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ORIGINAL ARTICLE

Interim PET-CT–guided therapy in elderly patients with Hodgkin lymphoma—a retrospective national multi-center study

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Abstract

Hodgkin lymphoma (HL), a disease of mostly young patients, also peaks in the elderly. Despite the profound improvement in the outcome of young patients, in the elderly, 5-year progression-free survival (PFS) rates are under 70%. Interim PET-CT (iPET) is known to be highly predictive for PFS in young HL patients, but it has not been sufficiently validated in the elderly patient population. In this multi-center collaboration, all consecutive elderly patients (age ≥ 60) diagnosed with HL between 1998 and 2016 were retrospectively reviewed. Baseline characteristics, outcome measures, and iPET results, classified according to the Deauville score, were recorded and analyzed. We identified 78 elderly HL patients (median age 69) who underwent iPET. ABVD was the treatment regimen in 52 (67%) patients. Eighty-three percent of patients had iPET scores of 1–3 while 17% had scores of 4–5. Patients with iPET scores of 1–3 had 5-year PFS and OS rates of 72% and 82% compared with 25% and 45%, respectively, in patients with scores of 4–5 ($p < 0.001$). Our findings show that iPET is highly predictive of outcome in elderly HL patients and provide evidence that iPET-guided therapy in this patient population may be key to achieving superior treatment outcome.

Keywords Hodgkin lymphoma · Interim PET-CT · Elderly

Introduction

Hodgkin lymphoma (HL) is most commonly diagnosed in young adults, but has a bimodal age distribution curve, with up to a quarter of cases presenting in patients aged 60 and above [1–3]. The profound improvement in the clinical outcome of young HL patients in the last decades, with long-term failure-free survival rates in excess of 80% [4–7], has only partially extended to elderly patients aged ≥ 60 [8–18].

Positron emission tomography-computed tomography (PET-CT) with 18F-fluorodeoxyglucose (FDG) has gained widespread use and endorsement in the treatment of HL [19–21]. Response-adapted therapy, tailored to the results of interim PET-CT (iPET) that is usually performed after 2 chemotherapy cycles, has emerged as a tool for guiding therapeutic decisions in HL. This tool has been examined extensively in cohorts of young HL patients, where it was shown to be both a predictor of long-term outcome as well as an effective guide for tailoring treatment intensity in the individual patient [22–29]. Yet, the role of iPET has not been validated in cohorts of elderly HL patients, a population in which the potential use of this tool to predict clinical outcome is markedly prominent. Elderly patients with HL have been underrepresented in large prospective trials, with less than 10% of the patients in the German Hodgkin Study Group (GHSG) trials HD5–HD11 [30, 31] being older than 60 years; hence, data regarding the prognostic role of iPET in these patients are scant. Traditional prognostic markers in HL have been

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reported mostly in young patients and even the value of the commonly used International Prognostic Score (IPS) is questionable in elderly patients [18, 32]. Moreover, there is still an ongoing debate regarding the risk-benefit ratio of the various chemotherapy protocols in elderly patients with HL [14, 31, 33–39] as elderly patients suffer from increased rates of treatment-related toxicity [8, 9, 12, 13, 30, 40] and treatment is often administered with only partial dose intensity [10, 41]. Adoption of an iPET-driven therapeutic approach, similar to that employed in young HL patients, may improve outcome in elderly patients. For example, earlier cessation of an ineffective treatment has the potential to reduce treatment-related toxicity and perhaps improve tolerability to subsequent therapy. The objective of the present study was to evaluate the significance of iPET in an elderly HL patient population.

Patients and methods

Study design and patient population

Data from all consecutive newly diagnosed classical HL patients aged 60 and above who were diagnosed and treated in five participating medical centers (Sourasky—Tel Aviv, Rambam, Hadassah—Jerusalem, Assaf Harofe, Ziv) between the years 1998 and 2016 were retrospectively reviewed. Biopsies were classified according to the WHO criteria [42, 43]. The study was approved by the local Institutional Review Boards. The inclusion criteria for this study were patients who had undergone iPET, defined as PET-CT completed after 2–3 treatment cycles and before completion of the planned treatment protocol. According to local treatment protocols in the participating sites, iPET was scheduled after 2 cycles of chemotherapy, 10–14 days after last chemotherapy administration.

