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THE ROLE OF FDG-PET SCANNING AND PET-ADAPTED THERAPY IN THE PRIMARY TREATMENT OF HODGKIN LYMPHOMA: A PRIMER FOR CLINICIANS

Introduction

The evolving treatment paradigm for classical Hodgkin lymphoma (cHL) remains focused on maintaining high rates of progression-free survival (PFS) and overall survival (OS), while seeking to reduce both short-term and late toxicities from chemotherapy and radiation. Functional imaging with fluoro-deoxyglucose (FDG)-positron emission tomography (PET) combined with computed tomography (CT) is recognized as standard for staging and response evaluation of Hodgkin lymphoma (HL).[1,2] Recent randomized controlled trials evaluating FDG-PET-guided therapy for patients with limited stage and advanced stage Hodgkin lymphoma provide clinicians and patients with meaningful data upon which to base individualized treatment approaches.[3-9] FDG-PET scanning after two cycles of therapy (interim PET or PET2) represents the most important determinant of further appropriate treatment and subsequent outcomes, and is now the cornerstone of risk-adapted therapy for all patients receiving curative-intent initial therapy for Hodgkin lymphoma. For patients with limited stage cHL, post-chemotherapy assessment (after two or four cycles of treatment depending on the regimen used) is also a key determinant of the need for the addition of involved site or nodal radiation as part of combined modality therapy. This review summarizes the important role of interim and end of chemotherapy FDG-PET scanning to guide individualized initial therapy for patients to achieve optimal treatment outcomes.

FDG-PET CT scanning has an established role in the staging of patients with Hodgkin lymphoma prior to therapy. It is more accurate than cross-sectional imaging with contrast CT scanning[1] and has a high positive and negative predictive value for the presence of bone marrow involvement. This renders bone marrow biopsy unnecessary as part of baseline staging,[10,11] other than in cases of unexplained cytopenias without specific uptake on PET scan.

Total metabolic tumour volume (TMTV) at baseline provides an accurate measure of overall tumour burden and has been shown to be prognostic in early stage HL, with patients having greater TMTV experiencing worse PFS.[12,13] Baseline PET scanning also greatly facilitates the interpretation of interim and end-of-treatment scans used for clinical decision-making as described below and should be standard for all patients with cHL.

Clinical tools such as the international prognostic score (IPS) and baseline serum thymus and activation-regulated chemokine/CCL17 (TARC) levels provide information regarding prognosis with currently available chemotherapy regimens for the treatment of cHL.[14,15] Efforts to improve our ability to identify patients at diagnosis who have a high risk of treatment failure, such as by gene expression profiling of tumour samples, have yet to reliably define

a group of patients who would benefit from treatment intensification vs those who can be prescribed standard or reduced intensity therapy.[16,17] Evaluation of circulating tumour DNA together with FDG-PET scanning appears to hold promise as part of early response assessment but is beyond the scope of this review.

Interim and End-of-Treatment PET Scanning in Early Stage cHL

Early favourable

Initial observations of the poor prognosis associated with a persistent positive PET scan after two cycles of ABVD and the desire to reduce the need for local radiotherapy for patients with limited stage HL led to three landmark prospective randomized clinical trials (RCTs) based on interim PET assessment. In all three trials (**Figure 1**)—the UK-NCRI RAPID study,[3] EORTC/LYSA/FIL H10[5] and the GHSG HD16[8] trials—patients with a negative PET2 scan who had omission of end-of-treatment radiation had inferior PFS vs those treated with involved field radiation therapy (IFRT) or involved node radiation therapy (INRT). Omission of radiation in the per protocol analysis populations showed a reduction in PFS between 7% and 12%, although no OS difference has been reported in these studies. The largest reduction in PFS was observed in patients with early favourable HL enrolled in H10, where five-year PFS was 87.1% without INRT vs 99% for patients receiving radiation.[5] These data allow individualized treatment decisions, tailoring duration of chemotherapy and inclusion or omission of radiation, depending on individual circumstances. For example, it is appropriate to avoid extended field radiation therapy (EFRT) or IFRT for presentations involving the axilla, infraclavicular fossa and mediastinum in young women with cHL to reduce the excess breast cancer risk in this population, or if the potential cardiac dose would be high. Conversely, when the risk of secondary breast cancer is low (women over the age of 35 to 40 years[18] and in other circumstances where secondary cardiovascular or cancer risks are lower, and risk of

