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FDG PET-CT in lymphoma:

Has imaging-directed personalized medicine become a reality?

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Running title: Personalized lymphoma therapy using PET

Keywords: positron emission tomography, lymphoma, precision medicine

Noteworthy

- Standardisation of PET methods has been key to generating robust clinical trial data to support response-adapted treatment. (p3)
- PET directed personalized approaches have improved outcomes for patients with Hodgkin lymphoma, using less chemotherapy and more selective radiotherapy. (p4-7)
- 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. (p7)
- 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 (p7)
- PET predicts outcome in patients with follicular lymphoma treated with rituximab and chemotherapy, warranting prospective trials to test response-adapted approaches (p8)

ABSTRACT

Positron emission tomography with computed tomography (PET-CT) using 18F- fluorodeoxyglucose (FDG) is an essential part of the management of patients with lymphoma. Efforts to standardize PET acquisition and reporting, including the five-point 'Deauville scale', have enabled PET to become a surrogate for treatment success/failure in common lymphoma subtypes. This review summarizes the key evidence from clinical trials 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 NHL have however proved ineffective in patients treated with rituximab and chemotherapy. Trials are underway to determine whether PET can obviate the need for 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.

INTRODUCTION

PET-CT has become integral to the management of patients with FDG-avid lymphomas, enhancing staging and response assessment available with CT *(1)*. Better disease characterisation has also allowed smaller radiotherapy treatment 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 to de-escalate therapy for good responders using PET-CT, whilst intensifying treatment for the minority who respond less well. In the aggressive B-cell non-Hodgkin lymphomas (NHL), patients affected tend to be older, with low chances of cure if initial therapy is unsuccessful. In NHL, the focus has generally been whether PET-CT can guide treatment escalation in poor responders to improve remission rates, although the potential to reduce mediastinal radiotherapy (RT) 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/failure. The 'Deauville criteria', a five-point scale, developed during these trials, has high interobserver agreement, particularly using the liver threshold *(1)*. In earlier trials, investigators were concerned to minimise the risk of under-treatment of good prognosis disease and Deauville scores (DS) 1 and 2 (≤ normal mediastinal uptake) were used to de-escalate treatment *(4)*. In other trials, where

concern was more about over-treating patients and as camera sensitivity has improved, scores 1-3 (≤ normal liver uptake) have increasingly been used for complete metabolic response (CMR). PET methods established in the trials are now recommended for best clinical practice *(3)*. Advancements such as scan reconstruction using resolution recovery, mean reporting thresholds may change, but will require proper validation to avoid over-treating patients.

Hodgkin Lymphoma (Table 1)

De-escalation Strategies.

Early stage HL has been routinely treated with 2-4 cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy and 20-30 Gy involved field radiotherapy. Two trials tested whether RT could be omitted in patients with a negative PET-CT, during ABVD treatment. The PET-directed therapy for early-stage Hodgkin's lymphoma 'RAPID' trial and the H10 trial used the mediastinal threshold, (DS 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-year progression free survival (PFS) was 97.1% for patients receiving involved field radiotherapy vs. 90.8% for no further treatment in a per-protocol analysis [HR= 2.36; 1.13,4.95, p = 0.02]. Similar results were reported in the H10 trial, where patients received 4-6 cycles of ABVD alone for favorable or unfavorable disease respectively, if randomized to a PET-driven treatment schema and in CMR after 2 ABVD, or standard therapy with 3-4 cycles of ABVD then involved-node radiotherapy *(6)*. Five-year PFS was 99.0% (favourable) and 92.1% (unfavorable) with standard therapy vs. 87.1% (favorable) and 89.6% (unfavorable) for patients having chemotherapy alone [HR = 15.8; (3.79-66.0) (favorable) and HR = 1.45 (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 upon overall survival 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 > 2.5cm. The adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma trial 'RATHL' tested whether, after 2 months of ABVD, patients with CMR based on a DS 1-3, could omit bleomycin (B) in cycles 3-6, continuing either ABVD or AVD and not routinely undergoing radiotherapy *(7)*. 3y-PFS was equivalent at 85.7% for ABVD vs. 84.4% for AVD [HR 1.13; -0.81, +1.57, p=0.48], but AVD was associated with significantly less fatigue, febrile neutropenia, dyspnoea and respiratory events. 3-y 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 of 20%. 3y overall survival (OS) however was good in both arms, at 97.2% vs. 97.6% and radiotherapy was used in only 2-4% of patients with negative PET2. Evidence is emerging that baseline metabolic tumour burden may improve response prediction and combining PET with non-imaging 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)*.