Data collection—definitions

Baseline characteristics, treatment protocol, and outcome measures were recorded. PET-CT results at diagnosis, interim analysis (iPET), and end of treatment (EOT) were recorded and analyzed. Response to treatment was evaluated by iPET and EOT-PET-CT scans using the 5-point scale Deauville score (DS), according to the level of residual FDG uptake at involved sites [19, 21]. iPET DSs of 1–3 were considered negative, similar to studies that examined iPET in young HL patients [26, 27]. In cases which were treated before the incorporation of the DS into common practice, the imaging was reviewed locally, and the DS was used to evaluate response. Staging and response to treatment were assessed according to the 2014 Lugano classification [21]. Prognostic groups for early-stage and advanced-stage disease were defined according to the German Hodgkin Study Group (GHSG) [44, 45].

Statistical analysis

Statistical analysis was carried out with SPSS software (Chicago, IL). Demographics and baseline characteristics were summarized using descriptive statistics. *t* tests were used to compare means of normally distributed variables in two groups. Proportions across categories were compared using chi-squared tests. Progression-free survival (PFS) was defined as the time from diagnosis of HL to death or disease relapse/progression, including less than complete remission (CR) at the end of the treatment protocol. Overall survival (OS) was defined as the time from diagnosis of HL to death or last follow-up. The Kaplan-Meier method was used to assess survival patterns; two or more groups were compared using the log-rank test. Univariable associations between clinical/laboratory variables and outcome were derived using the Cox proportional hazards model. Variables with a p value < 0.05 in univariable analyses were entered into the multivariable Cox proportional hazards model in a stepwise fashion.

Results

Baseline characteristics

Ninety-five patients aged 60 and above, who were diagnosed with classical HL, were identified. Of these, 78 (82%) had undergone iPET and were included in the study. Patient characteristics are listed in Table 1. Forty (51%) patients were males and 38 (49%) were females. The median age was 68.7 (range 60–89) years. Forty-two percent of the patients had a clinically significant heart or lung disease.

Staging at diagnosis was performed by PET-CT in 68 (91%) patients and by CT in 7 (9%) patients. Twenty-two (28%) patients presented with early-stage disease (11 favorable, 11 unfavorable) and 56 (72%) patients presented with advanced-stage disease. Only one patient in this study group had a bulky mediastinal mass. The mean IPS for patients with advanced-stage disease was 3.4 ± 1.4.

Histological subtype was nodular sclerosis in 34 (44%) patients, mixed cellularity in 20 (26%) patients, lymphocyte rich in 2 (3%), and not specified in 22 (28%) patients.

Treatment

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) was the most commonly used treatment regimen and was administered to 52 (67%) patients, baseline BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) was administered to 10 (13%) patients, and AVD (doxorubicin, vinblastine, dacarbazine) to 7 (9%) patients. Eight patients were treated with various combination chemotherapies such as COPP

Table 1 Patient baseline characteristics

	All ($n = 78$)	ABVD-treated ($n = 52$)[¥]
Age		
Median (range)	68.7 (60–89)	68.6 (60–84)
Gender		
Male	40 (51%)	25 (48%)
Female	38 (49%)	27 (52%)
Subtype		
Nodular sclerosis	34 (44%)	26 (50%)
Mixed cellularity	20 (26%)	12 (23%)
Lymphocyte rich	2 (2%)	2 (4%)
Uncertain/missing*	22 (28%)	12 (23%)
Stage		
I	4 (5%)	2 (4%)
II	17 (22%)	13 (26%)
III	29 (38%)	24 (47%)
IV	27 (35%)	12 (23%)
Prognostic group		
Early favorable	11 (14%)	7 (14%)
Early unfavorable	11 (14%)	9 (17%)
Advanced	56 (72%)	36 (69%)
B symptoms	39 (53%)	23 (45%)
Mediastinal bulk	1 (1%)	1 (2%)
IPS (advanced disease only)		
1–2	14 (26%)	12 (35%)
3–7	40 (74%)	22 (65%)
ECOG		
0	32 (46%)	25 (52%)
I	27 (40%)	18 (38%)
II	5 (7%)	4 (8%)
III	3 (4%)	1 (2%)
IV	2 (3%)	0(0%)
EF < 60%	11 (19%)	8 (20%)
Significant heart/lung disease**	33 (42%)	19 (37%)
Initial treatment protocol***		
ABVD	52 (67%)	52 (100%)
Baseline BEACOPP	10 (13%)	–
Other	16 (20%)	–
Radiation treatment	10 (13%)	7 (14%)

Mediastinal bulk mass over 10 cm or a maximum width of mass > 0.33 of intrathoracic diameter; *IPS* international prognostic score; *EF* ejection fraction; *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine; *Baseline BEACOPP* bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone