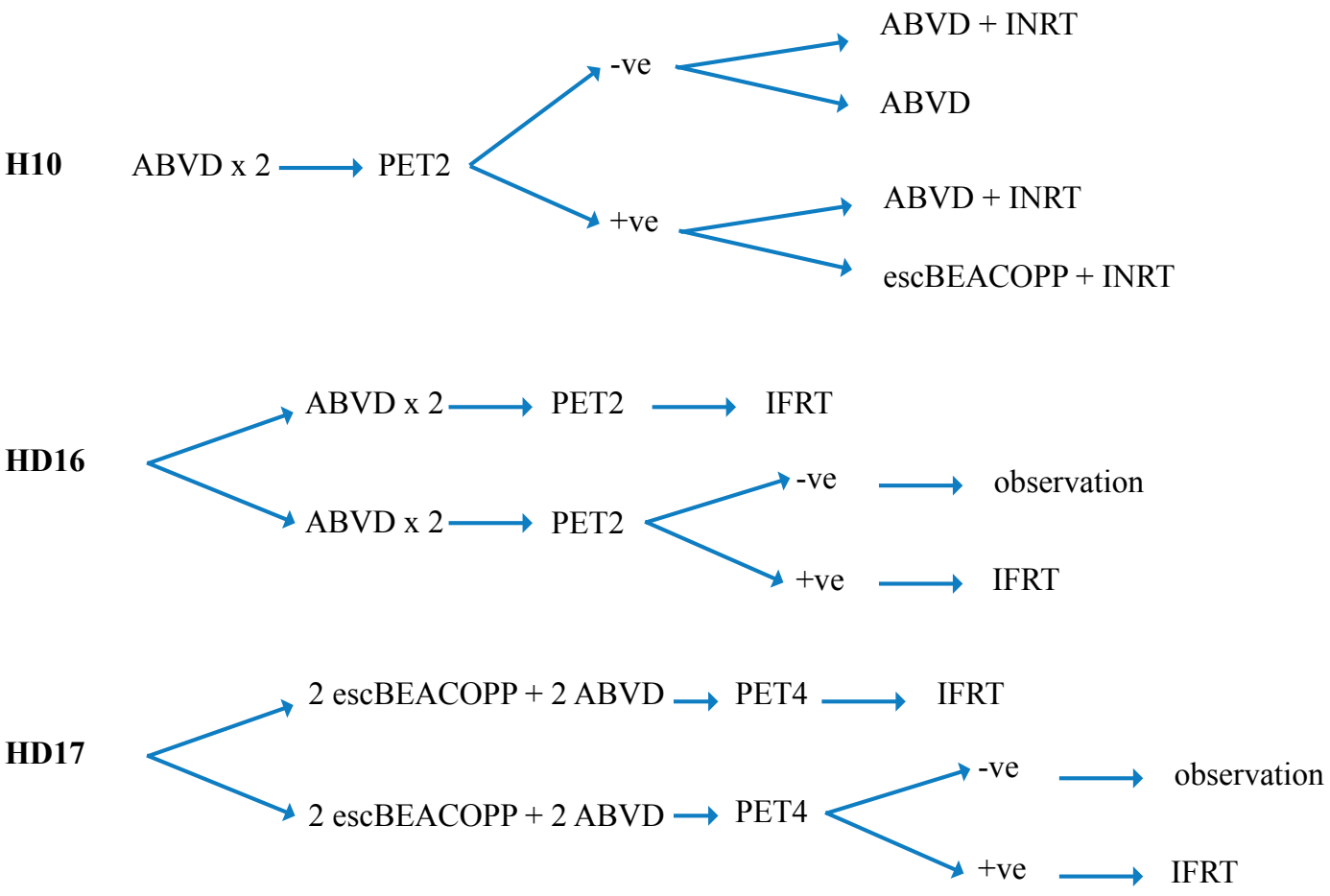

Figure 1. *Recent FDG-PET-adapted trials in early stage HL: H10 depicts the per-protocol analysis of patients with early favourable or unfavourable HL and negative PET2 after two cycles ABVD; and the combined analysis of patients in both subgroups with positive PET2; HD16 and HD17 compared outcomes of PET-adapted omission of IFRT for patients with a negative end-of-treatment PET scan after two (early favourable patients) or four (early unfavourable patients) cycles of chemotherapy vs standard CMT; per protocol analyses compared outcomes for patients with negative PET scans with or without radiation; courtesy of Michael Crump, MD, FRCPC.*
INRT: *involved nodal radiation;* ***IFRT:*** *involved field radiation.*

treatment failure is higher (e.g., women or men over age 50), radiotherapy should be included to provide optimal PFS.

For the 15% to 20% of patients with Stage I-II cHL treated with ABVD who have a positive interim PET scan, intensification of treatment with two cycles of escalated BEACOPP followed by INRT is considered standard based on the significant PFS and possible OS benefit demonstrated in EORTC H10.[5] To date, this is the only patient subgroup in which therapy escalation has been shown to improve outcomes in a randomized trial. Furthermore, it established this as an important consideration for all patients with a positive PET2 not already receiving intensive induction therapy such as escBEACOPP.

Early unfavourable (early stage intermediate)

Prior to the routine use of PET guided therapy, standard approaches for patients with Stage I-II HL and risk factors (**Table 1**), based on RCTs, included four cycles of ABVD and 30 Gray IFRT, or two cycles of escalated BEACOPP followed by two cycles of ABVD (2+2) with IFRT.