Interim PET-directed therapy in limited-stage Hodgkin lymphoma initially treated with ABVD

Limited-stage Hodgkin lymphoma (HL) is a highly curable malignancy when treated with combination chemotherapy with or without radiotherapy (RT).[1-5] The majority of patients experience long-term survival but remain at risk for late treatment-related complications, particularly those related to RT, including second malignancies and cardiovascular disease.[6,7]

In an attempt to balance the risks and benefits of the use of RT for patients with limited stage HL, especially potential long-term toxicity, the Lymphoma Tumor Group at BC Cancer introduced a treatment policy change in July 2005 recommending an approach based on 18F-fluorodeoxyglucose (FDG) positron emission tomography after two cycles of chemotherapy (PET2). Patients achieving a complete response (CR) after two cycles of ABVD, defined as a negative PET2, were recommended to receive two additional cycles of ABVD without RT. Patients with a positive PET2 were switched to involved nodal radiotherapy (INRT), with the rationale that using non-cross-resistant RT has the potential to eradicate possible residual disease implied by persistent PET positivity despite ABVD.[8]

Patients age >15 years diagnosed with limited stage classical HL between July 2005 and April 2016 were identified in the BC Cancer Lymphoid Cancer Database. Limited stage was defined as Ann Arbor stage IA, IB or IIA, with or without associated contiguous extranodal extension, and with the largest single mass measuring <10 cm. Patients were not otherwise categorized into favorable or unfavorable subgroups because erythrocyte sedimentation rate is not routinely tested at our institution. Diagnostic biopsies were reviewed by an expert BC Cancer hematopathologist and classified according to the World Health Organization Classification.[9,10]

PET2 scans were performed and reported centrally at the BC Cancer – Vancouver Cancer Centre. Before January 2014, PET scans were interpreted based on the International Harmonization Project to categorize PET2 results as negative, indeterminate, or positive to guide therapy.[11] Those with an indeterminate score were recommended to be treated as PET positive and receive INRT. This was replaced by the 5-point Deauville (D) scale in January 2014 where D1 and D2 were considered PET negative (i.e., a CR), D3-5 were considered PET positive, and cases with new uptake not felt to represent lymphoma were assigned a 'X' score.[12,13] Importantly, both systems considered the PET2 as positive if the maximum uptake was greater than the mediastinum and, therefore, requiring RT (i.e., including those with an indeterminate score).

A total of 286 prospectively diagnosed patients with stage IA, IB, or IIA HL diagnosed between 2005 – 2016 were identified. Of these, 47 were excluded for the following reasons: 37 nodular lymphocyte predominant HL, 9 illness/frailty at baseline precluding a PET-driven curative approach, and 1 in whom PET2 was not performed. Clinical characteristics of the 239 patients included in the current analysis are listed in Table 1. Patients were intended to receive two cycles of ABVD with curative intent, although 4 patients received a third cycle due to difficulty scheduling PET scans and 5 patients received ABVD-based alternating or hybrid regimens, which were considered to be equivalent to ABVD, by physician choice.[14,15] Following two cycles of initial chemotherapy, PET2 was negative in 210 (88%) patients, and positive in 29 (12%). The IHP response criteria were applied in 173 (72%) patients while Deauville criteria were applied to the remaining 66 (28%) patients, with no difference in the proportion of patients achieving a PET2 negative scan (88% *vs.* 86%, respectively, P=0.660).

Among the 210 PET2-negative patients planned for treatment with 2 additional cycles of ABVD, the majority (n=206, 98%) received 2 additional cycles of ABVD, although 4 of the 206 were not able to complete all 4 cycles (total 2 cycles [n=1], 3 cycles [n=3]) due to patient refusal (n=2) or chemotherapy toxicity (n=2, both with severe fatigue), and did not receive further therapy. The remaining 4 PET2-negative patients were immediately switched to INRT after the two initial cycles of ABVD by physician/patient preference due to perceived intolerance to chemotherapy.

All 29 PET2-positive patients (median SUVmax 2.8 [range 1.5 – 26]) received consolidative INRT. Of these

Table 1. Baseline characteristics according to treatment group. IHP: International Harmonization Project.