*Cases in which subtype was not mentioned in the pathology report or subtype was inconclusive, e.g., cases diagnosed with core needle biopsy

**Designation made by the treating physician

***The initial treatment plan administered until complete remission, primary progression, or relapse

[¥] ABVD was tailored according to adverse events

(cyclophosphamide, vincristine, procarbazine, prednisone) or MOPP (mustargen, vincristine, procarbazine, prednisone), administered alone or as part of ABVD hybrids ($n = 6$) and variations of BEACOPP protocols ($n = 2$). A single patient who declined chemotherapy and presented with impaired performance status was treated with brentuximab vedotin monotherapy. In 10 (13%) patients, chemotherapy was followed by involved field radiotherapy, 9 of which presented with an early-stage disease.

Response to treatment and outcomes

Analysis of iPET scan results showed a DS of 1 in 49 (63%) patients, a score of 2 in 7 (9%) patients, a score of 3 in 9 (12%) patients, a score of 4 in 8 (10%) patients, and a score of 5 in 5 (6%) patients. Two patients died during administration of the initial treatment protocol (an 87-year-old female with stage IV disease, IPS 4, who achieved an iPET score of 3 and completed 5 treatment cycles of ABVD and a 76-year-old female with stage III disease, IPS 3, who achieved an iPET score of 1 and completed 3 treatment cycles of ABVD; both succumbed to infectious complications). Of 76 evaluable patients, 73 completed EOT-PET: 62 (86%) patients achieved CR, 3 (4%) patients achieved partial response (PR), and 8 (11%) patients had evidence of progressive disease (PD); none had stable disease (SD) according to the Lugano classification [21].

With a median follow-up of 5 years (range 2 months–15 years), 10 out of 62 patients with EOT-CR, experienced relapse. Five-year PFS and OS rates for the entire group were 65% and 75%, respectively.

When evaluated according to prognostic groups, the 5-year PFS rates were 91%, 70%, and 57% for early favorable, early unfavorable, and advanced-stage disease, respectively, and the 5-year OS rates were 90%, 91%, and 69% for early favorable, early unfavorable, and advanced disease, respectively (Fig. 1). There were no statistically significant differences in outcome according to prognostic groups. However, patients' outcome varied significantly according to the iPET DS, with patients having low scores faring better than those with higher scores. Patients with iPET scores of 1–3 had 5-year PFS and OS rates of 72% and 82% compared with 25% and 45% in patients with iPET scores of 4–5, respectively, $p < 0.0001$ (Fig. 1). The negative predictive value of iPET (scores 1–3) was 76% and the positive predictive value of iPET (scores 4–5) was 75%.

Outcome of patients with advanced disease, treated with ABVD

Thirty-six patients with advanced HL were treated with ABVD. The mean IPS was 3 ± 1.4 (range 1–6).

Patients with advanced-stage HL that were treated with ABVD had 5-year PFS and OS rates of 58% and 80%, respectively. Twenty-six (72%) patients had an iPET score of 1, 1

