# $^{18}$F-FDG PET/CT in Lymphoma: Has Imaging-Directed Personalized Medicine Become a Reality?

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PET/CT using $^{18}$F-FDG is an essential part of the management of patients with lymphoma. Efforts to standardize PET acquisition and reporting, including the 5-point Deauville scale, have enabled PET to become a surrogate for treatment success or failure in common lymphoma subtypes. This review summarizes the key clinical-trial evidence that supports PET-directed personalized approaches in lymphoma. PET-guided therapy has improved outcomes in Hodgkin lymphoma, using less chemotherapy and more selective radiotherapy. Attempts to intensify chemotherapy in aggressive non-Hodgkin lymphomas have, however, proved ineffective in patients treated with rituximab and chemotherapy. Trials are under way to determine whether PET can obviate consolidation radiotherapy in patients with diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma. More recently, PET has been reported to be a reliable predictor of outcome in follicular lymphoma requiring treatment, and prospective trials to test PET-guided therapy in this disease are anticipated.

**Key Words:** positron emission tomography; lymphoma; precision medicine

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PET/CT has become integral to the management of patients with $^{18}$F-FDG–avid lymphomas, enhancing the staging and response assessment available with CT (*1*). Better disease characterization has also allowed smaller radiotherapy volumes. PET-guided treatment has been explored in international trials with practice-changing results, particularly in Hodgkin lymphoma (HL).

Many lymphomas are curable, but treatment side-effects reduce the length and quality of patients' lives (*2*). Long-term toxicities include infertility, premature coronary and valvular heart disease, pulmonary fibrosis, and second malignancies. HL, although uncommon, remains the most frequent malignancy in teenagers and young adults, and trials have tested the possibility of deescalating therapy for patients showing a good response on PET/CT while intensifying treatment for the minority who respond less well. In the aggressive B-cell non-Hodgkin lymphoma (NHL), the affected patients tend to be older, with low chances of cure if initial therapy is unsuccessful. In NHL, the focus has generally been on whether PET/CT can guide treatment escalation in poor responders to improve remission rates, although the potential to reduce mediastinal radiotherapy in primary mediastinal B-cell lymphoma is another important area of ongoing research.

Successful conduct of trials, which have included thousands of patients, has involved standardization of PET/CT for quality control, acquisition, and reporting (*3*). Response-adapted treatment required confidence that PET/CT was a robust and reliable surrogate of treatment success or failure. The Deauville criteria, a 5-point scale developed during these trials, have high interobserver agreement, particularly using the liver threshold (*1*). In earlier trials, investigators were concerned about minimizing the risk of undertreatment of good-prognosis disease, and a Deauville score (DS) of 1 or 2 (≤normal mediastinal uptake) was considered to indicate the need to deescalate treatment (*4*). In trials where the concern was more about overtreating patients—and as camera sensitivity has improved—scores of 1–3 (≤normal liver uptake) have increasingly been used in indicate a complete metabolic response (CMR). PET methods established in the trials are now recommended as the best clinical practice (*3*). Advancements such as scan reconstruction using resolution recovery indicate that reporting thresholds may change but will require proper validation to avoid overtreating patients.

## HL

### Deescalation Strategies

Early-stage HL has been routinely treated with 2–4 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy and 20–30 Gy of involved-field radiotherapy (Table 1). Two trials tested whether radiotherapy could be omitted in patients with negative PET/CT results during ABVD treatment. The RAPID trial, which investigated PET-directed therapy for early-stage HL, and the H10 trial used the mediastinal threshold (DS of 2) to define CMR. In the RAPID trial, 75% of patients had CMR after 3 cycles and were randomized to receive involved-field radiotherapy or no further treatment (*5*). The 3-y progression-free survival (PFS) was 97.1% for patients receiving involved-field radiotherapy versus 90.8% for no further treatment in a per-protocol analysis (hazard ratio [HR], 2.36; 95% confidence interval [CI], 1.13 to 4.95; $P = 0.02$). Similar results were reported in the H10 trial; patients who were in CMR after 2 cycles of ABVD

