if not received previously). Patients with a score of Deauville 5 with a positive biopsy may be treated with ISRT (if not received previously) or managed as described for refractory disease.

Rituximab may be used in combination with ABVD or other chemotherapy regimens that are most commonly used at NCCN

Member Institutions (CHOP or CVP). Ongoing clinical trials may clarify the role of observation, rituximab, or combination chemotherapy options for patients with NLPHL.

Follow-up after Completion of Treatment

Recommendations included in the guidelines are based largely on the clinical practices at NCCN Member Institutions and are not supported by high-level evidence, since there are very few data available on the follow-up and monitoring of late effects in patients with HL, after completion of treatment.[123]

The follow-up schedule should be individualized, depending on clinical circumstances such as patient's age, stage of disease, and initial treatment modality. The panel overwhelmingly agrees that, given the long-term risks of the therapies for HL, patients should be followed up by oncologists who are aware of these risks and complications, especially during the first 5 years and then annually because of the risk for late complications, including secondary cancers and cardiovascular disease.

Interim physical examinations and blood tests (CBC, platelets, ESR if elevated at initial diagnosis and chemistry profile) are performed every 3 to 6 months for 1 to 2 years and then every 6 to 12 months for the next 3 years and then annually. An annual influenza vaccination is recommended for all patients. Repeat imaging studies of initially involved sites are important, as are surveillance studies of the chest and abdomen.[124] Chest imaging (chest X-ray or chest CT) and abdominal or pelvic CT should be performed every 6 to 12 months during the first 2 to 3 years. PET scans are not recommended for routine surveillance due to the risk of false positives.[24-26] Patients should be encouraged to undergo counseling on issues regarding survivorship, long-term treatment effects (secondary cancers, cardiac disease, and reproduction), health habits, and psychosocial issues.

Monitoring for Late Effects

Secondary cancers, cardiovascular disease, hypothyroidism, and fertility issues are the most serious late effects in long-term survivors of HL. The incidence of these late effects increases with longer follow-up time. The risk may be less with current treatment programs compared to those used more than 10 years ago.

Secondary Cancers

Solid tumors are the most common secondary cancers and most develop more than 10 years after the completion of treatment. The risk of developing secondary cancers is highest when RT is used as a component of first-line treatment. Recent meta-analysis by Franklin and colleagues showed that the risk of developing secondary cancers was lower with combined modality treatment than with RT alone as the initial treatment.[125] The risk was marginally higher with combined modality treatment when compared with chemotherapy alone as initial treatment. No significant differences in the risk of developing secondary cancers were seen with IFRT vs. EFRT, although the risk of developing breast cancer was substantially higher for EFRT. Risks for secondary lung cancer, non-Hodgkin's lymphoma (NHL), and leukemia were significantly higher after treatment with chemotherapy alone, whereas combined modality therapy was associated with a higher risk for these and several other cancers.[126] Lung cancer and breast cancer are the most common secondary cancers in patients with HL.

Surveillance chest imaging should be considered for patients at increased risk for lung cancer (patients treated with chest irradiation or alkylating agent chemotherapy, and those with a smoking history).[124] Chest imaging is optional after 5 years for patients who were treated

with nonalkylating agent chemotherapy, did not undergo RT, and have no other risk factors.

Annual breast screening [mammography or MRI] beginning no later than 8 to 10 years after completion of therapy or at age 40 (whichever occurs earlier) is recommended for women who have received chest or axillary irradiation.[124] They should also be encouraged to perform monthly self-breast examination and undergo yearly breast examination by a health care professional. The guidelines recommend breast MRI in addition to mammography for women who received irradiation to the chest between 10 and 30 years of age, which is consistent with the recommendation of the American Cancer Society Guidelines.[127]

Cardiovascular Disease

Mediastinal irradiation and anthracycline-based chemotherapy are the highest risk factors for developing cardiac disease, which may be asymptomatic.[128-130] RT-induced cardiotoxicity is observed usually more than 5 to 10 years after completion of treatment. However, cardiovascular symptoms may emerge at any age. Based on data regarding increased long-term risk of cardiac disease, annual blood pressure monitoring (even in asymptomatic individuals) and aggressive management of cardiovascular risk factors is recommended. [124] A baseline stress test or echocardiogram at 10 years after treatment (for patients treated with chest irradiation) and carotid ultrasound (for patients treated with neck RT) should be considered.