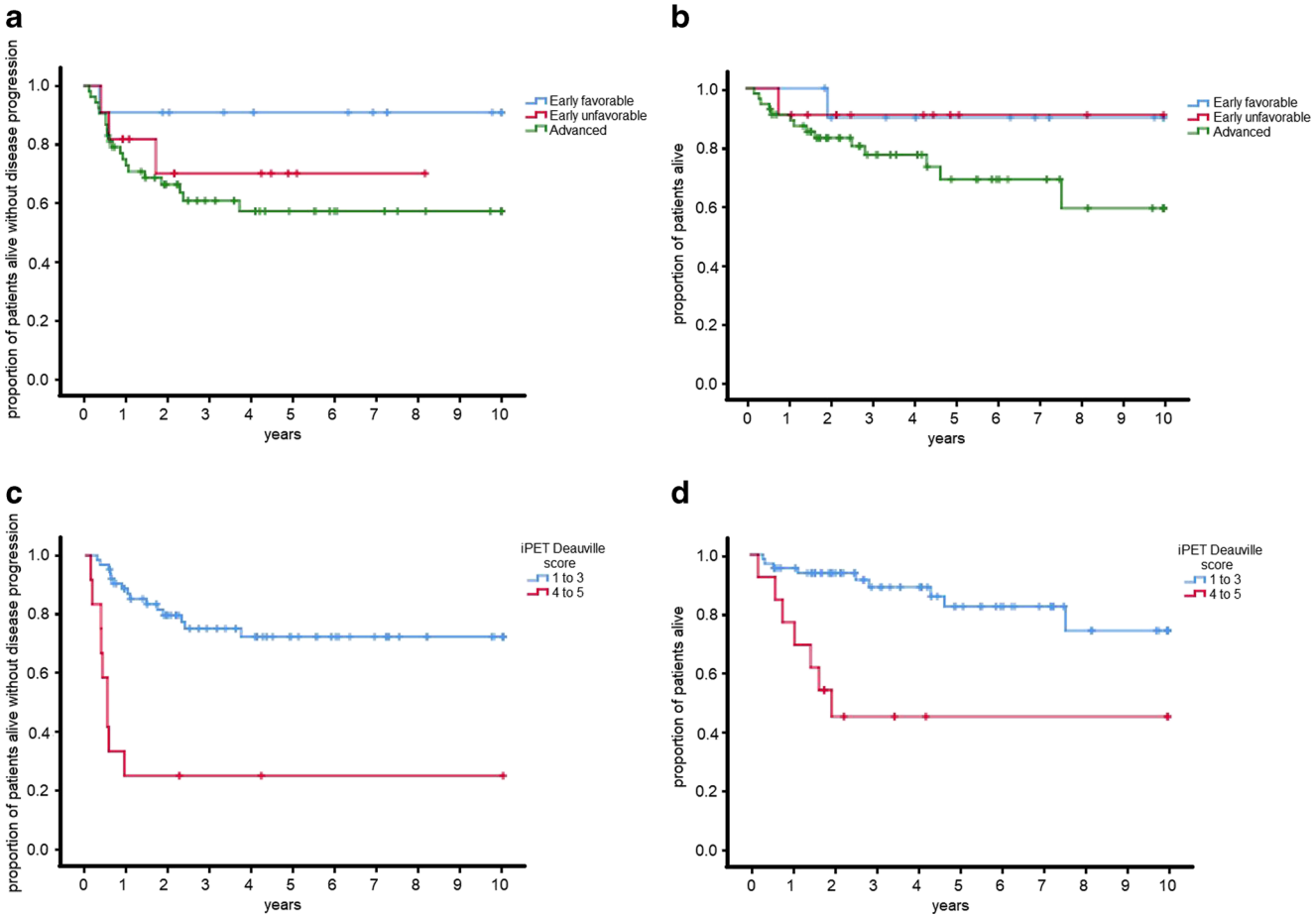

Fig. 1 Patient outcomes (the Kaplan-Meyer curves). **a** Progression-free survival by prognostic group, early favorable ($n = 11$) vs. early unfavorable ($n = 11$) vs advanced disease ($n = 53$), $p = 0.181$, not significant. **b** Overall survival by prognostic group, early favorable ($n = 11$) vs. early unfavorable ($n = 11$) vs advanced disease ($n = 56$), $p = 0.089$, not significant. **c** Progression-free survival by interim PET-CT, DS 1–3 ($n = 63$) vs. DS 4–5 ($n = 12$), $p < 0.0001$. **d** Overall survival by interim PET-CT, DS 1–3 ($n = 65$) vs. DS 4–5 ($n = 13$), $p < 0.0001$. DS the Deauville score

(3%) patient had a score of 2, 2 (6%) patients had a score of 3, 4 (11%) patients had a score of 4, and 3 (8%) patients had a score of 5.

Of the 36 patients with advanced-stage disease that were treated with ABVD, 2 succumbed to infectious complications prior to completion of the treatment regimen. Two of the patients with an iPET score of 5 were switched to platinum-based protocols after 2 cycles of ABVD. The third patient with an iPET score of 5 and all 4 patients with an iPET score of 4 completed 6 cycles of ABVD (Table 2). Of the remaining 27 patients (25 with an iPET score of 1, 1 with a score of 2, and 1 with a score of 3), 23 completed 6 cycles of ABVD, and the remaining 4 received 4–5.5 treatment cycles.

Twenty-seven (82%) patients achieved CR at EOT, 2 (6%) achieved PR, 4 (12%) had evidence of PD, and none had SD. Of the 27 patients with EOT-CR, 5 relapsed within 11–28 months: a single relapse within less than a year (iPET DS of 4) and four later relapses with DSs of 1–3.

Among patients with advanced-stage disease that were treated with ABVD, patients who had low iPET DSs (1–3) fared better than those with higher scores. Five-year PFS and OS rates were 69% and 87% for patients with iPET scores 1–3 vs. 14% and 57% for patients with iPET scores 4–5, respectively ($p < 0.0001$ for PFS and $p = 0.035$ for OS, Fig. 2).