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were randomized using a PET-driven schema to either standard therapy (3–4 cycles of ABVD followed by involved-node radiotherapy, for favorable and unfavorable disease, respectively) or 4–6 cycles of ABVD alone (for favorable and unfavorable disease, respectively) (*6*). Five-year PFS was 99.0% (for patients with favorable disease) and 92.1% (for patients with unfavorable disease) with standard therapy versus 87.1% (favorable disease) and 89.6% (unfavorable disease) with chemotherapy alone (HR, 15.8; 95% CI, 3.79 to 66.0 [favorable] and HR, 1.45; 95% CI, 0.84–2.50 [unfavorable]; $P = 0.03$). Combined-modality therapy thus resulted in a small improvement in disease control in both trials, although the high PFS and lack of effect on overall survival (OS) suggest that many patients may be cured using chemotherapy alone.

The treatment options for advanced-stage HL are generally regarded to be either 6–8 cycles of ABVD or the more intensive escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone (BEACOPPesc), with consolidation radiotherapy to initially bulky sites or residual masses larger than 2.5 cm. The RATHL trial, which investigated adapted treatment guided by interim PET/CT in advanced HL, tested whether, after 2 mo of ABVD, patients with CMR based on a DS of 1–3 could omit bleomycin (B) in cycles 3–6, continuing either ABVD or AVD (doxorubicin, vinblastine, and dacarbazine) and not routinely undergoing radiotherapy (*7*). Three-year PFS was equivalent at 85.7% for ABVD versus 84.4% for AVD (HR, 1.13; 95% CI, −0.81 to +1.57; $P = 0.48$), but AVD was associated with significantly less fatigue, febrile neutropenia, dyspnea, and respiratory events. Three-year PFS was lower than the 95% previously reported in retrospective series, and patients with the most advanced stage at presentation showed the highest risk of progression, 20%. Three-year OS, however, was good in both arms, at 97.2% versus 97.6%, and radiotherapy was used in only 2%–4% of patients with negative PET after cycle 2 (PET2) results. Evidence is emerging that baseline metabolic tumor burden may improve response prediction and that combining PET with nonimaging biomarkers, such as gene expression, to refine risk is an area for research (*8*). The trial also confirmed that PET could replace the bone marrow biopsy during staging. There was good agreement between local and central reviewers, meaning that a RATHL-style approach could be adopted after the trial (*9*).

**NOTEWORTHY**

- Standardization of PET methods has been key to generating robust clinical trial data to support response-adapted treatment.
- PET-directed personalized approaches have improved outcomes for patients with Hodgkin lymphoma, using less chemotherapy and more selective radiotherapy.
- PET predicts response in diffuse large B-cell lymphoma, but more intensive chemotherapy has failed to improve outcomes for patients with interim PET-positive scans.
- Clinical trials are currently evaluating whether consolidation radiotherapy can be omitted in patients with diffuse large B-cell lymphoma and bulky disease and with primary mediastinal B-cell lymphoma.
- PET predicts outcome in patients with follicular lymphoma treated with rituximab and chemotherapy, warranting prospective trials to test response-adapted approaches.

The HD15 trial of the German Hodgkin study group used a PET-directed approach to determine whether patients required consolidation radiotherapy after the much more intensive BEACOPPesc (*10*). Seventy-five percent of patients had a PET-determined CMR using the mediastinal threshold (equivalent to a DS of 2) at the end of treatment, and for these patients, radiotherapy was omitted. Four-year PFS was 92.6% for patients with a PET-determined CMR, with no difference observed between patients with a complete radiologic response and patients with a residual mass. Overall, 11% of patients received radiotherapy, compared with 71% in an earlier trial.

An option of starting therapy with BEACOPPesc and deescalating to ABVD for patients with a PET-determined CMR is being explored by the French–Belgian Lymphoma Study Association (*11*). Interim results reported a 2-y PFS of 94% for patients in the standard arm, who received 6 cycles of BEACOPPesc, versus 92% for patients in the experimental arm, who were randomized to continue BEACOPPesc or 4 cycles of ABVD. Mature results are awaited.