The German Hodgkin study group HD15 trial used a PET-directed approach to determine whether patients required consolidation radiotherapy after the much more intensive BEACOPPesc *(10)*. 75% of patients had PET CMR using the mediastinal threshold (equivalent to DS 2) at the end-of-treatment and for these patients, radiotherapy was omitted. 4y-PFS was 92.6% for patients with a PET CMR, with no difference observed between patients with a complete radiological response and patients

with a residual mass. Overall 11% of patients received radiotherapy compared with 71% in an earlier trial.

An option to start therapy with BEACOPPesc and de-escalate to ABVD for patients with PET-CMR is being explored by the French-Belgian Lymphoma Study Association *(11)*. Interim results reported 2y-PFS of 94% for patients in the standard arm who received 6 cycles of BEACOPPesc vs. 92% in the experimental arm, where patients with CMR are randomised 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 scan in early stage (≥ mediastinum) and advanced stage (≥ liver) respectively *(6-7)*. Only H10 randomised patients to ABVD or BEACOPPesc, whereas in 'RATHL' all patients with positive PET2 received BEACOPPesc . 19% of early stage patients (DS 3,4,5) and 16% of advanced stage patients (DS 4,5) had PET2 positive scans, potentially sparing more than 80% of patients treatment with BEACOPP with its worse side-effect profile. In H10, 5y-PFS was 90.6% for patients receiving BEACOPPesc and involved-node radiotherapy vs. 77.4% for patients receiving ABVD and involved-node radiotherapy after a positive PET2 scan [HR 0.42; 0.23,0.74, p=0.002]. A trend for improved OS was also observed, with 5y-OS of 96.0% vs. 89.3% [HR 0.42; 0.19, 1.07, p = 0.062]. The 'RATHL' trial reported 3y-PFS of 65.7% and 5y-OS of 85.1% for advanced HL patients receiving escalated treatment, a result confirmed in other large prospective trials (*12,13*), compared to earlier reports of 2-3y PFS of 13-28% for patients continuing ABVD after a positive PET2 (*14,15*). Only 12% of patients with a PET2-positive scan received consolidation radiotherapy.

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

The German Hodgkin study group recently reported 3y-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 3y-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. 34% of patients received consolidation radiotherapy, based on an end-of-treatment scan.

Taken together, the trials suggest that the negative predictive value of PET2 is influenced by disease severity at presentation and intensity of treatment given in the first 2 months. This paves the way for risk-adapted initial therapy combined with a PET2 response-adapted strategy to enable de-escalation of chemotherapy and omission of radiotherapy for those with the highest chance of cure.

Non-Hodgkin Lymphoma (Table 2)

Diffuse large B-cell lymphoma is the most common aggressive NHL and is treated with 6-8 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) or 3-4 cycles and radiotherapy for early stage non-bulky disease. Strategies to intensify treatment have mostly failed to improve PFS, despite interim PET predicting prognosis in a large randomised and a phase II study *(17,18)*. A single phase II study reported similar PFS and OS for patients with PET negative scans after 4 cycles of R-CHOP to patients with PET positive scans, who received salvage treatment, Zevalin and ASCT *(19)*. Recent data have suggested a potential for de-escalation in diffuse large B-cell lymphoma. In the

