

Received:
22 November 2015Revised:
1 March 2016Accepted:
3 March 2016<http://dx.doi.org/10.1259/bjr.20150983>

Cite this article as:

Ciammella P, Filippi AR, Simontacchi G, Buglione M, Botto B, Mangoni M, et al. Post-ABVD/pre-radiotherapy ¹⁸F-FDG-PET provides additional prognostic information for early-stage Hodgkin lymphoma: a retrospective analysis on 165 patients. *Br J Radiol* 2016; **89**: 20150983.

FULL PAPER

Post-ABVD/pre-radiotherapy ¹⁸F-FDG-PET provides additional prognostic information for early-stage Hodgkin lymphoma: a retrospective analysis on 165 patients

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Objective: To evaluate the prognostic role of both interim fluorine-18 fludeoxyglucose positron emission tomography (¹⁸F-FDG-PET) and end-of-chemotherapy fluorine-18 fludeoxyglucose positron emission tomography (eoc-¹⁸F-FDG-PET) in patients with early-stage Hodgkin lymphoma (HL).

Methods: We screened 257 patients with early-stage HL treated with combined modality therapy between March 2003 and July 2011. All were staged using fluorine-18 fludeoxyglucose positron emission tomography (¹⁸F-FDG-PET) before chemotherapy and after two doxorubicin, bleomycin, vinblastine and dacarbazine cycles (i-¹⁸F-FDG-PET); 165 patients were also evaluated by ¹⁸F-FDG-PET at the end of chemotherapy (eoc-¹⁸F-FDG-PET).

Results: After revision, 85% of patients were negative for i-¹⁸F-FDG-PET and 15% were positive. After eoc-¹⁸F-FDG-PET revision, 23 patients had a positive scan. The median follow-up was 56 months. The 5-year overall survival (OS) and progression-free survival (PFS) for the whole cohort were 97.5% and 95.6%, respectively. For i-¹⁸F-FDG-PET-negative and i-¹⁸F-FDG-PET-positive patients, the 5-year PFS rates were 98% and 84%, respectively; for

eoc-¹⁸F-FDG-PET-negative and eoc-¹⁸F-FDG-PET-positive patients, the 5-year PFS rates were 97% and 78%, respectively. Combining the i-¹⁸F-FDG-PET and eoc-¹⁸F-FDG-PET results, the 5-year PFS were 97%, 100% and 82% in negative/negative, positive/negative and positive/positive groups, respectively. The 5-year OS rates were 98% and 83% in eoc-¹⁸F-FDG-PET-negative and eoc-¹⁸F-FDG-PET-positive patients, respectively; the 5-year OS was 98%, 100% and 83% in negative/negative, positive/negative and positive/positive groups, respectively.

Conclusion: This study provides additional information on the prognostic role of i-¹⁸F-FDG-PET and eoc-¹⁸F-FDG-PET in early-stage HL. As data are accumulating and the clinical scenario is rapidly evolving, we might need to rethink the use of ¹⁸F-FDG-PET as a prognostic marker for early-stage HL in the near future.

Advances in knowledge: This study provides additional information on the prognostic role of i-¹⁸F-FDG-PET and eoc-¹⁸F-FDG-PET in early-stage HL. On the basis of the present data, we may suggest to use eoc-¹⁸F-FDG-PET as a strong prognostic marker, especially for patients with i-¹⁸F-FDG-PET positivity.