### Escalation Strategies

The H10 and RATHL studies also attempted to determine whether BEACOPP could be reserved for patients with a positive PET2 result in early-stage disease (≥mediastinum) and advanced-stage disease (≥liver), respectively (*6,7*). Only H10 randomized patients to ABVD or BEACOPPesc, whereas in RATHL all patients with positive PET2 results received BEACOPPesc. Nineteen percent of early-stage patients (DS of 3, 4, or 5) and 16% of advanced-stage patients (DS of 4 or 5) had PET2-positive results, potentially sparing more than 80% of patients from BEACOPP treatment, with its worse side-effect profile. In H10, 5-y PFS was 90.6% for patients receiving BEACOPPesc and involved-node radiotherapy versus 77.4% for patients receiving ABVD and involved-node radiotherapy after positive PET2 results (HR, 0.42; 95% CI, 0.23 to 0.74; $P = 0.002$). A trend for improved OS was also observed, with 5-y OS of 96.0% versus 89.3% (HR, 0.42; 95% CI, 0.19 to 1.07; $P = 0.062$). The RATHL trial reported 3-y PFS of 65.7% and 5-y OS of 85.1% for advanced-HL patients receiving escalated treatment, a result confirmed in other large, prospective trials (*12,13*), compared with earlier reports of 2- to 3-y PFS of 13%–28% for patients continuing ABVD after a positive PET2 result (*14,15*). Only 12% of patients with PET2-positive results received consolidation radiotherapy.

In the Italian HD0801 study, an alternative approach was tested, escalating patients with positive (DS of 3–5) PET2 results from ABVD to salvage treatment and autologous stem cell transplantation (*12*). Similar 2-y PFS was observed between patients with PET-positive scans (74%) and patients with negative scans (81%).

The German Hodgkin study group recently reported 3-y PFS for PET2-positive patients (≥mediastinum) after 2 cycles of BEACOPPesc, randomizing patients to receive 6 more cycles or 6 cycles and rituximab (*16*). Adding rituximab did not improve outcomes, but 3-y PFS was high for both groups, at 91.4% and 93.0%, respectively. PET2 did not appear to predict for worse prognosis with this more intensive treatment. Thirty-four percent of patients received consolidation radiotherapy on the basis of an end-of-treatment scan.

Taken together, the trials suggest that the negative predictive value of PET2 is influenced by disease severity at presentation