Outcome of patients with advanced-stage HL, treated with baseline BEACOPP

Ten patients, all diagnosed with advanced-stage HL, were treated with baseline BEACOPP. The mean IPS was 4.3 ± 1.3 (range 3–6). The average number of treatment cycles was 5.2 ± 1.6. None of these patients had bulky mediastinal disease and none received radiation therapy. These patients had 5-year PFS and OS rates of 65% and 75%, respectively. Four of the 10 patients had an iPET score of 1, 3 patients had a score of 2, and 3 patients had a score of 3. At EOT, nine patients achieved CR and a single patient had PR. None of the patients died during the treatment. Of the 9 patients with EOT-CR, 2 experienced relapse, within 12 and 22 months (both with iPET DSs of 1). The association between iPET

Table 2 Detailed outcome of ABVD-treated patients with iPET scores of 4–5

Patient no.	Age at diagnosis	Prognostic group	IPS	iPET score	Action taken after iPET	EOT PET-CT	OS (yr)	Comments
1	72	Advanced	5	5	Transferred to platinum-based regimen	PD	1.44	
2	66	Advanced	1	5	Transferred to platinum-based regimen	PD	1.64	Continued to autologous and then allogeneic stem cell transplant
3	68	Advanced	4	5	Continued to ABVDX6	PD	0.59	DS = 5 based on uptake markedly higher than liver and no new lesions.
4	77	Advanced	3	4	Continued to ABVDX6	CR	2.24	DS = 4 based on uptake moderately higher than liver and no new lesions. Did not relapse.
5	77	Advanced	2	4	Continued to ABVDX6	CR	3.45	DS = 4 based on uptake moderately higher than liver and no new lesions. Relapsed after 12 months.
6	78	Advanced	4	4	Continued to ABVDX6	PR	1.77	DS = 4 based on uptake moderately higher than liver and no new lesions.
7	61	Advanced	2	4	Continued to ABVDX6	PD	13.35	DS = 4 based on uptake moderately higher than liver and no new lesions. Continued to autologous stem cell transplant.
8	67	Early unfavorable	4	5	Continued to ABVDX6	PD	0.77	DS = 5 based on uptake markedly higher than liver and no new lesions.
9	65	Early favorable	1	4	Continued to ABVDX5	CR	11.18	DS = 4 based on uptake moderately higher than liver and no new lesions. Did not relapse.

iPET interim PET-CT; *EOT* end of treatment; *OS* overall survival, *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine; *PD* progressive disease; *CR* complete remission; *DS* the Deauville score

score and outcome was not statistically significant, probably due to the small group size.

Outcome of ABVD-treated patients with early-stage HL

Sixteen patients with early-stage disease, 7 without unfavorable risk factors and 9 with unfavorable risk factors, were treated with ABVD. Six (38%) patients were treated with combined modality, having an additional radiotherapy, after two to four courses of ABVD.

Nine patients had an iPET score of 1, 3 patients had a score of 2, 2 patients had a score of 3, 1 patient had a score of 4, and 1 patient had a score of 5. At EOT, 14 patients achieved CR while 2 patients, one with an iPET score of 5 and one with an iPET score of 3, had PD at EOT. Of the 14 patients who achieved CR, only one patient relapsed. This was a patient with unfavorable risk who had an iPET score of 1 and relapsed 1.5 years after completing six courses of ABVD.