INTRODUCTION

The combination of brief chemotherapy and radiotherapy (RT) has shown excellent results in early-stage Hodgkin lymphoma (HL), with cure rates >90%.¹ As the risk of late treatment-related toxicity is still a matter of debate, over the past two decades, a great effort has been made to tailor

treatment strategies on the basis of prognostic factors. Studies on advanced stages of HL showed that early interim fluorine-18 fludeoxyglucose positron emission tomography (i-¹⁸F-FDG-PET) is the most powerful tool to predict clinical outcome.^{2–4} Recent retrospective data suggest that i-¹⁸F-FDG-PET is prognostic also for patients with early-stage

HL undergoing combined modality therapy.^{5–8} In two large co-operative positron emission tomography (PET)-response-adapted prospective trials,^{9,10} i - ^{18}F -FDG-PET negative-predictive value reached 90%. Although the evidence in favour of the use of i - ^{18}F -FDG-PET in early stages is increasing, the role of fluorine-18 fludeoxyglucose positron emission tomography (^{18}F -FDG-PET) at the end of chemotherapy (eoc) before RT [*i.e.* after four doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) cycles in most cases] has been poorly investigated. Preliminary studies on eoc- ^{18}F -FDG-PET reported a negative-predictive value for 2-year progression-free survival (PFS) of 94–100% for patients who received ABVD,^{11,12} with a positive-predictive value of 91–92%. Interestingly, Barnes et al¹² in retrospective series of 96 patients found no difference in PFS according to i - ^{18}F -FDG-PET, whereas eoc- ^{18}F -FDG-PET resulted a strong prognostic factor. The ability of both i - ^{18}F -FDG-PET and eoc- ^{18}F -FDG-PET to predict prognosis is, however, influenced by multiple factors, including (a) timing in relation to chemotherapy, (b) image interpretation, (c) disease stage, (d) bulky disease, (e) chemotherapy scheme and (f) radiation therapy administration. In order to reduce the risk of misinterpretation, the 2007 International Harmonization Project criteria, the 5-point Deauville criteria, the Lugano classification and the 2015 recommendations of the International Conference on Malignant Lymphoma imaging and clinical working groups reset the rules for response evaluation.^{13–15} The interpretation key proposed by International Conference on Malignant Lymphoma for both interim and end-of-treatment PET is the Deauville 5-point scale, using the classic visual assessment.^{15,16} A previous collaborative study was able to show that the majority of patients with a positive i - ^{18}F -FDG-PET after two ABVD cycles (Deauville scores 4–5) can still be cured by the continuation of chemotherapy followed by radiation.⁶

The aim of the present study was to analyse a group of patients with early-stage HL treated with combined modality that had both i - ^{18}F -FDG-PET and eoc- ^{18}F -FDG-PET information, allowing for a comparison of outcomes and prognostic role.

METHODS AND MATERIALS

In this multicentre retrospective study, we reviewed medical records of patients affected with early-stage HL diagnosed between March 2003 and July 2011, all treated with combined modality therapy in four haematology/radiation oncology departments. Full outcome data and i - ^{18}F -FDG-PET results of this population were already reported.⁶ For the present report, we retrieved patients who had both i - ^{18}F -FDG-PET (after two cycles, immediately before the third cycle) and eoc- ^{18}F -FDG-PET scans. All patients had biopsy-proven early-stage HL, classified as favourable and unfavourable according to the European Organisation for Research and Treatment of Cancer (EORTC) criteria, and were treated with an intention-to-treat chemotherapy programme, with 3–4 cycles of ABVD followed by involved field RT. All patients started chemotherapy with ABVD; the number of cycles and any subsequent chemotherapy modification, after both i - ^{18}F -FDG-PET and eoc- ^{18}F -FDG-PET, were at the discretion of the treating physicians; all patients received

consolidation RT limited to the initial sites of disease presentation; and the radiation dose ranged between 20 and 40 Gy delivered in 1.8 or 2 Gy daily fractions, at the discretion of the treating radiation oncologist. Bulky disease was defined

Table 1. Baseline demographic and clinical characteristics

Characteristics	<i>n</i>	%
Total number	165	100
Age (years) (median)	31 (19–67)	
Gender		
Male	72	44
Female	93	56
Ann Arbor Stage		
I	2	1
II	163	99
“B” symptoms		
Yes	34	21
No	131	79
Bulky		
Yes	69	42
No	96	58
Number of sites		
0–3	113	68
≥4	52	32
Favourable	49	30
Unfavourable	116	70
Chemotherapy		
ABVD	161	97
Other	4	3
Number of cycles		
3	16	10
4	127	77
5	3	2
6	19	11
Interim PET		
Positive	25	15
Negative	140	80
End-of-chemotherapy PET		
Positive	23	14
Negative	142	86
RT dose (Gy)		
≤30.6	123	75
>30.6	42	25