**TABLE 1**
Published Studies with PET-Adapted Therapy in HL

| Study | Design | Patient population | *n* | PET after | "Positive" equivalent to | PET-negative therapy | PET-positive therapy | Median follow-up | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Radford RAPID 2015 (*5*) | RCT | Stage IA–IIA nonbulky | 571 | 3×ABVD | DS 3–5 | IFRT or NFT | 1×ABVD+IFRT | 60 mo | 3-y PFS PET-neg: IFRT 94.6% vs. NFT 90.8% (intention-to-treat analysis); IFRT 97.1% vs. NFT 90.8% (per-protocol analysis) |
| | | | | | | | | | 3-y OS PET-neg: IFRT 97.1% vs. NFT 99.0% |
| | | | | | | | | | 3-y PFS PET-pos: 87.6% |
| André H10 2017 (*6*) | RCT | Stage I–II supradiaphragmatic | 1,925 | 2×ABVD | DS 3–5 | 1×ABVD+INRT or 2×ABVD (favorable); 2×ABVD+INRT or 4×ABVD (unfavorable) | 1×ABVD+INRT or 2×BEACOPPesc+ INRT (favorable); 2×ABVD+INRT or 2×BEACOPPesc+ INRT (unfavorable) | 4.5 y | 5-y PFS PET-neg: INRT 99% vs. NFT 87.1% (favorable); INRT 92.1% vs. NFT 89.6% (unfavorable) |
| | | | | | | | | | 5-y OS PET-neg: INRT 96.7% vs. NFT 98.3% (favorable); INRT: 92.1% vs. NFT 89.6% (unfavorable) |
| | | | | | | | | | 5-y PFS PET-pos: ABVD+INRT 77.4% vs. BEACOPPesc+INRT 90.6% |
| | | | | | | | | | 5-y OS PET-pos: ABVD+INRT 89.3% vs. BEACOPPesc+INRT 96.0% |
| Johnson RATHL 2016 (*7*) | RCT | Stage IIB adverse features, III–IV | 1,119 | 2×ABVD | DS 4,5 | 4×ABVD or 4×AVD | BEACOPP-14 or BEACOPPesc | 41 mo | 3-y PFS PET-neg: ABVD 85.7% vs. AVD 84.4% |
| | | | | | | | | | 3-y OS PET-neg: ABVD 97.2%; AVD: 97.6% |
| | | | | | | | | | 3-y PFS PET-pos: BEACOPP 67.5% |
| | | | | | | | | | 3-y OS PET-pos: 87.8% PET-pos |
| Engert HD15 PET substudy 2012 (*10*) | RCT | Stage IIB+adverse features, III–IV with PR&>2.5 cm residual mass | 1,578 | 6× or 8× BEACOPPesc or 8×BEACOPP14 | DS 3–5 | NFT | RT | | 4-y PFS: 92.6% PET-neg; 86.2% PET-pos |
| Press S0816 2016 (*13*) | Ph II | Stage III–IV | 336 | 2×ABVD | DS 4,5 | 4×ABVD | 6xBEACOPPesc | 39.7 mo | 2-y PFS: 81% PET-neg; 64% PET-pos; 98% 2-y OS |
| Zinzani HD0801 PET2-pos 2016 (*12*) | Ph II | Stage IIB–IV | 103 | 2×ABVD | DS 3–5 | Not applicable | 4×IGEV+BEAM ASCT or melphalan allograft | 27 mo | 2-y PFS PET2-pos: 81% PET4-neg; 76% PET4-pos; 97% 2-y OS |
| Borchmann HD18 PET2-pos 2017 (*16*) | RCT | Age 18–60 y; stage IIB+adverse features, III–IV | 440 | 2×BEACOPPesc | DS 3–5 | Not applicable | 6×BEACOPPesc or R-6BEACOPPesc | 33 mo | 3-y PFS PET2-pos: BEACOPPesc 91.4% vs. R-BEACOPPesc 93.0% |
| | | | | | | | | | 3-y OS PET2-pos: BEACOPPesc 96.5% vs. R-BEACOPPesc 94.4% |

RCT = randomized clinical trial; ph II = prospective phase II study; IFRT = involved-field radiotherapy; NFT = no further treatment; neg = negative; pos = positive; INRT = involved-node radiotherapy; RT = radiotherapy; IGEV = ifosfamide, gemcitabine, and vinorelbine; BEAM = carmustine, etoposide, cytarabine, and melphalan; ASCT = autologous stem cell transplantation; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PR = partial response.

and intensity of treatment given in the first 2 mo. This paves the way for risk-adapted initial therapy combined with a PET2 response-adapted strategy to enable deescalation of chemotherapy and omission of radiotherapy for those with the highest chance of cure.

### Non-HL

Diffuse large B-cell lymphoma is the most common aggressive NHL and is treated with 6–8 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or 3–4 cycles and radiotherapy for early-stage nonbulky disease (Table 2). Strategies to intensify treatment have mostly failed to improve PFS, despite the fact that interim PET predicted the prognosis in a large, randomized study and in a phase II study (*17,18*). A single phase II study reported that PFS and OS were similar between patients with PET-negative scans after 4 cycles of R-CHOP and patients with PET-positive scans, who received salvage treatment, ibritumomab tiuxetan, and autologous stem cell transplantation (*19*). Recent data have suggested a potential for deescalation in diffuse large B-cell lymphoma. In the OPTIMAL study, which investigated improvement of therapy in elderly patients with CD20-positive diffuse large B-cell lymphoma using an optimized rituximab-schedule and liposomal vincristine, patients older than 60 y with bulky disease who did not receive consolidation radiotherapy after R-CHOP on the basis of a PET-determined CMR (DS of 1–3) were not at a disadvantage compared with patients in a prior study treated with R-CHOP and radiotherapy (*20*).

