Pretransplant functional imaging and outcome in pediatric patients with relapsed/refractory Hodgkin lymphoma undergoing autologous transplantation

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Abstract
Background: Pretransplant functional imaging (FI), particularly a negative positron emission tomography (PET), is a strong predictor of outcome in adults with relapsed or refractory Hodgkin lymphoma (HL), but data in pediatrics are limited.

Methods: The medical records of 49 consecutive pediatric patients, who received autologous transplant at a single institution, were retrospectively analyzed. All patients had either gallium or PET scan before transplant and were conditioned with carmustine, etoposide, cytarabine, and melphalan (BEAM). Deauville scores were retrospectively assigned for patients with PET (score ≥ 4 positive).

Results: Of the 49 patients (median age, 16.2 years), 41 (84%) were pretransplant FI negative and eight (16%) were pretransplant FI positive, after first- to fourth-line salvage therapy, and a median of two salvage cycles. Eighteen patients (37%) received posttransplant radiation. At a median follow up of 46 months, 45 patients (92%) were alive and disease free, and there were three nonrelapse deaths and only one relapse death (Deauville score of 5). The 4-year progression-free survival (PFS) for the entire cohort was 92% (95% confidence interval [CI]: 78–97), and PFS based on pretransplant disease status was 95% (95% CI: 82–99) in the negative FI group versus 75% (95% CI: 31–93) if positive FI (P = 0.057).

Conclusion: Our analysis revealed outstanding outcomes for children and adolescents with relapsed/refractory HL. There were too few relapses to identify the predictive value of pretransplant metabolic status, but pediatric patients with relapsed/refractory HL and a negative pretransplant FI had excellent survival.

KEYWORDS
autologous transplantation, FDG-PET, functional imaging, Hodgkin lymphoma, relapse

1 | INTRODUCTION

Children and adolescents with Hodgkin lymphoma (HL) have excellent long-term survival exceeding 95% after combined modality treatment.1 However depending on disease stage, about 5–15% will either relapse after initial therapy or have primary refractory disease.2-5 Many of these patients cannot be salvaged with chemotherapy and/or radiotherapy (RT) alone, hence salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (ASCT) has become the standard of care for majority of pediatric patients with relapsed or refractory HL.6

In adults, achieving a complete remission by functional imaging (FI), particularly a negative 18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) after salvage chemotherapy is a strong predictor of outcome after ASCT.7,8 Adams et al. recently published...
a systematic review examining the prognostic value of FDG-PET in
patients with relapsed/refractory HL who received ASCT. The authors
concluded there was only moderate quality evidence to suggest that
pretransplant PET was predictive of outcome, given a considerable
proportion of PET positive patients in the studies analyzed remained
disease free and some PET negative patients had relapsed post-ASCT.9

The majority of published literatures in pediatric cohorts have
employed computed tomography (CT) measurements to assess pre-
transplant disease status,10–12 and data on the predictive value of
pretransplant FI in pediatrics are very limited. Based on the adult
experience, the treatment approach at the Dana Farber/Boston Chil-
dren's Cancer and Blood Disorders Center (DF/BC CBDC) has focused
on getting patients with relapsed or refractory HL into complete
metabolic remission before autologous transplant. This often involves
administering additional lines of salvage chemotherapy to patients
who failed to achieve metabolic remission after first-line salvage
chemotherapy. We report our experience and the outcome of forty-
ine consecutive children and adolescents, who underwent ASCT for
relapsed or refractory HL at our institution.

2 | PATIENTS AND METHODS

This retrospective study was reviewed and approved by the Institu-
tional Review Board. Between January 1, 2001 and December 31,
2014, 49 patients with relapsed or refractory HL received autologous
transplantation at our institution. All but one of the 49 patients had
biopsy-proven confirmation of disease at the time of relapse or refrac-
tory disease. The only patient without histological confirmation of dis-
ease at time of treatment failure was deemed to have refractory dis-
ease based on persistent areas of gallium avidity at the end of planned
upfront chemotherapy.