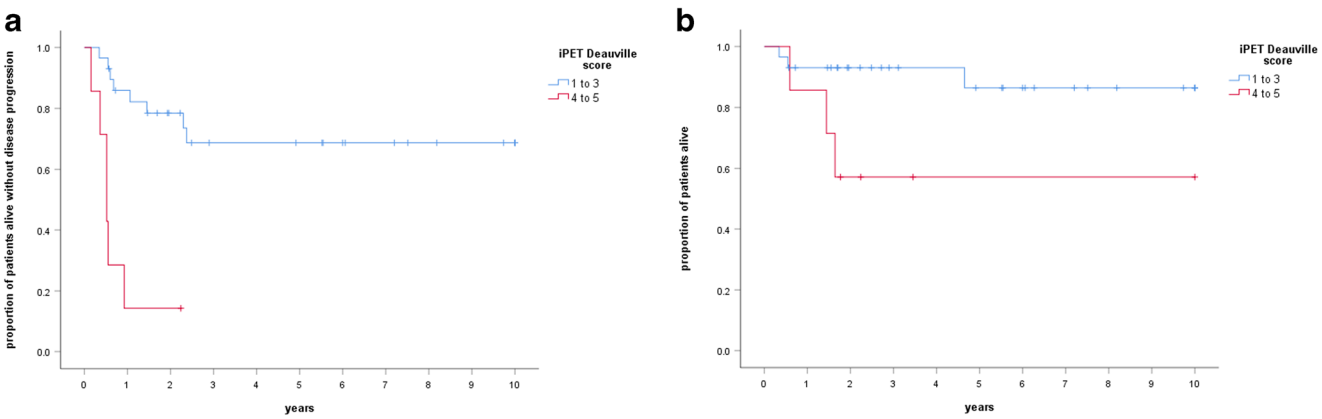

Fig. 2 Outcomes of patients with ABVD-treated advanced-stage disease. **a** Progression-free survival by interim PET-CT, DS 1–3 ($n = 29$) vs. DS 4–5 ($n = 7$), $p < 0.0001$. **b** Overall survival by interim PET-CT, DS 1–3 ($n = 29$) vs. DS 4–5 ($n = 7$), $p = 0.035$. DS the Deauville score

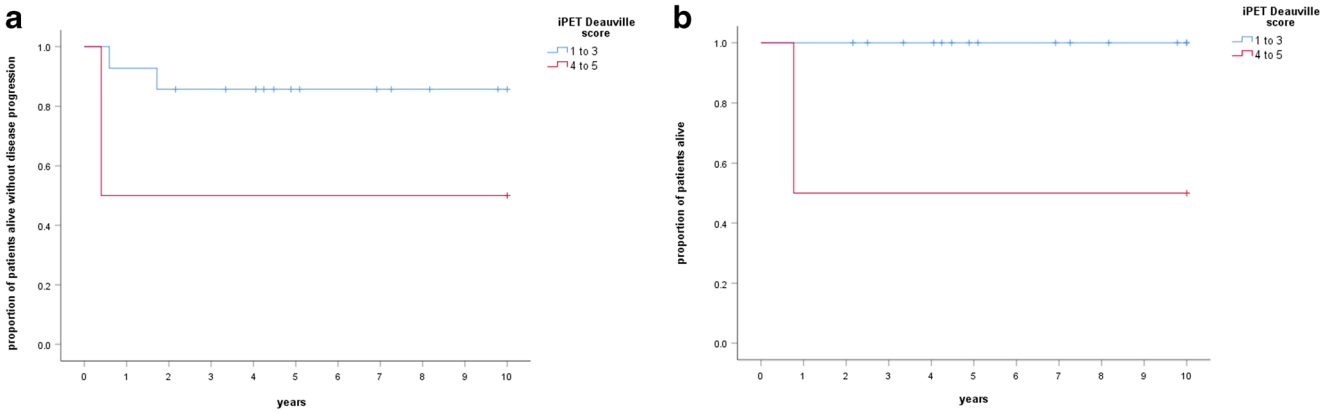

Fig. 3 Outcomes of patients with ABVD-treated early-stage disease. **a** Progression-free survival by interim PET-CT, DS 1–3 ($n = 14$) vs. DS 4–5 ($n = 2$), $p < 0.131$, not significant. **b** Overall survival by interim PET-CT, DS 1–3 ($n = 14$) vs. DS 4–5 ($n = 2$), $p = 0.008$. DS the Deauville score

Early-stage patients treated with ABVD with low iPET scores fared better than patients with higher scores, with 5-year OS rates of 100% for scores 1–3 vs. 50% for score 4–5 ($p < 0.01$) (Fig. 3).

Univariable and multivariable analysis

Univariable analysis of common prognostic factors in HL [18, 31, 32, 36, 46] was performed in this population of elderly patients and results are summarized in Table 3. In univariable analysis, iPET was predictive of outcome (PFS and OS) for the entire study group, in advanced-stage patients and ABVD-treated patients. IPS was not predictive for PFS or OS in patients with advanced-stage disease. Stage and prognostic group were not predictive of outcome.

In multivariable regression analysis, iPET maintained its prognostic value for the entire cohort. For example, compared with patients with DSs of 1–3, patients with scores of 4–5 had a HR of 8.5 (95% CI 1.8–40.3, $p = 0.007$) for progression and 6.9 (95% CI 1.2–40.8, $p = 0.031$) for death. None of the variables maintained their prognostic significance in multivariable analysis of patient sub-populations.