ABVD, adriamycin, bleomycin, vinblastine and dacarbazine; PET, positron emission tomography; RT, radiotherapy.

according to the European Organisation for Research and Treatment of Cancer criteria. All ^{18}F -FDG-PET scans (i- ^{18}F -FDG-PET and eoc- ^{18}F -FDG-PET) were reviewed by local nuclear medicine physicians, blinded for clinical outcome, and independently re-interpreted according to the Deauville 5-point scoring system. Positive scans (PET+) were defined by a Deauville score ≥ 4 (i.e. uptake moderately more than liver uptake). The institutional review boards approved the study.

Statistical considerations

Categorical variables were reported as absolute and percentage frequency. To verify a change between the paired-data, i- ^{18}F -FDG-PET and final ^{18}F -FDG-PET, the McNemar test was used. The ability to predict the final ^{18}F -FDG-PET status from i- ^{18}F -FDG-PET was expressed as sensitivity (true-positive rate, proportion of final PET positive correctly identified from positive interim PET) and specificity (true-negative rate, proportion of negative final PET correctly identified from negative interim PET). PFS was defined at the time from the date of diagnosis to the date of last observation, progression, relapse or death from any cause. Overall survival (OS) was defined from the date of diagnosis to the date of last follow-up or death from any cause. Survival estimates were calculated using the Kaplan–Meier method, and the log-rank test was used to compare survival between different cohorts. Cox proportional hazard regression model was used to perform univariate and multivariate analyses. The effect of covariates was reported as hazard ratio (HR), with confidence interval at 95% (95% CI).

RESULTS

eoc- ^{18}F -FDG-PET and i- ^{18}F -FDG-PET information were available for 165 out of 257 screened patients. Pre-treatment and treatment characteristics of the whole cohort are described in detail in Table 1. After revision, 140 patients were i- ^{18}F -FDG-PET negative (Deauville scores 1–3), and 25 were i- ^{18}F -FDG-PET positive (Deauville scores 4–5). Among patients with a negative i- ^{18}F -FDG-PET scan, 138 continued with ABVD chemotherapy (4 total cycles) and only 2 patients received different chemotherapy regimens. Among positive patients, 3 were shifted to other chemotherapy regimens (DHAP, BEACOPP and

MINE) plus RT, whereas 22 continued with ABVD and RT. After eoc- ^{18}F -FDG-PET revision, 23 patients had a positive scan (19 were also positive at i- ^{18}F -FDG-PET and 4 changed from negative to positive). Table 2 describes the concordance between i- ^{18}F -FDG-PET and eoc- ^{18}F -FDG-PET. Four patients turned out to be positive while being negative at interim scan, three with a Deauville score of 4 and one with a Deauville score of 5. Figure 1 describes in detail ^{18}F -FDG-PET results and treatments received for the whole cohort.

Patients were treated with a large RT dose spectrum. 42/165 (25.4%) patients received a total dose of ≥ 36 Gy and the remaining 123 (74.6%) received a total dose of < 36 Gy. In the eoc-PET-positive group, 18 patients (18/23, 78%) received ≥ 36 Gy, while the remaining 5 patients received 30 Gy; all 3 relapsed patients received a total dose of ≥ 36 Gy.

After a median follow-up of 56 months (range 9–163 months), 158 patients were alive without evidence of disease, 1 alive with disease and 6 dead (4 due to disease and 2 due to other causes). Three out of four lymphoma-related deaths occurred in eoc- ^{18}F -FDG-PET-positive patients. Among the eoc- ^{18}F -FDG-PET-negative patients, three relapses occurred: one died of progressive disease and two obtained a second complete remission after salvage high-dose chemotherapy and autologous transplantation. The 5-year OS and disease-specific survival rate was 97.5% and 98.3%, respectively; 7 out of 165 (4.2%) patients had disease relapse/progression and the 5-year PFS for the whole cohort was 95.6%.