Twenty-two out of 49 patients in this analysis received salvage
chemotherapy at other institutions and were referred to DF/BC CBDC
for ASCT. The choices of salvage chemotherapy regimens were at
the treating physician's discretion. All patients received standard con-
ditioning regimen with Carmustine, etoposide, cytarabine, melphalan
(BEAM) as follows: Carmustine (BCNU) 300 mg/m² on day –6; etopo-
side 200 mg/m² every 12 hr on days –5, –4, –3, cytarabine 100 mg/m²
every 12 hr on days –5, –4, –3, –2; and melphalan 140 mg/m² on day –1.
This was followed by stem cell infusion on day 0. Granulocyte colony
stimulation factor was begun on day +5 until absolute neutrophil count
> 2,000 cells/μl for two consecutive days. Posttransplant involved-
field radiotherapy (IFRT) was given if no prior RT had been adminis-
tered to the site(s) of relapse or if there was persistent gallium or FDG-
avid disease pretransplant.

2.1 | Pretransplant metabolic status

All patients had CT, and either FDG-PET or gallium at the time of
relapse, after each line of salvage chemotherapy and prior to ASCT.
All 49 patients had a positive FI at the time of relapse, and in all cases
imaging was obtained within 2–4 weeks of admission for ASCT to
document final pretransplant disease status. Six patients transplanted
before December 2004, had gallium scans, and 43 subsequent patients
had FDG-PET (Fig. 1).

The study period began prior to the publication of the five-point
Deauville criteria,13 hence available FDG-PET images were indepen-
dently reviewed and retrospectively assigned Deauville scores by two
of the authors (H.M.D. and F.D.G) who were blinded to the clinical
data and outcomes. Any discrepancies in scoring were reconciled after
a joint review by both authors. All patients who did not have PET
images for review had outside radiology reports documenting negative
FDG-PET by visual inspection before transplant. In the remaining cases
where scans were available for retrospective review, there was a high
concordance between a negative FDG-PET report and the Deauville
scores assigned. No patient with a negative FDG-PET report had a
Deauville score >2 on retrospective review. Negative FI was defined
as interval resolution of previous gallium-avid disease, a documented
negative FDG-PET, or Deauville score ≤3 on retrospective review. Per-
sistence or new foci of abnormal increased gallium uptake or Deauville
score ≥4 defined a positive FI.

2.2 | Definitions of refractory disease or relapse

Refractory disease was defined as no response to primary treatment
or progression (increase in size of known lesions and/or a new dis-
 ease site) on or within 3 months of completion of planned treatment.
A relapse occurring 3–12 months after completion of therapy was
defined as an early relapse, and any relapse >12 months postcomple-
tion of initial therapy was called a late relapse. The time to relapse was
calculated from the date of completion of upfront treatment to the
documented date of relapse.

2.3 | Statistical analysis

Overall survival (OS) was calculated from the date of stem cell infu-
sion to death from any cause. Progression-free survival (PFS) was cal-
culated from date of stem cell infusion to relapse of HL or death from
any cause. Survival distributions were examined using Kaplan–Meier
curves and the differences between groups analyzed using the log-rank
test and a significant P value < 0.05. All statistical analyses were per-
formed using Stata version 14.1 (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics are detailed in Table 1. The median age at the
time of transplant was 16.2 years (range 7–23.3 years) and 55% were
males. Eighteen patients (37%) had refractory disease, 22 patients
(45%) relapsed early (3–12 months from completion of primary ther-
apy), and nine patients (18%) had experienced a late relapse (>12
months). Fourteen patients (29%) had extranodal disease at the time of
relapse. Of the 31 patients (63%) who received upfront involved-field
radiation, 81% relapsed within their initial radiation field.
**Figure 1** Distribution of pediatric patients with relapsed or refractory Hodgkin lymphoma who underwent autologous transplantation. ASCT, autologous stem cell transplantation; FI, functional imaging.