Characteristic	Total (n=239)	Treatment Group ABVD x4 (n=206)	ABVD x2 and RT (n= 33)
	n (%)	n (%)	n (%)
Age, median (range)	32 (16-75)	32 (16-75)	32 (20-74)
Sex			
Female	120 (50)	106 (51)	14 (42)
Male	119 (50)	100 (49)	19 (58)
Performance status			
0	132 (55)	115 (56)	17 (52)
1	100 (42)	85 (41)	15 (45)
2-3	7 (3)	6 (3)	1 (3)
Histological subtype			
Nodular sclerosis	171 (72)	149 (72)	22 (67)
Mixed cellularity	31 (13)	24 (12)	7 (21)
Not otherwise specified	21 (9)	18 (9)	3 (9)
Lymphocyte-rich	15 (6)	14 (7)	1 (3)
Lymphocyte-depleted	1 (1)	1 (1)	0
Ann Arbor stage			
IA	42 (18)	36 (18)	6 (18)
IB	4 (2)	4 (2)	0
IIA	193 (80)	166 (82)	27 (82)
Staging PET			
Yes	88 (37)	78 (38)	10 (30)
No	151 (63)	128 (62)	23 (70)
Largest mass size			
<5 cm	144 (60)	129 (63)	15 (45)
≥5 cm	95 (40)	77 (37)	18 (55)
PET2 interpretation criteria			
IHP criteria	173 (72)	151 (73)	22 (67)
Deauville 5-point scale	66 (28)	55 (27)	11 (33)
PET2 result			
Negative*	210 (88)	206 (100)	4 (12)
Positive	29 (12)	0	29 (88)

*13/66 patients had Deauville X and were managed as PET2-negative. 41/173 originally interpreted with IHP criteria were retrospectively assigned DX; only one was managed as PET2-positive.