For i- ^{18}F -FDG-PET-negative and i- ^{18}F -FDG-PET-positive patients, the 5-year PFS rates were 98% and 84%, respectively ($p = 0.0014$); for eoc- ^{18}F -FDG-PET-negative and eoc- ^{18}F -FDG-PET-positive patients, the 5-year PFS rates were 97% and 78%, respectively ($p < 0.0001$). Combining interim and eoc results, the 5-year PFS rate was 97%, 100% and 82% in negative/negative, positive/negative and positive/positive groups, respectively ($p < 0.0001$). The 5-years OS rates were 98% and 83% in eoc- ^{18}F -FDG-PET negative and positive patients ($p = 0.0001$), respectively; 5-years OS was 98%, 100% and 83% in negative/negative, positive/negative and positive/positive groups, respectively ($p < 0.00001$). The Kaplan–Meier graphs displaying these findings are shown in Figures 1 and 2.

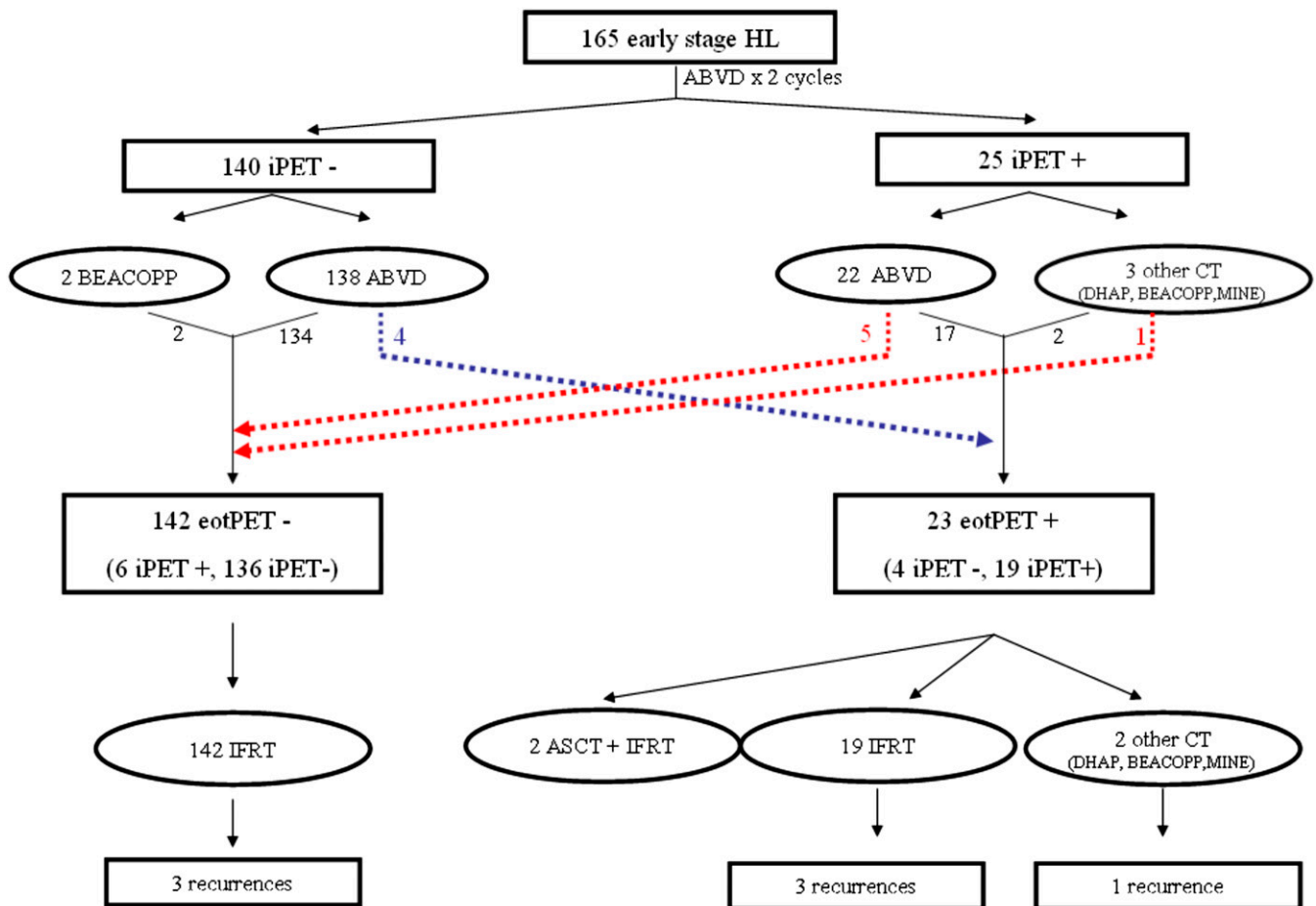
69 patients (69/165, 42%) had bulky disease at presentation; 58/69 (84%) were i- ^{18}F -FDG-PET negative (Deauville scores 1–3) and 11/69 (16%) were i- ^{18}F -FDG-PET positive (Deauville scores 4–5). After eoc- ^{18}F -FDG-PET revision, 10 patients were positive at scan (9 were also positive at i- ^{18}F -FDG-PET and 1 changed from negative to positive). In 3 out of 69 (4%) patients, the eoc- ^{18}F -FDG-PET result was changed and in 66/69 (96%) was unchanged. The correlation between i- ^{18}F -FDG-PET and eoc- ^{18}F -FDG-PET in bulky disease was 0.83 (Spearman's test of correlation $p < 0.0001$). Among patients with bulky disease, 5-year disease-free survival (DFS) and OS were 98% (95% CI 88–100%) and 60% (95% CI 25–83%) ($p < 0.0001$), and 98% (95% CI 88–100%) and 70% (95% CI 33–89%) ($p = 0.0002$) for eoc- ^{18}F -PET-negative and eoc- ^{18}F -PET-positive patients, respectively (Figure 3).

