HHS Public Access

Author manuscript

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2018 July 05.

Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2017 February 01; 97(2): 333–338. doi:10.1016/j.ijrobp.2016.10.029.

Chemotherapy Response Assessment by FDG-PET-CT in Early-stage Classical Hodgkin Lymphoma: Moving Beyond the Five-Point Deauville Score

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Abstract

Purpose—In early-stage classical Hodgkin lymphoma, fluorodeoxyglucose positron emission tomography (PET)-computed tomography (CT) scans are performed routinely after chemotherapy, and the 5-point Deauville score is used to report the disease response. We hypothesized that other PET-CT parameters, considered in combination with Deauville score, would improve risk stratification.

Methods and Materials—Patients treated for stage I to II Hodgkin lymphoma from 2003 to 2013, who were aged ≥18 years and had analyzable PET-CT scans performed before and after chemotherapy, were eligible. The soft tissue volume (STV), maximum standardized uptake value, metabolic tumor volume, and total lesion glycolysis were recorded from the PET-CT scans before and after chemotherapy. Reductions were defined as 1 − (final PET-CT value)/(corresponding initial PET-CT value). The primary endpoint was freedom from progression (FFP).

Results—For 202 patients treated with chemotherapy with or without radiation therapy, the 5-year FFP was 89% (95% confidence interval 85%–93%). All PET-CT parameters were strongly associated with the Deauville score ($P<.001$) and FFP ($P<.0001$) on univariate analysis. The

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Conflict of interest: none.

Deauville score was highly predictive of FFP (C-index 0.89) but was less discriminating in the Deauville 1 to 4 subset (C-index 0.67). Therefore, we aimed to identify PET-CT parameters that would improve risk stratification for this subgroup (n=187). STV reduction was predictive of outcome (C-index 0.71) and was dichotomized with an optimal cutoff of 0.65 (65% reduction in STV). A model incorporating the Deauville score and STV reduction predicted FFP more accurately than either measurement alone in the Deauville 1 to 4 subset (C-index 0.83). The improvement in predictive accuracy of this composite measure compared with the Deauville score alone met statistical significance (P=.045).

Conclusions—The relative reduction in tumor size is an independent predictor of outcome. Combined with the Deauville score, it might improve risk stratification and contribute to response-adapted individualization of therapy.

Introduction

Early-stage classical Hodgkin lymphoma (HL) is highly curable, with combined modality therapy resulting in progression-free survival rates of ≥85% (1, 2). Given these excellent outcomes, minimizing the adverse effects of treatment, while maintaining effective disease control, is critical. Therefore, significant effort has been invested to decrease the intensity of therapy for most patients, who have excellent prognoses (3). In contrast, a small subset of patients with early-stage HL will develop refractory or relapsed disease, which can be fatal. In both scenarios, a tool that predicts outcome and allows individualization of therapy is highly desirable to ensure that fewer patients are under- or overtreated.

Currently, the accepted imaging modality for response assessment in HL is fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT). Disease response assessed using PET-CT is reported using the 5-point Deauville score, which describes the tumor's FDG-avidity relative to 2 reference points within the individual patient: the mediastinal blood pool and the liver (4, 5). Although the Deauville score is highly associated with patient outcome, numerous other CT and PET parameters are available that might improve risk stratification and contribute to the individualization of therapy. We analyzed the postchemotherapy PET-CT scans of patients with early-stage HL treated at a single institution and assessed for radiographic parameters associated with freedom from progression (FFP). We hypothesized that complementary PET-CT data, considered in combination with the Deauville score, would improve the outcome prediction.

Methods and Materials

Patients

After approval by the institutional review board, all patients treated for stage I to II HL at our institution from January 1, 2003, to December 31, 2013, were identified retrospectively. Only patients with analyzable FDG-PET-CT scans performed before and after chemotherapy were eligible for analysis. Clinical information was retrieved from the electronic medical record.

Definitions

Bulk at any site was defined as a tumor diameter >10 cm in any dimension. FFP was defined as the interval from the initial diagnosis to a diagnosis of relapsed or refractory disease. Cases of relapsed or refractory disease were typically confirmed by biopsy. For cases in which no biopsy was performed, disease was defined as relapsed or refractory based upon the radiographic findings and clinical impression.