### Table 1 Patient characteristics

| Characteristics                           | Negative pre-ASCT FI (N = 41) (%) | Positive pre-ASCT FI (N = 8) (%) | All ASCT (N = 49) (%) |
|-------------------------------------------|-----------------------------------|----------------------------------|-----------------------|
| Age at ASCT, in years, median ± SE        | 16.3 ± 3.2                        | 15.7 ± 3.1                       | 16.2 ± 3.1            |
| Range in years                            | 7.1–23.3                          | 11–20.9                          | 7.1–23.3              |
| Sex                                       |                                   |                                  |                       |
| Male                                      | 24 (59)                           | 3 (38)                           | 27 (55)               |
| Female                                    | 17 (41)                           | 5 (62)                           | 22 (45)               |
| Ann Arbor stage at diagnosis              |                                   |                                  |                       |
| I                                         | 1 (2)                             | 0 (0)                            | 1 (2)                 |
| II                                        | 29 (71)                           | 2 (25)                           | 31 (63)               |
| III                                       | 3 (7)                             | 0 (0)                            | 3 (6)                 |
| IV                                        | 8 (20)                            | 6 (75)                           | 14 (29)               |
| B symptoms at diagnosis                   |                                   |                                  |                       |
| Nodular sclerosing                        | 35 (85)                           | 6 (75)                           | 41 (84)               |
| Type of treatment failure                 |                                   |                                  |                       |
| Refractory disease                        | 14 (34)                           | 4 (50)                           | 18 (37)               |
| Early relapse (3–12 months)               | 19 (46)                           | 3 (38)                           | 22 (45)               |
| Late relapse (>12 months)                 | 8 (20)                            | 1 (12)                           | 9 (18)                |
| B symptoms at relapse                     | 4 (10)                            | 2 (25)                           | 6 (12)                |
| Extranodale disease at relapse            | 9 (22)                            | 5 (63)                           | 14 (29)               |
| Radiation in upfront therapy              | 28 (68)                           | 3 (38)                           | 31 (63)               |
| Relapse in previous radiation field       |                                   |                                  |                       |
| Yes                                       | 22 (54)                           | 3 (38)                           | 25 (51)               |
| No                                        | 6 (15)                            | 0 (0)                            | 6 (12)                |
| ≥2 salvage regimens prior to ASCT         | 9 (22)                            | 5 (63)                           | 14 (29)               |
| Posttransplant radiation                  | 13 (32)                           | 5 (63)                           | 18 (37)               |

ASCT, autologous stem cell transplant; FI, functional imaging; SE, standard error.

#### 3.2 Response to salvage chemotherapy

Front-line and salvage therapy regimens are shown in Table 2. The most common first-line salvage regimen used was ifosfamide, carboplatin, and etoposide (ICE), which was administered to 55% of patients. Gemcitabine/vinorelbine was the most common second-line salvage regimen. The median number of salvage chemotherapy cycles administered pre-ASCT was two cycles (range two to eight cycles).

Thirty-two patients (65%) were in complete remission by either PET or gallium after two cycles of first-line salvage therapy (Fig. 2).

Of the 17 patients who did not respond adequately, nine patients had primary refractory disease, six of them were early relapses, and two patients had a late relapse. Three of these 17 patients proceeded to ASCT without further salvage therapy, whereas the remaining 14 patients received additional second-line salvage therapy. As shown in Fig. 2, of the 14 patients who received second-line salvage, seven (50%) went into metabolic remission, whereas four patients (28%) with persistently positive FI proceeded to ASCT. The remaining three patients received third-line, and in one case a fourth-line salvage treatment, with two of these achieving negative FI prior to ASCT. In total, nine out of the 14 patients (64%) who received additional salvage regimens later achieved complete metabolic remission. Of the patients who did not respond to the additional lines of salvage therapy, half of them had primary refractory disease.
TABLE 2  Front-line and salvage chemotherapy regimens