Table 2. Distribution of interim fluorine-18 fludeoxyglucose positron emission tomography (i- ^{18}F -FDG-PET) and end-of-chemotherapy fluorine-18 fludeoxyglucose positron emission tomography (eoc- ^{18}F -FDG-PET) results

i- ^{18}F -FDG-PET	eoc- ^{18}F -FDG-PET, n (%)		Total
	Negative (–)	Positive (+)	
Negative (–)	136 (96)	4 (17)	140 (85)
Positive (+)	6 (4)	19 (83)	25 (15)
Total	142	23	165

Spearman test of correlation: 0.76 ($p < 0.0001$). 4/140 (2.8%) change from i- ^{18}F -FDG-PET negative to eoc- ^{18}F -FDG-PET positive; 6/25 (24%) change from i- ^{18}F -FDG-PET positive to eoc- ^{18}F -FDG-PET negative; 155/165 (94%) unchanged. McNemar's exact test, $p = 0.754$. Sensitivity, 83%; specificity, 96%; receiver-operating characteristic area, 89%; positive-predictive value, 76%; negative-predictive value, 97%.

Figure 1. Treatment details and outcomes according to both interim fluorine-18 fludeoxyglucose positron emission tomography and end-of-chemotherapy fluorine-18 fludeoxyglucose positron emission tomography. ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; ASCT, autologous stem cell transplantation; eotPET, positron emission tomography response at the end of treatment; HL, Hodgkin lymphoma; IFRT, involved fields radiotherapy; iPET, positron emission tomography response at interim.