[19,20] The PFS advantage for the latter strategy in the GHSG HD14 trial, compared to four cycles of ABVD, was approximately 7%, with no demonstrated difference in OS. To identify whether or not IFRT could be safely omitted, the GHSG conducted HD17, randomizing patients to either a standard approach (2+2 followed by radiation) or a PET-adapted approach where patients with a negative PET scan following completion of chemotherapy (PET4) were observed without radiation, and those positive PET scan (Deauville score 4) completed IFRT (**Figure 1**). PFS was 97% at five years in the standard combined-modality treatment arm and 95% in the PET-guided arm, meeting the study's non-inferiority endpoint.[6] PFS among patients with a negative end-of-treatment (EOT) (PET4) scan was 97.7% and 95.9%, respectively. For those with a positive PET4 scan (Deauville score 4), five-year PFS was only 81.6% with the inclusion of IFRT. However, the overall treatment results were excellent with the standard combined modality therapy (CMT) or PET-guided approaches, with a 5-year OS of 98.8% among the patients in the per protocol analysis and 98.6% in the intention to treat (ITT) population.

EORTC favourable*	GHSG favourable*
No large mediastinal adenopathy (MTR <0.35)	No large mediastinal adenopathy (MTR <0.33)
ESR <50 (or <30 with B symptoms)	ESR <50 (or <30 with B symptoms)
Age <50	No extranodal disease
1–3 lymph node sites involved	1–2 lymph node sites involved

Table 1. *Prognostic factors in Stage I and II Hodgkin lymphoma; courtesy of Michael Crump, MD, FRCPC.*
** Presence of any one of these factors designates the presentation as early unfavourable with regard to treatment planning*
EORTC: *European Organization for Research and Treatment of Cancer;* ***GHSG:*** *German Hodgkin Study Group;* ***MTR:*** *mediastinal thoracic ratio (at T5/6).*

As reported in HD17, chemotherapy dose reductions for acute toxicities occurred in 17% of patients during the escBEACOPP cycles and in 22% of patients during the ABVD cycles.[6] Importantly, only 1% percent of patients in both arms developed a second cancer; however, follow-up for this important outcome is still too short to capture all potential events.