| Regimen                              | Total N = 49 (%) |
|--------------------------------------|------------------|
| Front-line chemotherapy              |                  |
| ABVD                                 | 9 (18)           |
| Stanford V                           | 17 (35)          |
| ABVE-PC                              | 13 (27)          |
| VAMP                                 | 4 (8)            |
| OPPA/COPP                            | 3 (6)            |
| Other                                | 3 (6)            |
| First-line salvage regimen           |                  |
| ICE                                  | 27 (55)          |
| Ifosfamide/vinorelbine ± bortezomib  | 14 (29)          |
| Gemcitabine containing regimen       | 4 (8)            |
| Other                                | 4 (8)            |
| Second-line salvage regimens, n = 14 |                  |
| Gemcitabine/vinorelbine              | 8 (57)           |
| Ifosfamide/vinorelbine               | 3 (22)           |
| DHAP                                 | 2 (14)           |
| ICE                                  | 1 (7)            |
| Third-line salvage regimens, n=3     |                  |
| DHAP                                 | 1                |
| ChlVPP                               | 1                |
| Cyclophosphamide/etoposide           | 1                |

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; ChlVPP, chlorambucil, vinblastine, procarbazine, prednisone; DHAP, dexamethasone, high-dose Ara C, cisplatin; FI, functional imaging; VAMP, vinblastine, doxorubicin, methotrexate, prednisone; ICE, ifosfamide, carboplatin, etoposide; OPPA/COPP, vincristine, prednisone, procarbazine, doxorubicin/cyclophosphamide, vincristine, prednisone, and procarbazine.

Forty-one patients (84%) had negative FI and eight patients (16%) had positive FI pretransplant. Of the eight positive FI patients, Deauville score was 4 (five patients) or 5 (three patients). No patient had a positive pretransplant gallium.

Eighteen patients (37%) received posttransplant IFRT to previously nonirradiated sites of disease or areas of persistent PET avidity pretransplant: five patients in the positive FI group and 13 patients in the negative FI group. The dose of posttransplant radiation administered was 19.5–36 Gy, although most patients received a dose of 25.5 Gy. The only patient who received 36 Gy IFRT had bulk disease at time of relapse and intense PET avidity (Deauville 5) before transplant. Radiation was delivered in daily fractions of 1.5 Gy. The median duration of follow up posttransplant was 3.8 years (0.1–15 years).

3.3  Survival and outcome analysis

Forty-five patients were alive and disease free at the median follow up of 3.8 years. Posttransplant events included two early deaths from transplant-related complications (one patient in each FI group), one motor vehicle accident (negative FI group), and one relapse 6 months posttransplant in a patient who had positive FI pretransplant. The only patient in the cohort who relapsed had a pretransplant Deauville score of 5 and died of disease 12 months postASCT. The 4-year PFS (PFS also equivalent to OS) for entire cohort was 92% (95% confidence interval [CI]: 78–97). (Fig. 3A) The 4-year PFS based on pretransplant disease status was 95% (95% CI: 82–99) in the negative FI group versus 75% (95% CI: 31–93) in the positive FI group (P = 0.057) (Fig. 3B).

In a univariate analysis, known prognostic factors, including remission status less than 12 months, refractory disease, extranodal disease at relapse, B symptoms at relapse, in radiation field relapse, or failure to respond to first-line salvage chemotherapy, did not have any significant impact on PFS or OS (Supplementary Table S1). This was not unexpected given the rarity of events. Also, Cox proportional hazard ratios could not be performed on multivariate analysis for the same reasons.