At univariate analysis, B symptoms ($p = 0.035$), positive $i\text{-}^{18}\text{F}$ -FDG-PET ($p = 0.014$) and positive $eoc\text{-}^{18}\text{F}$ -FDG-PET ($p = 0.0001$) resulted being associated with a worse OS; the same factors were associated with worse PFS (B symptoms $p = 0.0114$; positive $i\text{-}^{18}\text{F}$ -FDG-PET $p < 0.0001$; $eoc\text{-}^{18}\text{F}$ -FDG-PET $p < 0.0001$). Cox regression analysis adjusted by age, B-symptoms, stage, histology and chemotherapy cycles showed that positive $eoc\text{-}^{18}\text{F}$ -FDG-PET was the only significant predictor of disease recurrence (HR 8.30, 95% CI 1.87–36.9, $p = 0.001$) and worse OS (HR 11.9, 95% CI 2.07–68.2, $p = 0.005$). Comparing $i\text{-}^{18}\text{F}$ -FDG-PET and $eoc\text{-}^{18}\text{F}$ -FDG-PET results in terms of predictive value on PFS, a significant difference was detected, with integrated area under the curve (AUC) of 0.685 and 0.872 for $i\text{-}^{18}\text{F}$ -FDG-PET and $eoc\text{-}^{18}\text{F}$ -FDG-PET, respectively (Wilcoxon test, $p = 0.003$).

DISCUSSION

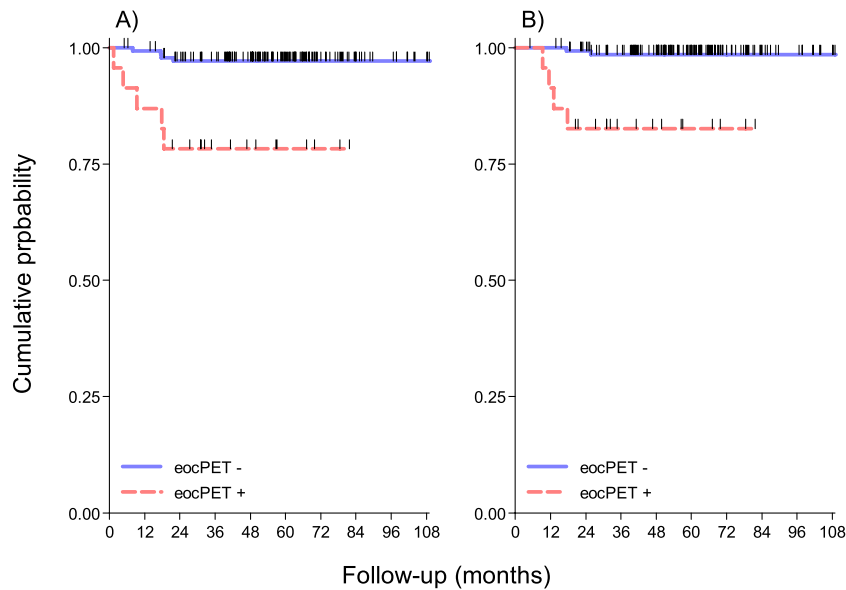
In this observational study, we aimed to explore the potential prognostic value of $eoc\text{-}^{18}\text{F}$ -FDG-PET in addition to early $i\text{-}^{18}\text{F}$ -FDG-PET in a cohort of 165 patients with early-stage HL who were treated with combined modality therapy. Our findings should be interpreted in light of previous observations on the prognostic role of $i\text{-}^{18}\text{F}$ -FDG-PET in early-stage HL.^{5–9} The

retrospective nature, the limited number of events and the absence of a centralized PET review represent the major limitations of our study. However, the use of the Deauville score system limited the interobserver variability in imaging interpretation, and local nuclear medicine physicians performed a blinded review.

Moreover, we here provide novel findings on the combination of metabolic information obtained at different time points. To date, $i\text{-}^{18}\text{F}$ -FDG-PET is frequently used as a prognostic tool in patients treated with ABVD plus RT outside clinical trials. However, the use of this prognostic information is still a matter of debate. In the context of a more conservative strategy, without response adaptation, $eoc\text{-}^{18}\text{F}$ -FDG-PET may provide only additional prognostic information, without any evidence in support of a change in terms of deintensification or intensification at this step.