Hypothyroidism

Abnormal thyroid function, mostly hypothyroidism, is reported in about 50% of long-term survivors who received neck or upper mediastinal irradiation.[123] A careful thyroid examination should be a part of the physical exam. Thyroid function tests should be done at least annually to rule out hypothyroidism, especially in patients treated with RT to the neck.

Myelosuppression

Myelosuppression is the most common side effect of chemotherapy and is associated with increased risk of infections. It is uncommon for myelosuppression to continue for very long beyond completion of the primary treatment program. However, patients who undergo HDT/ASCR or allogeneic hematopoietic stem cell transplant (HSCT) as salvage therapy may be at continued risk for infection. Pneumococcal, meningococcal, and H-flu revaccination is recommended every 5 years for patients treated with splenic RT or splenectomy.

Pulmonary Toxicity

Bleomycin-induced pulmonary toxicity (BPT) is well documented in patients with HL treated with bleomycin-containing chemotherapy regimens. Risk factors include older age, cumulative bleomycin dose, pulmonary irradiation, and prior history of lung disease. Some reports have suggested that the use of growth factors increases the incidence of pulmonary toxicity. Martin and colleagues reported that BPT significantly decreases the 5-year OS rate, especially in patients 40 years or older.[131] They also showed that the use of growth factor with chemotherapy significantly increases the incidence of BPT (26% vs. 9%). Recently, two separate studies confirmed that ABVD chemotherapy can be safely administered at the full-dose intensity without any growth factor support.[132,133] Five-year EFS (87.4% vs. 80%, respectively) and OS (94.1% vs. 91.3%, respectively) rates in patients who received ABVD with no growth factors were comparable to those in patients who received prophylactic growth factor support with the ABVD regimen.[133]

Leukopenia is not a risk factor for reduction of dose intensity. The NCCN Guidelines do not recommend the routine use of growth factors.

Refractory or Relapsed Disease

Classical Hodgkin Lymphoma

Two randomized phase III studies performed by the British National Lymphoma Investigation[134] and the GHSG/European Group for Blood and Marrow Transplantation[135] have compared HDT/ASCR with conventional chemotherapy in patients with relapsed or refractory HL. Both studies showed significant improvement in EFS and PFS and FFTF (with no difference in OS) for patients with relapsed or refractory HL who underwent HDT/ASCR compared with conventional chemotherapy alone. HDT/ASCR is the best option for patients with HL that is not cured with primary treatment, even though it does not improve OS.

Allogeneic HSCT with myeloablative conditioning has been associated with lower relapse rate in patients with relapsed or refractory disease; however, TRM was more than 50%. Allogeneic HSCT with reduced-intensity conditioning has been reported to have decreased rates of TRM.[136,137] However, this approach remains investigational. The panel has included allogeneic HSCT with a category 3 recommendation for patients with refractory or relapsed disease.

Several investigators have developed prognostic models to predict the outcome in patients with relapsed or refractory disease undergoing HDT/ASCR. Brice and colleagues used end-of-treatment to relapse interval (12 months or less) and extranodal disease at relapse as adverse prognostic factors to predict outcome of 280 patients undergoing HDT/ASCR.[138] The PFS rates were 93%, 59%, and 43%, respectively, for patients with 0, 1, or 2 of these risk factors. In a prospective study, Moskowitz and colleagues identified extranodal sites, CR duration of less than 1 year, primary refractory disease, and B symptoms as adverse prognostic factors associated with poor survival after HDT/ASCR.[139] In patients with none or one factor, 5-year EFS and OS were 83% and 90%, respectively, which decreased to 10% and 25% if all factors were present. This prognostic model has been used for the risk-adapted augmentation of salvage treatment in patients with relapsed or refractory disease to improve EFS in poorer risk patients.[140] In a retrospective analysis of 422 patients with relapsed disease, Josting and colleagues from the GHSG identified time to relapse, clinical stage at relapse, and anemia at relapse as independent risk factors to develop a prognostic score that classified patients into four subgroups with significantly different freedom from second failure and OS.[141] More recently, investigators of the GEL/TAMO group identified bulky disease at diagnosis, a short duration of first CR (less than one year), detectable disease at transplant, and the presence of more than one extranodal site as adverse factors for OS.[142] Other groups have identified extent of prior chemotherapy,[143] short time from diagnosis to transplant,[144] and disease status at transplantation[145] as significant prognostic factors for OS and PFS. Pretransplant functional imaging status has also been identified as an independent predictor of outcome in patients with recurrent/refractory HL.[146-149]