3.4  Treatment-related toxicity and deaths

There were three nonrelapse deaths. One patient whose pretransplant course had been complicated by Stevens–Johnson’s syndrome with a long period of intubation and skin problems, developed Strep viridans bacteremia on day +3 and died from acute respiratory distress syndrome a week later. One patient died 16 days posttransplant from multiple organ dysfunctions in the setting of fevers. No pathogenic organism was isolated. One patient died in a motor vehicle accident on day +100.
FIGURE 3 Progression-free survival (PFS): (A) Of all patients with relapsed or refractory Hodgkin lymphoma who received autologous transplantation from 2000 to 2014; (B) of all patients with relapsed or refractory Hodgkin lymphoma by pretransplant functional image (FI). CI; confidence interval

4 | DISCUSSION

This single center analysis revealed excellent survival outcomes for pediatric patients undergoing autologous transplantation for relapsed or refractory HL. Very few studies have evaluated the impact of ASCT in children/adolescents with relapsed/refractory HL, and these have reported event-free survival (EFS) between 31 and 65%.6,14–17 Most of these events were relapses or disease progression. In this study, pretransplant disease status was not defined by FDG-PET or gallium and remission was primarily assessed by anatomic shrinkage on CT. In contrast, response assessment by FDG-PET has largely replaced gallium as the FI of choice in the evaluation of HL. While we do not assume FDG-PET and gallium have equal sensitivity for detecting disease, two earlier studies demonstrated that both modalities were strongly predictive for outcome in relapsed/refractory HL without any difference in outcome for patients evaluated by these modalities pretransplant.7,8 Hence, our decision to include the six early patients who had gallium scans seemed justified and should not undermine our results.

We recognize that our patient population may have been selected, that may in part account for our excellent outcomes. However, the patients in our cohort were not the most favorable. Multiple studies have shown remission duration <1 year, presence of extranodal disease, and B symptoms at relapse to be important prognostic factors in relapsed/refractory HL.12,23–27 Likewise, a multivariate analysis of 606 children, adolescents, and young adults with relapsed or refractory HL (median age 23 years, range 3–29 years) who underwent ASCT demonstrated similar results.28 In our analysis, 82% of patients were in remission for less than a year and 29% had extranodal disease at the time of disease relapse. Our excellent outcomes despite having a significant percentage of high-risk patients (refractory disease and remission less than a year) may be the consequence of a high proportion of patients who were negative by FI pretransplant, after we had administered additional lines of salvage therapy to patients who were not in metabolic remission after first-line salvage. Also, the fact that most patients who had persistent PET avidity before transplant were administered posttransplant irradiation is postulated to improve survival for that group.

Pre-transplant FI was not predictive of outcome in our analysis (95 vs. 75%, P = 0.057). However, it is notable that the only secondary treatment failure observed was in a patient who was PET positive prior to transplant. There are few potential explanations for our results. Because of the small number of patients, the small proportion of patients who were pretransplant FI positive (16% in our cohort, whereas most adult studies report >30%7,20,21,29) and the lack of events, we may not have been sufficiently powered to demonstrate a difference in survival between the FI negative and positive groups. These same reasons also likely underlie our inability to identify any of the known prognostic factors (e.g., remission duration, extranodal disease, B symptoms at relapse) in our univariate analysis. Conversely, pretransplant FI may not be truly predictive in children and adolescents, which may reflect differences in disease biology between this age group and the adults.

Many of the adult studies have evaluated the prognostic significance of pretransplant FDG-PET. Given the era our patients were treated, six early patients had gallium scans instead of PET. FDG-PET has largely replaced gallium as the FI of choice in the evaluation of HL. We do not assume FDG-PET and gallium have equal sensitivity for detecting disease, two earlier studies demonstrated that both modalities were strongly predictive for outcome in relapsed/refractory HL without any difference in outcome for patients evaluated by these modalities pretransplant.7,8 Hence, our decision to include the six early patients who had gallium scans seemed justified and should not undermine our results.