Some authors¹⁷ questioned the use of both $i\text{-}^{18}\text{F}$ -FDG-PET and $eoc\text{-}^{18}\text{F}$ -FDG-PET in this patient population, as the rate of positivity is low (around 15% among favourable and unfavourable patients together); the number of lymphoma-related

Figure 2. (a) Kaplan-Meier projections of progression-free survival, stratified by end-of-chemotherapy fluorine-18 fludeoxyglucose positron emission tomography (eoc-¹⁸F-FDG-PET) positivity. Log-rank, $p = 0.0001$. (b) Kaplan-Meier projections of overall survival, stratified by eoc-¹⁸F-FDG-PET positivity. Log-rank $p = 0.0001$. eocPET, positron emission tomography response at the end of chemotherapy.

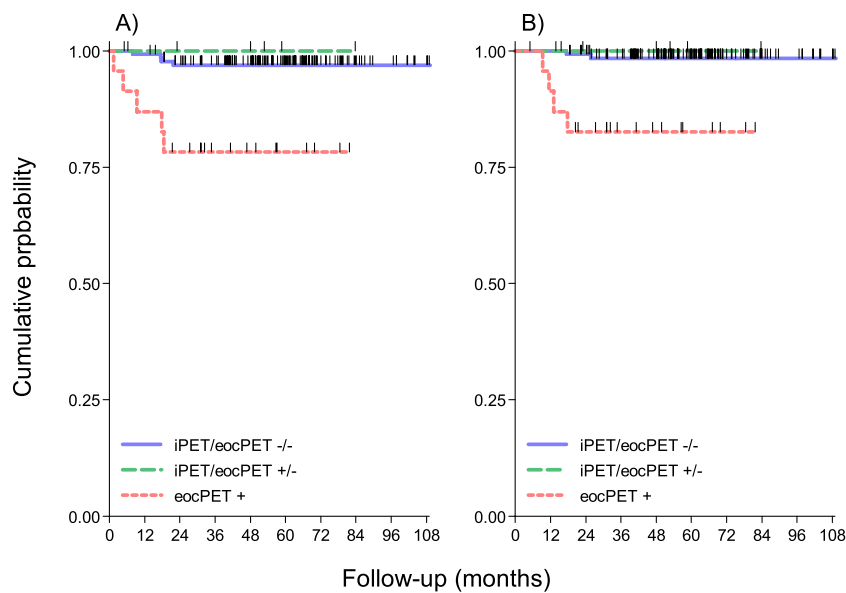


deaths is small; and the use of i-¹⁸F-FDG-PET/eoc-¹⁸F-FDG-PET would only provide a little absolute risk difference between a large group of negative and a very small group of positive patients in terms of OS. However, results of previous studies,⁵⁻⁹ as well as the present analysis, suggest a more complex scenario: ABVD plus RT is able to cure approximately 80% of interim-PET-positive patients, but with an unacceptable rate of disease relapse and mortality for non-responders. eoc-¹⁸F-FDG-PET-positive patients received higher radiation doses, however, the potential impact of RT dose in this setting is unclear, and

unfortunately, we cannot draw any conclusion on this issue from the present data.