The main potential of these prognostic factor studies is to facilitate comparison of outcomes at different centers, where the preparatory regimens may vary.

Several studies have shown the importance of cytoreduction with second-line chemotherapy before HDT/ASCR.[139,150-157] Newer regimens, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin),[158] IGEV (ifosfamide, gemcitabine, and vinorelbine),[159] and GCD (gemcitabine, carboplatin and dexamethasone)[160] have also been

effective for relapsed or refractory HL. However, none of these regimens has been studied in randomized trials.

Bendamustine, lenalidomide, and everolimus have also shown activity in patients with relapsed or refractory HL.[161-163] In an ongoing phase II trial, bendamustine was well tolerated and highly active in heavily pre-treated patients (including those who had failed HDT/ASCR) with relapsed or refractory disease, resulting in an ORR of 56% among evaluable patients (34 out of 36 patients enrolled).[161] The ORR by intent-to-treat analysis was 53% (33% CR and 19% PR). The median response duration was 5 months. Lenalidomide and everolimus have also shown single-agent activity in a small cohort of patients with relapsed or refractory HL, resulting in ORR of 19% and 47%, respectively.[162,163]

Brentuximab vedotin, a CD30-directed antibody-drug conjugate, has demonstrated activity in patients with relapsed or refractory CD30-positive lymphomas.[164] In a pivotal phase II multicenter study of 102 patients with relapsed or refractory HL after HDT/ASCR, brentuximab vedotin induced objective responses and complete remissions in 75% and 34% of patients, respectively, with a median follow-up of more than 1.5 years. The median PFS for all patients and the median duration of response for those in CR were 5.6 months and 20.5 months, respectively.[165] Based on the results of this study, the FDA approved brentuximab vedotin for the treatment of patients with Hodgkin's lymphoma after failure of HDT/ASCR or at least two prior chemotherapy regimens in patients who are not candidates for HDT/ASCR.

Josting and colleagues from the GHSG reported that second-line RT may be effective in a select subset of patients with relapsed or refractory disease.[166] The 5-year FFTF and OS rates were 28% and 51%, respectively. B symptoms and stage at the time of disease progression or relapse were identified as significant prognostic factors for OS. Moskowitz and colleagues have demonstrated the efficacy and feasibility of second-line RT with chemotherapy in patients with relapsed and refractory disease.[139] At a median follow-up of 43 months, the response rate to ICE (ifosfamide, carboplatin, and etoposide) and IFRT was 88% and the EFS rate for patients who underwent HDT/ASCR was 68%. Second-line RT may be effective in patients who are in good performance status with limited-stage late relapses and without B symptoms. It may be a very effective salvage regimen for patients with initial favorable stage I-II disease who are treated with chemotherapy alone and relapse in initially involved sites.