When a more intensive induction chemotherapy approach is warranted, patients with a negative PET scan after two escalated BEACOPP + 2 ABVD may have radiation safely omitted without detriment to tumour control. Conversely, following the approach of EORTC H10, starting with two cycles of ABVD, approximately 20% of patients will be expected to have a positive interim PET scan and require therapy escalation and inclusion of radiotherapy. For those with a negative PET2 after ABVD, the decision to continue with four cycles of AVD (omitting bleomycin as was done in the U.K. RATHL trial[4]) which has a higher risk of treatment failure with omission of radiation[22]; or two more cycles of chemotherapy plus INRT will depend on individual patient characteristics, and the tradeoff of local control vs the potential risk of late cardiac toxicity and second cancers.

Interim and end-of-treatment PET scanning in advanced cHL

There are currently two treatment approaches in the management of Stage III/IV cHL that are founded on therapy modification according to the results of PET2 tested in prospective trials. For patients commencing therapy with ABVD, the U.K. Response-Adjusted Therapy for Advanced Hodgkin Lymphoma (RATHL) trial provided guidance for treatment following two cycles of ABVD.[4] Patients with a negative PET2 scan (Deauville 1–3) were randomized between four more cycles of ABVD or bleomycin omission with AVD, while those with a positive PET2 scan were assigned to six cycles of BEACOPP-14 or four cycles of escBEACOPP. Consolidative radiotherapy was not recommended for PET2 negative patients but was allowed at the treating physician's discretion and was administered to 35/937 patients with a negative PET2 scan and 43/182 patients with a positive PET2 scan. One hundred fifty-four of 1088 patients enrolled (14%) had therapy escalated. Following a median follow-up of 69 months, the five-year PFS of the entire cohort was 81.4% and OS was 95.2%.[4]

A second approach starts with escBEACOPP, and treatment is either de-escalated in those with a negative PET2 (Deauville 1–3), or maintained for those where the PET2 scan is positive (Deauville 4). The GHSG HD18 trial randomized patients with Stages IIB-IV disease and negative PET2 to receive four additional cycles of escBEACOPP (total 6 cycles, standard arm), or two additional cycles (total four cycles, de-escalation arm).[7] PET2-positive patients (uptake greater than mediastinal blood pool) were randomized to receive four additional cycles escBEACOPP with or without the CD20 antibody

rituximab. The primary objectives of the study were to assess superiority of the escalation arm with a 5-year PFS improvement of at least 15% and non-inferiority of the de-escalated arm with a margin of 6%.

After a median follow-up of 66 months, the HD18 study met its primary end-point in the PET2 negative cohort, with 5-year PFS of 92% vs 91% and OS of 98% vs 95% for patients receiving four vs six cycles of chemotherapy, respectively. The addition of rituximab did not improve PFS for patients with a positive PET2 scan.[7]

The second trial of de-escalation of therapy for PET2 responders, Lymphoma Study Association (LYSA) AHL 2011, compared outcomes in Stage III/IV cHL using the standard six cycles of escBEACOPP, to a PET-guided strategy, where patients with a negative PET2 scan received four cycles of ABVD, while patients with a positive scan continued to complete four additional cycles of escBEACOPP. After a median follow-up of 50.4 months, the five-year PFS was 86% in both the standard and PET2 modified arms; OS was similar in both arms, 95.5%. Radiation was not part of the treatment protocol in this trial for those with positive end-of-treatment PET scan, but would be appropriate to apply to localized residual areas of FDG uptake as was performed in HD18.

Studies incorporating novel agents into front-line therapy of classical HL—an opportunity for PET-guided therapy?