improvement of therapy of elderly patients with CD20+ diffuse large B Cell lymphoma using rituximab optimized and liposomal vincristine 'OPTIMAL' study, patients over 60 years with bulky disease who did not receive consolidation radiotherapy after R-CHOP on the basis of PET-CMR (DS1-3) were not disadvantaged compared to 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 which affects younger patients, is more common in females and usually has an excellent prognosis. The negative predictive value of PET-CMR (DS1-3) after chemoimmunotherapy was 99% for 125 patients subsequently treated with consolidation radiotherapy in a prospective study *(21).* A study is currently randomizing patients with PET-CMR after chemoimmunotherapy to receive radiotherapy or no further treatment (https://clinicaltrials.gov/ct2/show/NCT0159955). Another phase II study reported 93% 5y-event-free-survival and 100% OS using infusional dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone and rituximab (DA-R-EPOCH) with only 2/51 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 radiotherapy treatment for 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 three prospective studies, 17% of patients had a positive PET at end-of-induction treatment (DS 4,5) with 4y-PFS of 23.2% vs. 63.4% for patients with CMR [HR 3.9; 2.5,5.9, $p<0.0001$] suggesting PET-CT could help determine patients who will benefit from treatment escalation and/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/refactory Hodgkin lymphoma 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 in both HL and NHL. These agents modulate the interaction between tumours and the immune system. The checkpoint inhibitors, ipilimumab and nivolumab have been reported to show delayed responses and 'flare' responses in solid tumours. Flare responses include an increase in tumor size and appearance of new lesions, suggestive of progressive disease but which later resolve or remain 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 response and 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 (IR) category. In the case of indeterminate response, biopsy or repeat imaging is suggested to re-classify indeterminate response as either true progression or pseudoprogression. The 3 imaging patterns that constitute indeterminate response are as follows:

1R1 - increase in the sum of the product of the diameters (SPD) of up to 6 measurable lesions by ≥ 50% in the first 12 weeks of therapy without clinical deterioration.

IR2 - new lesions or growth of one or more lesion(s) by ≥ 50% without overall progression ie < 50% increase in SPD of up to 6 lesions at any time during treatment.

IR3 - increase in FDG uptake of one or more lesions without a concomitant increase in lesion size meeting criteria for progression as described above.

A recent publication reported imaging response in 16 patients treated with nivolumab or pembrolizumab for relapsed Hodgkin Lymphoma (*30*). All nine patients with an objective response (CR or PR) had responded 3 months into treatment on PET scanning . No cases of pseudoprogression were observed at that time. Three patients with persistent FDG uptake had biopsies all of which showed Hodgkin lymphoma. Seven patients had indeterminate responses during treatment, 5 of whom had progressive disease confirmed at the next imaging assessment during the first 6 months of treatment. Two patients showed indeterminate responses more than 12 months after treatment with a transient rise then fall in SUV (one also had an increase in SPD) 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 SPD and metabolism (SUVmax, SUVmean, metabolic tumor volume and tumor lesion glycolysis) and increase in splenic SUVmax (possibly indicating a favourable immune response) compared to non-responders at 3 months. The mean Deauville score at 3 months did not predict best overall response. This could indicate that patients with persistent 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 five point scale was highly predictive of the outcome of individual Hodgkin lymphoma lesions.

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

CONCLUSION

Standardisation 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 personalised 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/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 in the selection of maintenance antibody therapy, but prospective trials are needed.

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TABLES

Table 1 . Published studies with PET adapted therapy in HL

Author Study	Design	Patient population	N	PET after	'Positive' equivalent to	PET negative therapy	PET positive therapy	Median FU	Outcome
Radford RAPID 2015 (*5*)	RCT	Stage IA-IIA non-bulky	571	3x ABVD	DS 3-5	IFRT or NFT	1xABVD + IFRT	60 mo	3-yr 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-yr OS PET neg IFRT 97.1% vs NFT 99.0% 3-yr PFS PET pos 87.6%
Andre H10 2017 (*6*)	RCT	Stage I-II supra-diaphragmatic	1925	2x ABVD	DS 3-5	Favorable: 1xABVD+INRT or 2x ABVD Unfavorable: 2xABVD+INRT or 4x ABVD	Favorable: 1xABVD+INRT or 2x BEACOPP-esc+ INRT Unfavorable: 2xABVD+INRT or 2x BEACOPP-esc + INRT	4.5 yr	5-yr PFS PET neg Favourable INRT 99% vs NFT 87.1%. Unfavourable INRT 92.1% vs NFT 89.6% 5-yr OS PET neg Favourable INRT 96.7% vs NFT 98.3%. Unfavourable INRT: 92.1% vs NFT 89.6% 5-yr PFS PET pos ABVD+INRT 77.4% vs BEACOPPesc+INRT 90.6% 5-yr OS PET pos ABVD+INRT 89.3% vs BEACOPPesc+INRT 96.0%.
Johnson RATHL	RCT	Stage IIB + adverse	1119	2x ABVD	DS 4,5	4xABVD or 4xAVD	BEACOPP-14 or BEACOPP-	41 mo	3-yr PFS PET neg ABVD 85.7% vs AVD 84.4%