Few other investigators also explored the prognostic significance of eoc-¹⁸F-FDG-PET positivity. Sher et al¹¹ analyzed 73 patients with HL treated with ABVD and RT; 13 patients out of the 73 (16%) were eoc-¹⁸F-FDG-PET positive before RT. Nine of these patients (69%) achieved a complete remission after RT, while four (31%) relapsed. Among the PET-negative group (60 patients), 57 (97%) remained in continuous complete remission while 3

Figure 3. (a) Kaplan-Meier projections of progression-free survival, stratified by positron emission tomography (PET) response at interim (iPET) or at the end of chemotherapy (eocPET). Log-rank $p < 0.0001$. (b) Kaplan-Meier projections of overall survival, stratified by fluorine-18 fludeoxyglucose (¹⁸F-FDG)-PET response during and after chemotherapy. Log-rank $p = 0.00005$.



relapsed. All three patients who relapsed despite eoc-¹⁸F-FDG-PET negativity obtained a continuous complete remission with a second line therapy, and only one of four in the PET-positive group, with a consequent inferior OS. We cannot provide data on response to second-line chemotherapy for our cohort, but the failure rate was significantly higher and OS projections were inferior in our study as well.

The latter finding suggests the potential ability of eoc-¹⁸F-FDG-PET to select patients at a worse prognosis among the cohort of i-¹⁸F-FDG-PET positive, with a higher predictive value on PFS of eoc-¹⁸F-FDG-PET as showed by Wilcoxon test with an integrated area under the curve of 0.685 and 0.872 for i-¹⁸F-FDG-PET and eoc-¹⁸F-FDG-PET, respectively ($p = 0.003$). Besides, despite i-¹⁸F-FDG-PET may be an attractive surrogate tool for response, the rate of positive/negative patients (6/25, 24%) raises significant concerns on treatment intensification at this stage. Patients who were converted from positive into negative at the end of treatment experienced similar outcomes as their i-¹⁸F-FDG-PET-negative counterparts. Therefore eoc-¹⁸F-FDG-PET may be beneficial in reducing the proportion of patients receiving intensified treatment on the basis of i-¹⁸F-FDG-PET results, and either as a single measurement or in combination with i-¹⁸F-FDG-PET adds important prognostic information, being the most relevant prognostic factor at Cox regression analysis. The recently presented results of the H10 trial (PET-positive arms) might partially change this scenario. i-¹⁸F-FDG-PET-positive patients who received BEACOPP-esc (escalated cyclophosphamide, doxorubicin, etoposide, procarbazine, prednisone, vincristine, bleomycin) plus RT had clearly superior PFS rates if compared with the continuation of ABVD plus RT (5-year PFS rate of 91% vs 77%; $p = 0.002$).¹⁸ This huge difference in PFS questions the continuation of ABVD plus RT in

favour of an intensified chemotherapy regimen followed by the same RT protocol. One may argue that a proportion of these patients could be overtreated (approximately 15% of the i-¹⁸F-FDG-PET-positive patients, according to the present study), but the expected global PFS is certainly higher. The information obtained by i-¹⁸F-FDG-PET and eoc-¹⁸F-FDG-PET could be therefore useless if the treatment strategy is unlikely to be changed, limiting its indications to patients with unfavourable presentations where early intensification is proposed if positive (as for H10 PET positive). Conversely, if i-¹⁸F-FDG-PET is planned and performed only in order to have prognostic information, the indication for a second eoc-¹⁸F-FDG-PET in the minority of i-¹⁸F-FDG-PET-positive patients (15%) may provide additional knowledge.

In this regard, the integration of new PET-based quantitative methods for measuring tumour burden, as for example total metabolic tumour volume or total lesion glycolysis,¹⁹ as well as other clinical and biological markers, are currently being developed for a better risk stratification and personalized therapy and will probably be used at the time of i-¹⁸F-FDG-PET response evaluation. In conclusion, this retrospective study provides additional information on the prognostic role of i-¹⁸F-FDG-PET and eoc-¹⁸F-FDG-PET in patients with early-stage HL treated with combined modality therapy. On the basis of the present data, we may suggest to use eoc-¹⁸F-FDG-PET as a strong prognostic marker especially for patients with i-¹⁸F-FDG-PET positivity. However, major uncertainties remain on the indication, interpretation criteria and exact role of ¹⁸F-FDG-PET in this setting. As data are accumulating and the clinical scenario is rapidly evolving, we might need to rethink the use of ¹⁸F-FDG-PET as a prognostic marker for early-stage HL in the near future.

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