Discussion

The prognosis of elderly patients with HL is inferior to that of their younger counterparts. The causes for poor outcome in older patients with HL are likely multifactorial, including different disease biology, the presence of comorbidities, lower performance status, and limited organ reserve, frequently resulting in the employment of less intensive regimens [17, 18]. Previous attempts to improve the outcome of elderly patients with HL were directed at better categorizing these patients according to prognostic markers and the employment of distinct treatment regimens in this patient group [14, 31, 33–39]. Yet, no strong and reproducible predictive prognostic factors have been identified in this age group and the optimal treatment protocol is still a matter of debate [17, 18]. PET-CT has gained a wide spread endorsement in the treatment of lymphoproliferative disease. The value of PET-CT has been demonstrated in initial disease staging, assessment of response to treatment and prediction of long-term outcome in HL, perhaps more than in any other lymphoproliferative disease [22–29]. Nonetheless, there is a paucity of data regarding its value in the treatment of HL in the elderly, despite the unmet clinical need in the growing population of elderly patients.

This cooperative retrospective, real-life study included HL patients aged 60 to 89. Almost a quarter of the patients in our cohort were older than 75 years. Patient and disease characteristics were comparable with previous reports of elderly HL patients, including significant comorbidities typical of this age group, an increased frequency of the mixed cellularity subtype and B symptoms, and a decreased incidence of bulky mediastinal disease [18, 30].

iPET scores were predictive of outcome in this cohort and specifically in the sub-group of ABVD-treated patients. Thirty-six patients in this trial had advanced-stage HL and were treated with ABVD. This group represents a common challenge for physicians, as treating elderly patients with 6 cycles of this regimen is often hampered by adverse events, preventing its completion. We were able to show that patients with advanced-stage disease, treated with ABVD, who had iPET scores of 1–3, fared better compared with patients with higher iPET scores. IPS was not predictive of PFS or OS in patients with advanced-stage disease. In this regard, iPET results have been previously shown to overshadow the value of traditional prognostic factors, such as IPS [24].

An early detection of insufficient response, strongly associated with a worse outcome, may serve as a platform for adopting a PET-CT-driven therapeutic approach. This treatment algorithm, though not explored yet in elderly HL patients, is highly relevant nowadays, considering the new therapeutic approaches available, including brentuximab vedotin

Table 3 Univariable analysis of prognostic factors

Prognostic factor	All patients ($n = 78$)						ABVD-treated HL ($n = 52$)						ABVD-treated advanced HL ($n = 36$)					
	PFS			OS			PFS			OS			PFS			OS		
	HR	95% CI	P	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age (continuous variable)	1.1	1.0–1.1	*0.049*	1.1	1.0–1.2	*0.004*	1.0	0.9–1.1	0.395	1.1	1–1.2	0.099	1.0	0.9–1.1	0.655	1.1	1.0–1.2	0.113
Age ≥ 70	1.8	0.79–3.9	0.168	2.0	0.7–5.4	0.166	1.4	0.6–3.7	0.462	2.0	0.4–8.9	0.368	1.2	0.4–3.4	0.097	3.0	0.5–16.4	0.207
Gender (female vs male)	1.6	0.7–3.6	0.26	1.5	0.6–4.1	0.408	1.9	0.7–5.1	0.211	2.6	0.5–13.3	0.259	1.5	0.5–4.5	0.466	1.9	0.3–10.2	0.48
Morphology at diagnosis (MC vs NS)	0.5	0.16–1.5	0.193	0.4	0.1–1.6	0.183	0.4	0.1–1.7	0.204	0.0	0–58.6	0.353	0.5	0.1–2.2	0.333	0.0	0–154.3	0.41
Stage (advanced vs early)	2.4	0.8–7.0	0.11	3.4	0.8–14.8	0.109	2.5	0.7–8.9	0.144	3.0	0.4–25.1	0.307						
ECOG	1.3	0.9–2.0	0.18	1.7	1.0–2.9	*0.039*	1.1	0.6–2.2	0.717	0.9	0.3–2.8	0.805	1.1	0.6–2.3	0.711	1.0	0.3–3.2	0.967
Significant heart/lung disease	1.6	0.7–3.5	0.268	3.4	1.2–9.7	*0.025*	2.0	0.8–5.2	0.15	4.7	0.9–24.2	0.065	3.3	1.1–9.7	*0.027*	8.4	1.0–72.3	0.052
IPS	1.2	0.9–1.6	0.231	1.5	1.0–2.1	*0.037*	1.1	0.8–1.7	0.497	1.5	0.8–2.7	0.176	0.9	0.6–1.4	0.737	1.2	0.6–2.2	0.56
B symptoms	1.2	0.5–2.6	0.722	2.9	0.9–9.1	0.069	1.2	0.5–3.2	0.671	3.5	0.7–18.2	0.134	0.5	0.2–1.5	0.231	1.6	0.3–8.9	0.573
Extranodal involvement	0.8	0.3–1.8	0.534	1.2	0.4–3.3	0.749	0.9	0.3–2.7	0.846	1.2	0.2–6.3	0.812	0.7	0.2–2.3	0.603	1.0	0.2–5.4	0.984
Relative dose intensity < 100%	1.0	0.5–2.4	0.924	1.1	0.4–3.0	0.865	1.3	0.5–3.3	0.63	2.1	0.5–9.7	0.32	0.9	0.3–2.7	0.919	3.2	0.6–18.1	0.179
iPET score (1–3 vs 4–5)	6.4	2.8–14.9	*< 0.001*	5.2	1.9–14.1	*0.001*	7.4	2.7–20.1	*< 0.0001*	7.5	1.7–34.3	*0.009*	8.8	2.7–28.6	*< 0.0001*	5.0	1.0–25.6	0.055