Individualized treatment is recommended for patients with refractory or relapsed disease since there are no data available to support a superior outcome with any of the treatment modalities. Everolimus is included as an option for second-line therapy for patients with relapsed or refractory CHL.[163] Bendamustine and lenalidomide are included as options for third-line therapy for patients with relapsed or refractory CHL.[161,162] Brentuximab vedotin is a treatment option for patients with relapsed or refractory CHL who have failed HDT/ASCR or at least two prior chemotherapy regimens.[165]

NCCN Recommendations for Refractory Disease

Histologic confirmation with biopsy is recommended before initiating treatment for refractory disease. Although further cytoreduction and HDT/ASCR (with RT if not previously given) are often appropriate, occasional clinical circumstances may warrant the use of RT or chemotherapy with or without RT. Conventional-dose second-line chemotherapy may precede HDT/ASCR. ISRT is recommended when the sites of relapse have not been previously irradiated. In

radiation-naïve patients, TLI may be an appropriate component of HDT/ASCR.[167]

Second-line chemotherapy followed by response assessment with PET is recommended for all patients. Patients with a score of Deauville 1-3 should be treated with HDT/ASCR or observation (short interval follow-up with PET-CT every 3–6 months until Deauville 1–2 or until no progression for 12 months or more), if HDT/ASCR is contraindicated. Additional second-line therapy (ISRT or second-line chemotherapy with or without ISRT) followed by another restaging is recommended for patients with a PET score of Deauville 4 or 5. Alternatively, those with a score of Deauville 4 can be treated with HDT/ASCR. If the repeat PET score (after additional second-line therapy) is Deauville 1-4, HDT/ASCR or observation (only if the patient has achieved CR and HDT/ASCR is contraindicated) is recommended. If the PET remains Deauville 5, patients should be retreated with ISRT or second-line chemotherapy with or without ISRT. Brentuximab vedotin is included as an option for patients with a score of Deauville 4 or Deauville 5 following second-line chemotherapy with or without RT.

Some studies have suggested that patients with CR to second-line therapy prior to HDT/ASCR or those with chemosensitive disease to second-line chemotherapy have improved outcomes following HDT/ASCR compared to those with resistant disease.[168,169] Moskowitz et al reported that the EFS, PFS, and OS were significantly better for patients responding to second-line chemotherapy (60%, 62%, and 66%, respectively) compared to those who had a poor response (19%, 23%, and 17%, respectively) ($P < .001$).[168] More recently Sirohi et al also reported similar findings; the 5-year OS rate was 79%, 59%, and 17%, respectively, for patients who were in CR, PR, or those with resistant disease at the time of HDT/ASCR ($P < .0001$), and the 5-year PFS rate was 69%, 44%, and 14%, respectively ($P < .001$).[169]

The consensus of the panel was that patients who are refractory to second-line chemotherapy should not proceed to HDT/ASCR and patients with refractory disease who are not chemosensitive after 2 second-line chemotherapy regimens should be given a trial of brentuximab vedotin prior to HDT/ASCR even though they may be candidates for transplant. Therefore, the panel has included brentuximab vedotin as an option for patients who have failed HDT/ASCR or at least two prior chemotherapy regimens, regardless of their eligibility for HDT/ASCR.

NCCN Recommendations for Relapsed Disease

While second-line chemotherapy is an appropriate treatment for any patient with relapsed disease, regardless of the length of initial remission,[170] some studies have also suggested that second-line chemotherapy may not be essential before proceeding to HDT/ASCR for patients with minimal residual disease at relapse.[171] In selected patients with long disease-free intervals and other favorable features, the selection of second-line chemotherapy should be individualized.

Suspected relapse should be confirmed with biopsy. Observation (with short-interval follow-up with PET/CT) is appropriate if biopsy is negative; however, clinical circumstances may warrant additional therapy even if the biopsy is negative. Restaging, with or without bone marrow biopsy is recommended for patients with positive biopsy. Second-line chemotherapy is recommended for all patients experiencing disease relapse after initial treatment with chemotherapy or combined modality therapy. Second-line chemotherapy with or without ISRT (followed by restaging) is the preferred treatment option for patients with stage IA to IIA disease who were initially treated with chemotherapy alone and experienced failure at the initial sites followed by restaging. ISRT alone may be appropriate for selected patients. Patients with a score of Deauville 1-3 should be treated with

HDT/ASCR or observation (in selected patients). Those with a score of Deauville 4-5 should be managed as described above for refractory disease.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma

NLPHL patients with refractory or relapsed disease can be managed with second-line therapy as described below. However, some patients have a chronic indolent disease and may not require aggressive treatment. Rituximab should be considered with all second-line chemotherapy regimens for patients with relapsed or refractory NLPHL.