Primary mediastinal B-cell lymphoma is a rare subtype of diffuse large B-cell lymphoma that affects younger patients, is more common in female individuals, and usually has an excellent prognosis. The negative predictive value of a PET-directed CMR (DS of 1–3) after chemoimmunotherapy was 99% for 125 patients subsequently treated with consolidation radiotherapy in a prospective study (*21*). A study is currently randomizing patients with a PET-directed CMR after chemoimmunotherapy to receive radiotherapy or no further treatment (https://clinicaltrials.gov/ct2/show/NCT01599559?term=NCT01599559&rank=1). Another phase II study reported 93% 5-y event-free survival and 100% OS using infusional dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, and rituximab (DA-R-EPOCH), with only 2 of 51 patients requiring consolidation radiotherapy (*22*). Patients with a positive end-of-treatment PET scan had a high conversion rate to CMR, suggesting a high incidence of inflammatory uptake at the end of immunochemotherapy. Investigators advocated this more intensive immunochemotherapy to avoid performing radiotherapy on a young population.

In follicular lymphoma, PET has recently been shown to predict prognosis better than CT for patients receiving chemotherapy and rituximab (*23*). In a pooled analysis of 3 prospective studies, 17% of patients had a positive PET result at end-of-induction treatment (DS of 4 or 5), with 4-y PFS of 23.2% versus 63.4% for patients with CMR (HR, 3.9; 95% CI, 2.5 to 5.9; $P < 0.0001$), suggesting PET/CT could help determine which patients will benefit from treatment escalation or maintenance antibody treatment.

### PET and New Therapies

New therapies have shown promising results for treating patients with refractory and relapsed lymphoma (*24–26*). Brentuximab vedotin, an antibody–drug conjugate, is effective in treating patients with relapsed or refractory HL and is currently being evaluated for first-line treatment combined with AVD (https://clinicaltrials.gov/ct2/show/NCT01712490). PET is also being used as an exploratory endpoint in studies using targeted agents in relapsed disease for both HL and NHL. These agents modulate the interaction between tumors and the immune system. The checkpoint inhibitors, ipilimumab and nivolumab, have been reported to show delayed responses and flare responses in solid tumors. Flare responses include an increase in tumor size and the appearance of new lesions, suggestive of progressive disease but later resolving or remaining stable, and can be associated with clinical benefit (*27*). In a large series of patients treated with pembrolizumab for melanoma, the incidence of pseudoprogression was 8% (*28*). Methods to document these types of responses and to differentiate true disease progression from pseudoprogression using PET and CT in lymphoma have been proposed (*29*) in the Lymphoma Response to Immunomodulatory Therapy (LYRIC) criteria with the introduction of an indeterminate-response category. In the case of an indeterminate response, biopsy or repeated imaging is suggested to reclassify the response as either true progression or pseudoprogression.

The 3 imaging patterns that constitute an indeterminate response are as follows: IR1, an increase in the sum of the product of the diameters of up to 6 measurable lesions by at least 50% in the first 12 wk of therapy without clinical deterioration; IR2, new lesions or growth of one or more lesions by at least 50% without overall progression (i.e., <50% increase in sum of the product of the diameters of up to 6 lesions at any time during treatment); and IR3, an increase in $^{18}$F-FDG uptake by one or more lesions without a concomitant increase in lesion size meeting the criteria for progression as described above.