RCTs incorporating brentuximab vedotin and nivolumab are poised to provide new therapeutic approaches to improve outcomes in cHL. The ECHELON1 trial comparing brentuximab vedotin (BV) added to AVD to ABVD for six cycles in Stage III/IV cHL demonstrated improved six-year PFS (82.3% vs 74.5%) and OS (93.9% vs 89.4%).[23] This study included assessment of response to therapy by FDG-PET after cycle two, but did not modify treatment based on these results. Six-year PFS for those with a negative PET2 scan was superior for BV-AVD compared to ABVD (85.0% vs 78.1%, HR 0.66 [0.50-0.87]). However, for patients with a positive PET2 scan, PFS was only 61% for those in the BV-AVD arm and 46% for ABVD. This suggests that patients receiving BV-AVD should have an early PET scan with consideration of escalation of therapy, such as switching to escBEACOPP as performed in the RATHL trial if the scan is positive, rather than continuing the same therapy, to ensure optimal outcomes.

The results of a planned interim analysis of the recently completed North American Intergroup trial S1826/CCTG HDC.1 in patients with Stage III/IV cHL comparing six cycles of nivolumab + AVD (n=489) to six cycles of BV-AVD (n=487) were recently reported at the International Conference on Malignant Lymphoma (ICML17).[24] The complete molecular response rate (CMR) by FDG-PET at EOT was 85.1% for nivo-AVD and 71.7% for BV-AVD. After a median follow-up of 12 months, PFS at one year was 94% in the nivo-AVD arm compared to 86% in patients receiving BV-AVD (HR 0.48, one sided P=0.0005). Data on outcomes according to interim PET scanning after two cycles to address prognostic value when treatment includes a PD1 antibody, or need for treatment modification, were not reported.

The GHSG trial HD21 incorporating BV into front-line therapy of advanced cHL was also reported at ICML17.[9] This trial evaluated a new regimen consisting of brentuximab vedotin, etoposide, doxorubicin, cyclophosphamide, dacarbazine, and dexamethasone (BrECADD)[24] compared to escBEACOPP in nearly 1500 patients with Stage IIB-IV cHL. HD21 used a PET2-guided design, with a reduction of number of cycles of therapy from six to four in patients with CMR after cycle two, which was achieved in 57% of patients in both arms. The trial met both of its co-primary endpoints, demonstrating superiority of BrECADD over escBEACOPP in treatment-related morbidity (any CTCAE Grade three or four organ toxicity or Grade four khematological toxicity [anemia, thrombocytopenia, infection]), and non-inferiority in three-year PFS (94.7% vs 92.3%).[9]

This latest PET-adapted approach yielded a treatment that meets the objectives of providing both less toxic and more effective therapy for patients with advanced cHL, and BrECADD has become the new standard for advanced stage cHL for the GHSG. PET-adapted strategies incorporating new agents into the treatment of early stage cHL[25] are being tested in the recently activated international RADAR study (CCTG HD.12; **Figure 2**) comparing BV-AVD to ABVD, and in the upcoming North American Lymphoma Intergroup trial adding nivolumab and BV to initial therapy in patients with Stage I-II disease.

Conclusion

The integration of functional imaging during and at end of treatment has transformed the delivery of chemotherapy and radiation for the treatment of classical HL. PET-guided treatment is the current standard that allows clinicians to provide individualized care for patients with a clearer depiction of the balance between toxicities and efficacy (summarized in **Table 2**). Functional imaging with FDG-PET will continue to inform the next generation of trials of new approaches integrating novel treatment regimens incorporating immune checkpoint inhibitors in the front-line and relapse/second-line setting