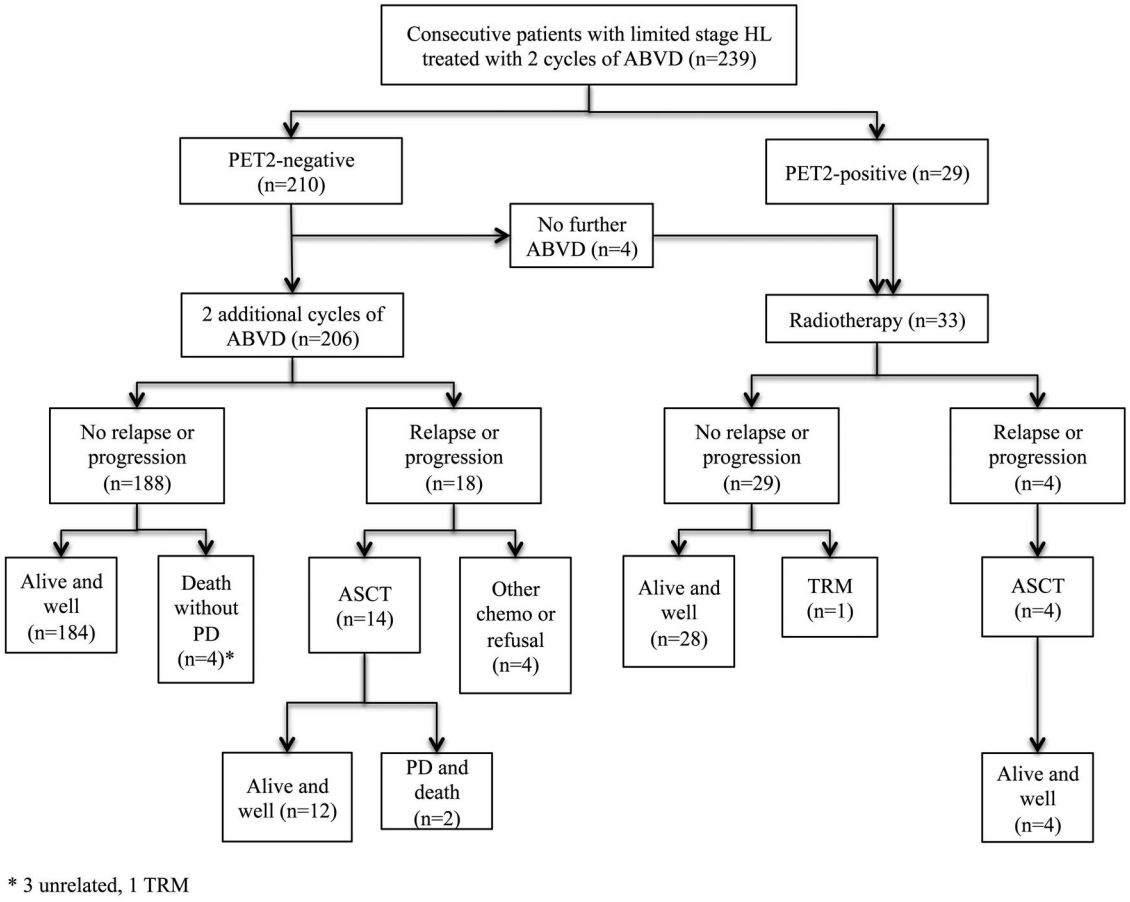

Figure 1. PET2 results, treatments, and outcomes. HL: Hodgkin lymphoma; PD: progressive disease; ASCT: autologous stem cell transplantation; TRM: treatment-related mortality (i.e., mortality related to ABVD +/- radiotherapy).

29, 25 received INRT after 2 cycles of ABVD, while 4 received INRT after >2 cycles of ABVD (range 2.5 – 4) for logistical/referral reasons. In the later era when Deauville scores were used, the PET2 was interpreted as positive in 9/66 (14%) patients using the Deauville criteria: score 3 (n=7), 4 (n=1), 5 (n=1).

Among the 33 patients who received INRT (29 PET2 positive and 4 PET2 negative), the median radiation dose was 35 Gy (range 25 – 38.5 Gy), administered over a median of 20 fractions (range 15-30). The radiation treatment volume encompassed all original sites of disease in 27 patients, including the 4 PET2-negative patients. However, the other 6 PET2-positive patients received INRT only to residual PET2-positive areas based on physician/patient preference.

Original reports and images of the 173 PET2 scans interpreted with the IHP criteria were retrospectively reviewed to assign a Deauville score, with the following results: score D1 (n=103), D2 (n=11), D3 (n=7), D4 (n=3), D5 (n=8), and DX (n=41). Under the Deauville criteria, PET2 interpretation would have been changed in 4 (2%) cases: positive to negative (n=2), negative to positive (n=1), and positive to DX (n=1). All 4 cases received treatment according to the original IHP assignment and remain alive and without evidence of recurrent HL. Only 13/239 (5%) patients would have been considered PET2-positive if scores D4 and D5 had been uniformly used to define a positive PET2.

With a median follow up of 5.5 years (range 10 months – 12 years) in living patients, 22 relapses have occurred: 18/206 (9%) after ABVD-only, 4/33 (12%) after ABVD and INRT. The median time from diagnosis to relapse was 14 months (range 5 months – 5.3 years). Figure 1 outlines all relapses, subsequent treatments, and deaths by treatment arm.

Within the ABVD-only group, 5 patients had primary refractory disease and 13 had relapsed HL. Nine patients progressed/relapsed in previously involved sites of disease, 2 in previously uninvolved sites, and 7 in both. The median time from diagnosis to progression/relapse was 1.1 years (range 0.4 – 3 years).

In the INRT-treated group, 4 relapses occurred, of which 3 occurred inside the irradiated treatment volume (2 of these had received RT to the PET2-positive disease only), while 1 occurred outside. The median time from diagnosis to relapse was 2.7 years (range 0.9 – 5.3 years), which was longer but not statistically significantly different from that of ABVD-only patients (P=0.198), and there were no cases with primary refractory HL.