Individualized treatment is recommended for patients with progressive or relapsed disease since there are no data available to support a superior outcome with any of the treatment modalities.

NCCN Recommendations for Refractory Disease

Asymptomatic patients should be observed whereas symptomatic patients should be treated with second-line therapy followed by restaging with PET. No further treatment is necessary if the PET score is Deauville 1-3. Patients with a score of Deauville 4-5 should be retreated with second-line therapy. Chemotherapy, rituximab, and RT are included as options (alone or in combination) for second-line therapy. Maintenance rituximab for 2 years is included as an option for patients treated with rituximab alone.[118]

NCCN Recommendations for Relapsed Disease

Late relapse or transformation to DLBCL has been reported in patients with NLPHL.[172-174] In a study of 95 patients diagnosed with NLPHL, with a median follow-up of 6.5 years, transformation to aggressive lymphoma was seen in 13 (14%) patients and the actuarial risk at 10 and 20 years was 7% and 30%, respectively.[174]

If relapse is suspected, re-biopsy should be considered to rule out transformation to aggressive lymphoma. Patients with a negative biopsy can be observed and those with confirmed relapsed NLPHL should be managed as described above for refractory disease. Patients with disease transformation to DLBCL should be managed as discussed in the NCCN Guidelines for Non-Hodgkin Lymphomas.

Summary

HL is an uncommon malignancy involving lymph nodes and the lymphatic system. The WHO classification divides HL into 2 main types: CHL and NLPHL. CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas NLPHL is characterized by the presence of lymphocytic and histiocytic cells.

Current management of CHL involves initial treatment with chemotherapy or combined modality therapy, followed by restaging with PET/CT to assess treatment response using the Deauville criteria. The value of interim PET scans remains unclear and the panel emphasizes that all measures of response should be considered in the context of management decisions.

Combined modality therapy (ABVD plus ISRT or Stanford V) or chemotherapy alone with ABVD are included as treatment options for patients with stage IA or IIA favorable CHL. Chemotherapy (ABVD or Stanford V or BEACOPP plus ABVD) followed by consolidative ISRT is recommended for patients with stage I-II unfavorable disease. Chemotherapy with ABVD or Stanford V or escalated-dose BEACOPP is recommended for patients with stage III-IV disease.

HDT/ASCR is the best treatment option for patients with refractory or relapsed CHL, although it does not improve OS. Second-line therapy (RT or conventional-dose second-line chemotherapy with or without

RT) may be given prior to HDT/ASCR. The panel has included brentuximab vedotin as an option for patients with progressive disease after HDT/ASCR or at least two prior chemotherapy regimens for all patients regardless of their eligibility for HDT/ASCR.

NLPHL has a different natural history and response to therapy compared with CHL. ISRT is the preferred treatment for patients with stage IA or IIA non-bulky disease. Observation may be an option for highly selected patients with stage IA disease with a completely excised solitary node. A brief course of chemotherapy plus ISRT with or without rituximab is recommended for patients with stage IB or IIB disease and for very rare patients presenting with stage IA or IIA bulky disease. Chemotherapy with or without ISRT or rituximab is recommended for all patients with stage III-IV disease.

Late relapse or transformation to DLBCL has been reported in patients with NLPHL. In patients with suspected relapse, re-biopsy should be considered to rule out transformation to DLBCL. Patients with refractory or relapsed NLPHL can be managed with second-line therapy. However, some patients have a chronic indolent disease and may not require aggressive treatment, unless they are symptomatic. Maintenance rituximab for 2 years is included as an option for patients treated with refractory disease treated with rituximab alone.

HL is now curable in most patients because of the introduction of more effective and less toxic regimens. However, survivors may experience late treatment-related side effects. For this reason, long-term follow-up by an oncologist is essential after completion of treatment. Counseling about issues of survivorship and careful monitoring for late treatment-related side effects should be an integral part of follow-up. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

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