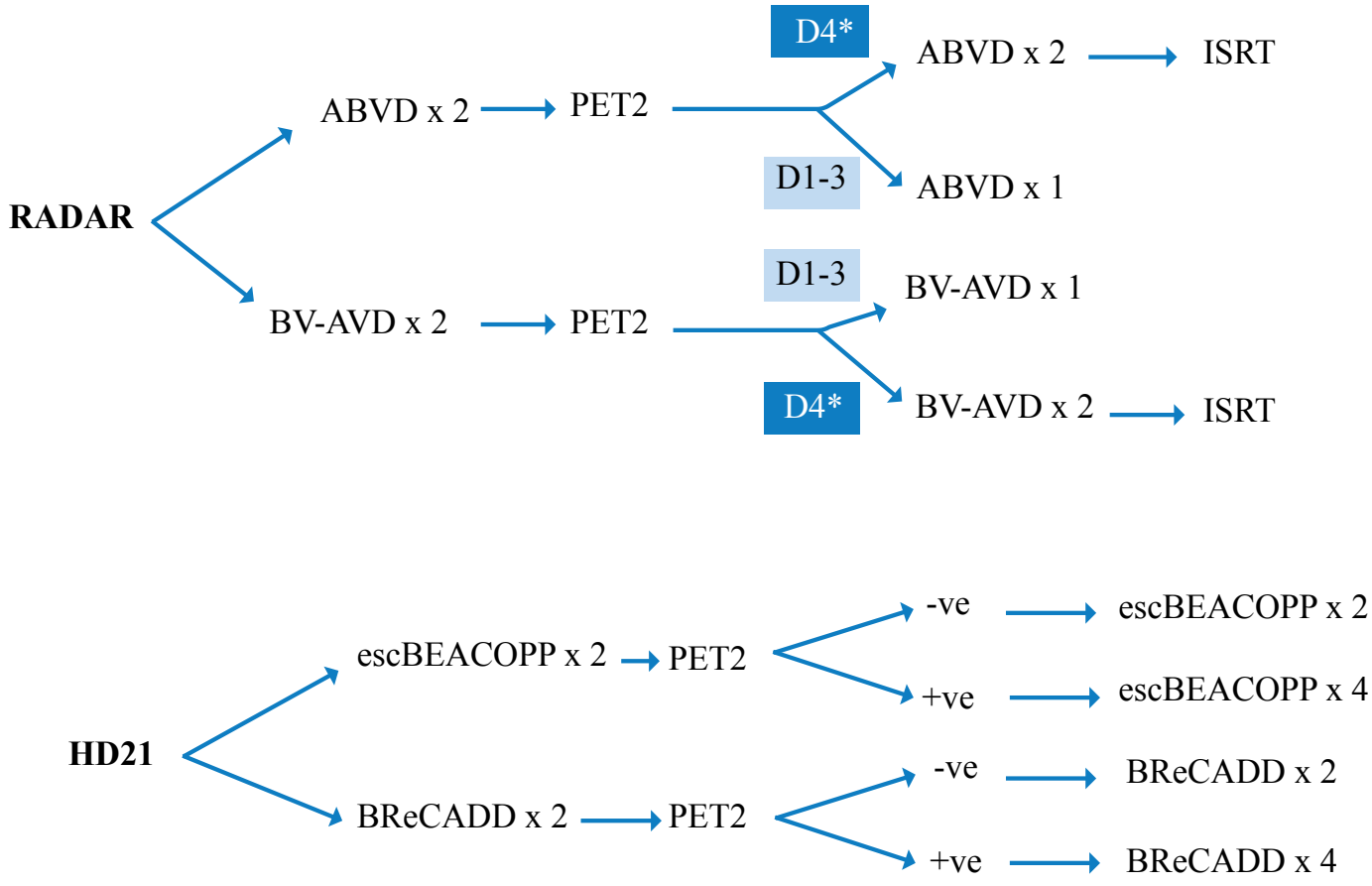

Figure 2. *PET-adapted trials incorporating brentuximab vedotin (BV) into therapy for Stage I-II cHL (RADAR; opened to accrual 2022) and Stage IIE-IV cHL (GHSG HD21).*[9]
**Patients with Deauville (D) score 5 receive alternative therapy.*
ISRT: *involved site radiation;* ***BrECADD:*** *brentuximab vedotin, etoposide, doxorubicin, cyclophosphamide, dacarbazine, dexamethasone;* ***escBEACOPP:*** *escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.*