Univariable analysis. HR > 1 indicates a factor with poor prognosis, whereas HR < 1 indicates a factor with favorable prognosis

ABVD adriamycin, bleomycin, vinblastine, dacarbazine; *HL* Hodgkin lymphoma; *Baseline BEACOPP* bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; *MC* mixed cellularity; *NS* nodular sclerosis; *IPS* international prognostic score; *iPET* interim positron emission tomography-computed tomography

These are the accronyms that were used in the table

that can substitute bleomycin [47]. Studies exploring this PET-CT-guided strategy are warranted, aiming to improve the outcome of elderly HL patients. PET-CT-guided strategy may save unnecessary toxicity of non-effective therapy and promote earlier induction of second line regimens, considering these elderly patients' ineligibility for high dose therapy and autograft.

Treatment with baseline BEACOPP was chosen by the physicians for 10 patients, representing almost 20% of advanced disease patients in this cohort. All patients achieved DS ≤ 3 and none died during treatment. This protocol may serve as a feasible option in selected elderly patients with HL, especially with a carful iPET-guided response-adapted therapy plan.

This trial has several limitations. Relative dose intensity [35] and complete geriatric assessment [18], previously suggested as prognostic tools in elderly HL patients, were not available to us; rather, performance status was used. The DS, now commonly used to direct response-adapted therapy in patients with HL [19, 21, 26], was not used in all patients in the original interpretation of their iPET, as 29 patients were diagnosed before the original publication in 2010 [19]. At the time when part of our patients were treated, visual assessment was considered adequate for determining PET scan results, and the use of standardized uptake values (SUV) was not deemed necessary in the response criteria published in 2007 [48]. Accordingly, of the 9 patients who had iPET scores of 4 and above, treatment was upgraded to platinum-based salvage protocols in only 2 patients whereas the other 7, who all had residual uptake in iPET with no new lesions, continued the original treatment regimen (Table 2). Thus, iPET results did not serve to guide further treatment, in most cases, in this cohort. The adherence to the original treatment protocol, regardless of iPET scores, could reflect the spirit of that era, an uncertainty regarding optimal treatment approaches for HL evident by the early termination of treatment arms in several prospective trials such as HD13 and H10 which evaluated drug omission [49] and response-adapted therapy [50].

In summary, there is an unmet clinical need for defining the optimal therapeutic regimen in elderly patients with HL. To the best of our knowledge, this study is the first to specifically address the role of iPET in the management of elderly patients with HL. Patients with low iPET DS fared better than patients with evidence of disease on iPET and had improved 5-year PFS and OS. Those elderly patients with a positive iPET had worse prognosis and should be considered for additional treatment or incorporation of novel agents into their treatment plan. iPET was predictive of outcome and surpassed the predictive value of traditional prognostic factors such as prognostic group and IPS. Safe incorporation of iPET into the management of elderly patients with HL may allow for necessary chemotherapy dose reductions and perhaps even for very careful but crucial treatment escalations. Proper utilization of this means is an integral part in the transition from pre-treatment analysis–based therapy to response-adapted therapy for elderly patients with HL.

Authorship contribution OSB and EP analyzed the data and performed the statistical analysis; IA and CP designed the research study; OSB wrote the paper; all authors managed the patients and collected the data, reviewed the manuscript, and provided input.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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