2016 (*7*)		features, III-IV					esc		<u>3-yr OS PET neg</u> ABVD 97.2%; AVD: 97.6% <u>3-yr PFS PET pos</u> BEACOPP 67.5% <u>3-yr OS PET pos</u> PET pos: 87.8%
Engert HD15 PET substudy 2012 (*10*)	RCT	Stage IIB + adverse features, III-IV with PR & >2.5cm residual mass	1578	6x or 8xBEACOPPesc or 8xBEACOPP14	DS 3-5	NFT	RT		<u>4-yr PFS</u> PET neg 92.6% PET pos 86.2%
Press S0816 2016(*13*)	Ph II	Stage III-IV	336	2x ABVD	DS 4,5	4x ABVD	6x BEACOPP-esc	39.7 mo	<u>2-yr PFS</u> PET neg 81% PET pos 64% 2-yr OS: 98%
Zinzani HD0801 PET2 pos pts 2016 (*12*)	Ph II	Stage IIB-IV	103	2X ABVD	DS 3-5	NA	4xIGEV + BEAM ASCT or melphalan allograft	27 mo	<u>2-yr PFS PET2 pos</u> 81% (PET4neg) 76% (PET4pos) 2-yr OS: 97%
Borchmann HD18 PET2 pos pts 2017 (*16*)	RCT	Age 18-60 Stage IIB + adverse features, III-IV	440	2x BEACOPPesc	DS 3-5	NA	6xBEACOPPesc or R-6BEACOPPesc	33 mo	<u>3-yr PFS PET2pos</u> BEACOPPesc 91.4% vs R-BEACOPPesc 93.0% <u>3-yr OS PET2 pos</u> BEACOPPesc 96.5% vs R-BEACOPPesc 94.4%

Abbreviations; HL: *Hodgkin lymphoma*, N: *number*, PET: *positron emission tomography*, FU: *follow-up*, RCT: *randomized clinical trial*, ph II: *prospective phase II study*, ABVD: *doxorubicin, bleomycin, vinblastine, dacarbazine*, DS: *Deauville score*, IFRT: *involved field radiotherapy*, NFT: *no further treatment*, mo: *months*, yr: *years,* PFS: *progression free survival*, OS: *overall survival*, neg*: negative,* pos*: positive,* INRT: *involved node radiotherapy*, AVD: *doxorubicin, vinblastine and dacarbazine*, BEACOPP: *bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone*. Esc: *escalated,* RT: *radiotherapy*, IGEV: *ifosfamide, gemcitabine and vinorelbine*, BEAM: *carmustine, etoposide, cytarabine, melphalan*, ASCT: *autologous stem cell transplantation*

Table 2 . Published and presented studies with PET adapted therapy in NHL

Author Study	Design	Patient population	N	PET after	'Positive' equivalent to	PET negative therapy	PET positive therapy	Median FU	Outcome
Duehrsen PETAL 2014 (*17*)	RCT	aggressive NHL (80% DLBCL)	853	2x R-CHOP	<66% ΔSUV reduction	4x R-CHOP or 4xR-CHOP+2R	6x R-CHOP or 6x 'Burkitt protocol'	33 mo	2-yr TTF PET neg 79% PET pos 47% 2 R: 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	4x R-CHOP	DS 3-5	2xR-CHOP	4x R-ICE +RT if EOT PET pos	45 mo	4-yr PFS PET neg 91% PET pos 59% 4-yr OS PET neg 96% PET pos 73%
Hertzberg ALLG 2017 (*19*)	ph II	poor risk DLBCL	151	4x R-CHOP	DS 3-5	2x R-CHOP +2R	3x R-ICE + Z-BEAM ASCT	35 mo	2-yr PFS PET neg 74% PET pos 67% 2-yr OS PET neg 78% PET pos 88% (p =0.11)

Abbreviations (as table 1) and NHL: *Non-Hodgkin Lymphoma,* PETAL: *Positron Emission Tomography (PET) guided therapy of aggressive lymphomas,* DLBCL: *diffuse large B-cell lymphoma*, (R-)CHOP: *(rituximab,) cyclophosphamide, doxorubicin, vincristine, prednisone* SUV: *standardized uptake value*, 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, melphalan*,.