PET-CT acquisition

FDG-PET-CT imaging was performed at a single institution using 1 of 4 scanners (DST, 2 DRX, or DSTE; GE Healthcare, Milwaukee, WI). The corresponding CT scanners consisted of 8 slices (DST model), 16 and 64 slices (DRX model), or 64 slices (DSTE model). Patients fasted for 6 hours before the FDG injection. A normal fasting blood glucose level of <150 mg/dL was required. Patients were positioned supine, with their arms raised, in the PET-CT device. PET data acquisition was performed in 2-dimensional mode before January 2008 and in 3-dimensional mode after that date. For 2-dimensional imaging, an intravenous injection of 555 to 629 MBq (15 to 17 mCi) of FDG was administered in the arm or central venous catheter, and emission scans were acquired at 3 minutes per field of view, 70 ± 10 minutes after the FDG injection. The same procedure was used for 3-dimensional imaging, except that the injected dose of FDG was 333 to 407 MBq (9 to 11 mCi). PET images were reconstructed using standard vendor-provided reconstruction algorithms. CT images, from the skull to the mid-thigh, were acquired in helical mode (speed of 13.5 mm per rotation) during suspended mid-expiration using a 3.75-mm slice thickness, a tube voltage of 120 kVp, a 0.5-second rotation, tube current modulation, and a noise index of 30. All PET-CT scanners used in the present investigation routinely undergo a regimental quality assurance program that entails daily quality control testing and quarterly calibration to ensure accurate standardized uptake value (SUV) quantification. Additionally, the image reconstruction parameters on these systems have been optimized by varying the reconstruction kernel-to-yield relatively similar SUV. After image reconstruction, the PET-CT images were transferred to MIM software, version 6.4.9 (MIM Software Inc, Cleveland, OH) and fused for further analysis.

PET-CT analysis

Two of the authors (M.A., S.A.M.) analyzed all PET-CT scans. The soft tissue volume (STV), which encompassed all abnormal tissue noted on the CT scan, was contoured on each pre- and postchemotherapy scan. The analyzers (M.A., S.A.M.) reviewed each other's contours to ensure that a consensus STV was measured. A threshold segmentation method was used to delineate the metabolic tumor volume (MTV), defined as the volume within the STV with an SUV of ≥2.5 (6). The total lesion glycolysis (TLG) was defined as the MTV multiplied by the mean SUV of the MTV. To compare the values obtained from the pre- and postchemotherapy scans, the reduction in each parameter was defined as 1 – (value from the final PET-CT scan/corresponding value from the initial PET-CT scan).

To determine the Deauville score, a region of interest (ROI) encompassing the residual STV was contoured on each postchemotherapy PET-CT scan. Another ROI was drawn on 5 contiguous slices in the mediastinal blood pool at the level of the aortic arch, and a third ROI

was contoured within the liver parenchyma at mid-height. The ROI within the mediastinal blood pool and the liver was restricted to areas of physiologic uptake. The maximum SUV (SUV_{max}) of each ROI was calculated, and Deauville scores were assigned as previously reported (4, 5).

Statistical analysis

The primary outcome was FFP, defined as the interval from the initial diagnosis to a diagnosis of relapsed or refractory disease. If no event occurred, patients were censored at the time of last follow-up. Univariate Cox proportional hazard models were used to determine the effect of the covariates on FFP. Variable selection for the multivariate analysis was based upon clinical interest and predictive accuracy (measured using the C-index), with a selection of covariates that were not collinear, minimized overfitting, and were appropriately parsimonious according to the number of events (7). No covariate information was missing on multivariate analysis; therefore, no patients were excluded from the model owing to missing data.

To identify the cutoff value for STV reduction that best predicted FFP, the R Package “rpart” (recursive partitioning and regression trees) was used. This tool identified the optimal cutpoint to divide patients into the 2 groups with the greatest difference in FFP. The package was downloaded using the Comprehensive R Archive Network (available at: https://cran.r-project.org/web/packages/rpart/).

Harrell’s concordance index (C-index) quantified the predictive accuracy of the survival models, with a C-index of 1 indicating perfect accuracy and a C-index of 0.5 indicating no better than a random predictor (8). The bias-corrected C-index was calculated using a bootstrap internal validation procedure with 500 repeats. The predictive accuracy of the survival models was compared using U-statistics. Spearman correlation was used to assess the association among the continuous PET-CT parameters. Analyses were conducted using SAS, version 9.3 (SAS Institute, Cary, NC), S-Plus, version 8.0 (TIBCO Software Inc, Palo Alto, CA), and R, version 2.14.2, software.

Results

Patient, disease, and treatment characteristics

A total of 202 patients were eligible for the present analysis. A total of 116 patients (57%) were female and 146 (72%) were white (Table 1). The median age at diagnosis was 32 years (range 18–90). The disease was stage I in 29 patients (14%) and stage II in 173 patients (86%). Bulky disease was present in 60 cases (30%), and extranodal disease was present in 11 (5%). ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine) or ABVD-like chemotherapy was used in 194 cases (96%). Most patients received 4 (n=81; 40%) or 6 (n=100; 50%) cycles of chemotherapy. Consolidative radiation therapy (RT) was used in 143 cases (71%).