In the entire cohort, the 5-year PFS was 88.9% (95% confidence interval [CI] 88.6% - 89.2%), and the 5-year OS was 97.2% (95% CI 97.1% - 97.4%), as shown in Figure 2. There was no statistically significant difference in 5-year PFS between PET2-negative (89.5% [95% CI 89.2% - 89.8%]) and PET2-positive (84.9% [95% CI 82.4% - 87.4%], P=0.366) patients. Similarly, there was

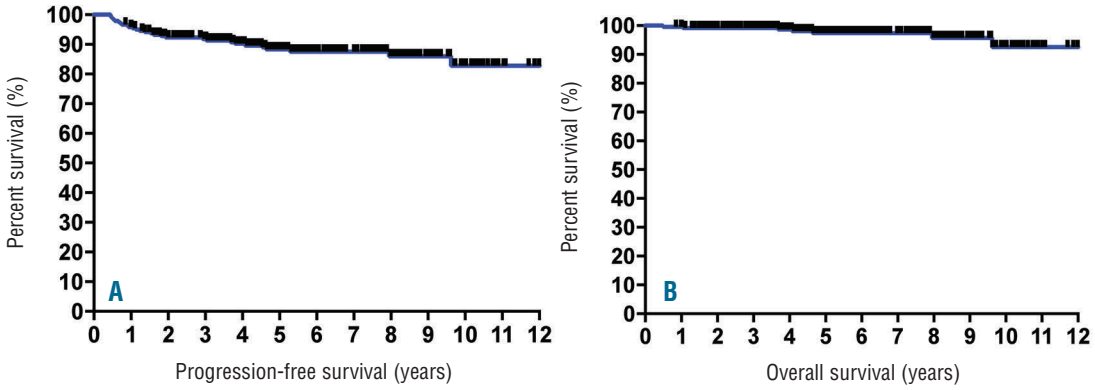

Figure 2. Outcomes for 239 patients with limited stage Hodgkin lymphoma managed with PET2-guided treatment. (A) Progression-free survival. (B) Overall survival.

no difference in 5-year OS between PET2-negative (97.3% [95% CI 97.1% - 97.5%]) and PET2-positive (96.6% [95% CI 95.4% - 97.8%], *P*=0.932) patients.

Our results are consistent with three large prospective clinical trials evaluating the omission of consolidative RT in patients with limited stage HL achieving a negative interim PET but extend the observation period to include a longer follow up. In the RAPID trial, which uses a similar definition of limited stage disease, the 3-year PFS was 91% in PET3-negative patients randomized to three cycles of ABVD alone.[3] In the EORTC/LYSA/FIL H10 trial, the 5-year PFS in PET2-negative patients treated with ABVD alone was 87% (early favorable) and 90% (early unfavorable).[1] Neither study demonstrated the non-inferiority of ABVD alone compared to combined-modality therapy. Additionally, in the Alliance/CALGB 50604 study, the 3-year PFS was 91% in PET2-negative patients receiving ABVD alone as per protocol.[5]

Collectively, all studies, including our own data, suggest a slight increased risk of relapse of 5-8% with the omission of RT. However, in all analyses, overall survival is not impacted given the excellent outcomes with salvage treatment including subsequent RT and ASCT. Conversely, similar to the RAPID study, RT was able to achieve high cure rates in patients with a PET2 positive scan suggesting that it remains a viable option with limited morbidity compared to chemotherapy intensification approaches.

Our data confirm the findings of prospective studies that RT can be safely omitted in a large proportion of patients with limited stage HL who are expected to have an excellent prognosis, based on a negative PET after 2 cycles of ABVD. This strategy has a failure rate of ~10%, and while most patients with relapsed/refractory HL can be salvaged with ASCT, further improvements could be introduced to first-line therapy. These may include the incorporation of novel agents such as brentuximab vedotin or immune checkpoint inhibitors, as well as evaluation of additional biomarkers that might reliably identify those with an excellent prognosis who can be safely treated with less therapy, and those with a poor prognosis in whom the benefits and risks of treatment intensification can be justified.

Diego Villa,[1] Laurie H. Sehn,[1] Christina Aquino-Parsons,[2] Petter Tonseth,[3] David W. Scott,[1] Alina S. Gerrie,[1] Donald Wilson,[3] François Bénard,[3] Randy D. Gascoyne,[4] Graham W. Slack,[4] Pedro Farinha,[4] James Morris,[2] Tom Pickles,[2] Joseph M. Connors[1] and Kerry J. Savage[1]

[1]BC Cancer Centre for Lymphoid Cancer and Division of Medical Oncology; [2]Division of Radiation Oncology; [3]Department of Functional Imaging and [4]Department of Pathology and Laboratory Medicine, BC Cancer and the University of British Columbia, Vancouver, BC, Canada

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Correspondence: dvilla@bccancer.bc.ca
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