Literature on the role of consolidative posttransplant RT in relapsed/refractory HL, though inconclusive, appears to suggest there might be a survival benefit. Shafer et al. observed that children irradiated after autologous transplant had a 2-year PFS of 88% (95% CI: 39–98) versus 52% (95% CI: 26–72) (P = 0.1) if RT was not administered.11 In that series, patients were selected for IFRT if they had bulky disease or were PET positive after transplant. Similarly, Moskowitz et al. found pretransplant radiation to be marginally significant for EFS (P = 0.055).13 More than 30% of our patients received...
The potential impact of the transplant conditioning and salvage chemotherapy regimens used also warrants consideration. Cyclophosphamide, carmustine and etoposide (CBV) and BEAM are the most common conditioning regimens used in relapsed/refractory HL. Only few studies have compared these two regimens, but there has never been a true head-to-head controlled comparison. Williams et al. reported lower risk of disease progression and longer survival associated with the use of BEAM versus CBV (5-year PFS of 92% vs. 73%, \( p = 0.002 \)). Yet, this may have been confounded by benefits related to improved supportive care and patient selection, given the more recent patients in that study received BEAM.

The salvage therapies used in our analysis were predominantly standard regimens for relapsed/refractory HL. Consequently, it will be difficult to determine their impact on our outcomes. Several investigators have shown that a favorable response to first-line salvage chemotherapy (chemosensitivity) (defined by at least 50% tumor reduction on bidimensional measurement on conventional CT) strongly predicts survival in patients with relapsed/refractory HL. Metzger et al. reported that children who had chemosensitive disease had a 5-year OS of 97.2%, compared to 17.9% in the group that did not respond \( (p < 0.0001) \) In that study, most of the patients who had chemosensitive disease were also in metabolic remission by PET. We did not include CT response in our analysis and our salvage regimens differed significantly from those of the authors, limiting comparison; but failure to achieve metabolic remission after first-line salvage therapy did not have any significant impact on our survival outcome. Furthermore, normalization of pre-ASCT FI after second-line salvage chemotherapy has been shown to result in improved survival, when compared to chemosensitive disease with persistent abnormalities on FI.

We observed that more than 60% of the patients who were PET positive after first-line salvage achieved metabolic remission after additional alternative noncross-resistant chemotherapy regimens. While this is encouraging, it also implies that some children will not get into metabolic remission with standard salvage chemotherapy. Although small numbers, we observed that patients with primary refractory disease were less likely to respond to additional salvage regimens, consistent with earlier observations of refractory disease being predictive of a poor response to salvage therapy. Patients deemed unresponsive to standard chemotherapy may be candidates for novel therapies before ASCT. The inclusion of the anti-CD30 antibody conjugate, brentuximab, and programmed death 1 inhibitors such as nivolumab and pembrolizumab have improved the success rate of salvage treatment in adult patients with relapsed/refractory HL. Furthermore, Brentuximab given as consolidation post-ASCT has been shown to improve PFS in adults with relapsed/refractory HL. Two active Children's Oncology Group trials are investigating incorporation of novel therapies in relapsed/refractory pediatric HL. AHOD1221 is evaluating the combination of brentuximab with gemcitabine (NCT01780662), while the recently approved AHOD1721 study is examining if a combination of nivolumab and brentuximab, followed by brentuximab and bendamustine (NCT02927769), is safe and effective in children, adolescents, and young adults who had failed first-line salvage therapy.

In conclusion, acknowledging the potential limitations of our retrospective design, small number of patients, and nonuniformity in modalities of FI and salvage therapies administered, our analysis reveals outstanding outcomes for children and adolescents with relapsed or refractory HL. There were very few relapses to identify the predictive value of pretransplant FI, but pediatric patients in metabolic remission either by PET or gallium pretransplant had a better survival than reported in the adult literature. Further studies are warranted to determine the true prognostic value of pretransplant FI in pediatrics.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

N.W.O and S.P.M. were responsible for the design of this study, data collection, and assembly. H.M.D and F.D.G read and scored FDG-PET scans. N.W.O, A.L.B., and S.P.M. wrote the manuscript. L.E.L. and A.S.L. provided critical review of the manuscript. All authors approved of the final version of this manuscript.

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