Baseline assessment of disease extent	Interim response assessment after two cycles of chemotherapy (PET2)	End-of-treatment response assessment:
• "Upstaging" of 5%–15% of patients presenting with clinical and CT scan evidence of limited stage HL • Assessment of presence or absence of bone marrow involvement: bone marrow biopsy no longer required for routine staging	• Limited stage cHL (I,II): After two cycles ABVD identification of patients for whom INRT could be omitted (Deauville score 1–3) and treatment completed with 2–4 additional cycles or patients with inadequate response for whom treatment should be escalated (Deauville score 4,5) • Advanced stage cHL (III,IV): Treatment reduction/de-escalation to reduce toxicity without decrease in PFS following favourable early response to therapy (Deauville score 1–3) ◊ Initial treatment with two cycles escBEACOPP: Continue with two further cycles (vs four cycles) or continue with four cycles A(B)VD ◊ Initial treatment with two cycles ABVD: Continue treatment with four cycles AVD (omission of bleomycin to reduce potential pulmonary toxicity) • Treatment intensification/continuation following unfavourable early response (Deauville 4) ◊ Positive PET2 after ABVD: Intensify therapy with four cycles escBEACOPP ◊ Positive PET2 after escBEACOPP: Continue with 4 cycles escBEACOPP	• Early favourable cHL: Identification of patients with incomplete response (Deauville 4) who may benefit from therapy escalation after two cycles ABVD (vs standard CMT), despite favourable characteristics at presentation • Early unfavourable cHL: Identification of patients after two cycles escBEACOPP + two cycles ABVD with complete metabolic response for whom INRT can be omitted without reduction in PFS. • Advanced stage (including IIB with risk factors) cHL: Identification of patients with bulky disease at presentation and favourable response after completion of chemotherapy (Deauville 1–3) for whom consolidative radiation can be omitted without reduction in PFS. • Advanced stage (including IIB with risk factors) cHL with less than CMR at end-of-treatment (PMR, Deauville 4) for whom further follow-up imaging is warranted or for whom a biopsy must be performed before change in therapy (Deauville 5)

Table 2. *Summary of role of FDG-PET scanning in primary treatment of classical Hodgkin lymphoma; courtesy of Michael Crump, MD, FRCPC.* ***INRT:*** *involved nodal radiation therapy;* ***CMR:*** *complete metabolic response;* ***PMR:*** *partial metabolic response;* ***RT:*** *radiation therapy;* ***CMT:*** *combined modality treatment.*

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References:

1. *Ricard F, Cheson B, Barrington S, et al. Application of the Lugano classification for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the PRoLoG Consensus Initiative (Part 1-Clinical). J Nucl Med. 2023 Jan;64(1):102-108.*
2. *Barrington SF, Kirkwood AA, Franceschetto A, et al. PET-CT for staging and early response: results from the response-adapted therapy in advanced Hodgkin lymphoma study. Blood. 2016;127(12):1531–1538.*
3. *Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med. 2015 Apr 23;372(17):1598-1607.*
4. *Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT Scan in advanced Hodgkin's lymphoma. N Engl J Med. 2016 Jun 23;374(25):2419-2429.*
5. *André M, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin Lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2017;35(16):1786-1794.*
6. *Borchmann P, Plütschow A, Kobe C, et al. PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021 Feb;22(2):223-234.*
7. *Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. Lancet. 2017 Dec 23;390(10114):2790-2802.*
8. *Fuchs M, Goergen H, Kobe C, et al. Positron Emission Tomography-guided treatment in early-stage favorable Hodgkin lymphoma: final results of the international, randomized Phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol. 2019;37(31):2835-2845.*
9. *Borchmann, P., Moccia, A.A., Greil R et al. BRECADD is non-inferior to eBEACOPP in patients with advanced stage classical Hodgkin lymphoma: efficacy results of the GHSG phase III HD21 trial. Hematol Oncol 2023; 41:881-882.*
10. *Adams HJ, Kwee TC, de Keizer B, et al. Systematic review and meta-analysis on the diagnostic performance of FDG-PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: is bone marrow biopsy still necessary? Ann Oncol. 2014;25(5):921-927.*
11. *Voltin CA, Goergen H, Baues C, et al. Value of bone marrow biopsy in Hodgkin lymphoma patients staged by FDG-PET: results from the German Hodgkin Study Group trials HD16, HD17, and HD18. Ann Oncol. 2018;29(9):1926-1931.*
12. *Cottereau AS, Versari A, Loft A, et al. Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. Blood. 2018 Mar 29;131(13):1456-1463.*
13. *van Heek L, Stuka C, Kaul H, et al. Predictive value of baseline metabolic tumor volume in early-stage favorable Hodgkin Lymphoma - data from the prospective, multicenter phase III HD16 trial. BMC Cancer. 2022 Jun 18;22(1):672.*
14. *Diefenbach CS, Li H, Hong F, et al. Evaluation of the International Prognostic Score (IPS-7) and a Simpler Prognostic Score (IPS-3) for advanced Hodgkin lymphoma in the modern era. Br J Haematol. 2015;171(4):530-538.*
15. *Sauer M, Plütschow A, Jachimowicz RD, et al. Baseline serum TARC levels predict therapy outcome in patients with Hodgkin lymphoma. Am J Hematol. 2013 Feb;88(2):113-115.*
16. *Scott DW, Chan FC, Hong F, et al. Gene expression-based model using formalin-fixed paraffin-embedded biopsies predicts overall survival in advanced-stage classical Hodgkin lymphoma. J Clin Oncol. 2013 Feb 20;31(6):692-700.*
17. *Jachimowicz RD, Klapper W, Glehr G, et al. Gene expression-based outcome prediction in advanced stage classical Hodgkin lymphoma treated with BEACOPP. Leukemia. 2021 Dec;35(12):3589-3593.*
18. *Swerdlow AJ, Cooke R, Bates A, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol. 2012 Aug 1;30(22):2745-2752.*
19. *Eich HT, Diehl V, Görgen 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 HD11 trial. J Clin Oncol. 2010 Sep 20;28(27):4199-4206.*
20. *Gillessen S, Plütschow A, Fuchs M, et.al. Intensified treatment of patients with early stage, unfavourable Hodgkin lymphoma: long-term follow-up of a randomised, international phase 3 trial of the German Hodgkin Study Group (GHSG HD14). Lancet Haematol. 2021 Apr;8(4):e278-e288.*
21. *Fiaccadori V, Neven A, Fortpied C, et al. Relapse patterns in early-PET negative, limited-stage Hodgkin lymphoma (HL) after ABVD with or without radiotherapy-a joint analysis of EORTC/LYSA/FIL H10 and NCRI RAPID trials. Br J Haematol. 2023 Mar;200(6):731-739.*
22. *Ansell SM, Radford J, Connors JM, et al; ECHELON-1 Study Group. Overall survival with brentuximab vedotin in stage III or IV Hodgkin's lymphoma. N Engl J Med. 2022 Jul 28;387(4):310-320.*
23. *Herrera AF, LeBlanc M, Castellino, SM, et al Nivolumab(N)-AVD improves progression-free survival compared to brentuximab vedotin(BV)-AVD in advanced stage (as) classic Hodgkin lymphoma (HL): results of SWOG S1826. Hematol Oncol. 2023 41:33-35.*
24. *Eichenauer DA, Plütschow A, Kreissl S, et al. Incorporation of brentuximab vedotin into first-line treatment of advanced classical Hodgkin's lymphoma: final analysis of a phase 2 randomised trial by the German Hodgkin Study Group. Lancet Oncol. 2017 Dec;18(12):1680-1687.*
25. *Fornecker LM, Lazarovici J, Aurer I, et al. Brentuximab vedotin plus AVD for first-line treatment of early-stage unfavorable Hodgkin lymphoma (BREACH): a multicenter, open-label, randomized, phase II trial. J Clin Oncol. 2023 Jan 10;41(2):327-335.*