A recent publication reported the imaging response in 16 patients treated with nivolumab or pembrolizumab for relapsed HL (*30*). All 9 patients with an objective response (complete or partial) had responded 3 mo into treatment on PET scanning. No cases of pseudoprogression were observed at that time. Three patients with persistent $^{18}$F-FDG uptake underwent biopsy, all of which showed HL. Seven patients had indeterminate responses during treatment, 5 of whom had progressive disease confirmed at the next imaging assessment during the first 6 mo of treatment. Two patients showed indeterminate responses more than 12 mo after treatment, with a transient rise and then fall in SUV (one also had an increase in the sum of the product of the diameters), but in both cases the lesions subsequently progressed. Three patients had immune reactions demonstrated on PET, including colitis, pneumonitis, and pancreatitis. Responders had a significant decrease in the sum of the product of the diameters and metabolism ($SUV_{max}$, $SUV_{mean}$, metabolic tumor volume, and tumor lesion glycolysis) and an increase in splenic $SUV_{max}$ (possibly indicating a favorable immune response) compared with nonresponders at 3 mo. The mean DS at 3 mo did not predict the best overall response. This could indicate that patients with persistent $^{18}$F-FDG uptake early in treatment may still derive benefit or that there were simply too few patients to show an effect. On a lesional basis, the 5-point scale was highly predictive of the outcome of individual HL lesions.

These are very preliminary data but suggest that the incidence of pseudoprogression may be lower in patients with lymphoma than in patients with solid tumors, but the use of the LYRIC criteria to monitor response will inform our knowledge of imaging assessment with immunomodulatory agents.

**TABLE 2**
Published and Presented Studies with PET-Adapted Therapy in NHL

| Study | Design | Patient population | *n* | PET after | "Positive" equivalent to | PET-negative therapy | PET-positive therapy | Median follow-up | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Duehrsen PETAL 2014 (*17*) | RCT | Aggressive NHL (80% DLBCL) | 853 | 2×R-CHOP | <66% ΔSUV reduction | 4×R-CHOP or 4× R-CHOP+2R | 6×R-CHOP or 6× Burkitt protocol | 33 mo | 2-y TTF: PET-neg 79%; PET-pos 47%; 2R, no difference (HR 1.2, 95% CI 0.8–2.1) |
| | | | | | | | | | Intensification: no difference (HR 1.6, 95% CI 0.9–2.7) |
| Sehn BCCA 2014 (*18*) | Ph II | Advanced-stage DLBCL/PMBCL | 155 | 4×R-CHOP | DS 3–5 | 2×R-CHOP | 4×R-ICE+RT if EOT PET-pos | 45 mo | 4-y PFS: PET-neg 91%; PET-pos 59% |
| | | | | | | | | | 4-y OS: PET-neg 96%; PET-pos 73% |
| Hertzberg ALLG 2017 (*19*) | Ph II | Poor-risk DLBCL | 151 | 4×R-CHOP | DS 3–5 | 2×R-CHOP+2R | 3×R-ICE+Z-BEAM ASCT | 35 mo | 2-y PFS: PET-neg 74%; PET-pos 67% |
| | | | | | | | | | 2-y OS: PET-neg 78%; PET-pos 88% ($P$ = 0.11) |

PETAL = PET-guided therapy of aggressive lymphomas; DLBCL = diffuse large B-cell lymphoma; (R-)CHOP = (rituximab) cyclophosphamide, doxorubicin, vincristine, and prednisone; 2R = 2 cycles rituximab; TTF = time to treatment failure; BCCA = British Columbia Cancer Agency; (R-)ICE = (rituximab) ifosfamide, carboplatin, etoposide; EOT = end of treatment; ALLG = Australasian Leukaemia Lymphoma Study Group; Z-BEAM = ibritumomab tiuxetan, carmustine, etoposide, cytarabine, and melphalan; ASCT = autologous stem cell transplantation; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

## CONCLUSION

Standardization of PET acquisition and reporting in lymphoma has been key to generating robust evidence, such that PET-directed treatment has become a reality. In HL, PET-directed personalized approaches have improved patient outcomes using less chemotherapy and more selective radiotherapy. Baseline factors and treatment type influence the predictive value of PET2, and a combined risk- and response-adapted approach may improve outcomes further. In diffuse large B-cell lymphoma, PET predicts response, but interventions to escalate therapy are of limited efficacy. Preliminary data suggest PET might be used to omit consolidation radiotherapy in patients with bulky disease, and this strategy is also being tested in primary mediastinal B-cell lymphoma. In follicular lymphoma, PET may be able to guide more intensive treatment for patients with poorly responding disease and to select maintenance antibody therapy, but prospective trials are needed.

## DISCLOSURE

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