Patient outcomes

At a median follow-up of 4.4 years (range 1–12), 22 events were observed. In 19 cases (86%), the diagnosis of relapsed or refractory HL was confirmed by biopsy. In the remaining 3 cases (14%), the radiographic findings were considered sufficient to establish the diagnosis. For the total cohort, the actuarial 5-year FFP was 89% (95% confidence interval [CI] 85%–93%).

PET-CT analysis

The evaluated FDG-PET-CT parameters included the Deauville score, final STV, final SUV_{max}, final MTV, final TLG, STV reduction, SUV_{max} reduction, MTV reduction, and TLG reduction. These data for the 202-patient cohort are summarized in Table 2. Based on the Spearman correlation coefficients, each of these variables correlated strongly with all the others ($P<.001$ for all).

Patient outcome as a function of PET-CT parameters

The Deauville score was highly associated with FFP ($P<.0001$). Compared to patients with a postchemotherapy PET-CT scan that was a Deauville category 1 to 2, the risk of an event was greater for those with Deauville score 3 (hazard ratio [HR] 6.96), Deauville score 4 (HR 21.4), and Deauville score 5 (HR 258; Table 3). For the total cohort, the C-index for the Deauville score was 0.89, and the bias-corrected C-index was 0.90. Of the 15 patients with a Deauville score of 5, 13 developed relapsed or refractory disease. The event was biopsy proven in 12 cases and based upon radiographic findings in 1 case. The remaining 2 patients with a Deauville score of 5 received RT alone as part of upfront therapy and never experienced disease progression. Thus, a Deauville score of 5 accurately identified patients at high risk of progression.

The Deauville score was less discriminating prognostically when patients with a Deauville score of 5 were excluded. In the subset of patients with a Deauville score of 1 to 4 (n=187; 9 events), the C-index for the Deauville score (Deauville score 1–3 vs 4) was 0.67, and the bias-corrected C-index was 0.66. Thus, another predictive marker would be particularly useful for the Deauville 1 to 4 subgroup.

All the analyzed PET-CT parameters were significantly associated with FFP ($P\leq.0001$). We hypothesized that the consideration of other radiographic parameters, in addition to the Deauville score, would improve prognostication. We focused our analysis on the Deauville 1 to 4 subset, because the identification of an additional predictive marker would be particularly valuable in this group, for which the Deauville score is less discriminating. In addition to the Deauville score, the variables that most accurately predicted FFP were the final SUV_{max}, SUV_{max} reduction, and STV reduction (Table 4). The Deauville score is assigned based on the SUV; thus, we chose not to explore the SUV as a separate predictive parameter. In contrast, the Deauville score and STV reduction are distinct, complementary measures of therapeutic response, representing metabolic and anatomic information, respectively. Therefore, we explored whether consideration of STV reduction would improve the prognostication in the Deauville 1 to 4 group.

In the Deauville 1 to 4 subset, we identified the optimal cutoff value for a change in STV to dichotomize the group as demonstrating a “small” versus “large” relative reduction in tumor size. The cutoff value was 0.65, representing a 65% reduction in the STV between the pre- and postchemotherapy PET-CT scans. Patients with a small reduction in the STV (≤65%) experienced significantly worse FFP (HR 19.1, 95% CI 5.13–71.4, $P<.0001$). The 5-year FFP was 50% (95% CI 25%–100%) for patients with a small STV reduction versus 97% (95% CI 95%–100%) for those with a large reduction.

We hypothesized that a model incorporating the Deauville score and STV reduction would predict FFP more accurately than either measurement alone for the Deauville 1 to 4 subset. For the Deauville score (1–3 vs 4), the C-index was 0.67 and the bias-corrected C-index was 0.66 (Table 4). For STV reduction (≤65% vs >65%), the C-index was 0.69 and the bias-corrected C-index was 0.70. In a model incorporating both the Deauville score and STV reduction, the C-index was 0.83 and the bias-corrected C-index was 0.82. The predictive accuracy of these survival models was compared using U-statistics. The model incorporating both the Deauville score and STV reduction was significantly more predictive of FFP than the model with the Deauville score alone ($P=.045$). Thus, although the Deauville score was highly associated with FFP, the composite measure was even more accurately predictive of outcome.

Finally, we assessed the predictive value of the Deauville score and STV reduction in the entire cohort (Deauville score 1–5). In the total cohort, FFP was significantly associated with both the Deauville score and STV reduction on univariate and multivariate analysis ($P<.0001$). For the total cohort, we analyzed not only STV reduction, but also the absolute residual STV after chemotherapy. The mean postchemotherapy residual STV was 127 cm^3 (range 2–714) in the patients with disease relapse versus 27 cm^3 (range 0–302) in the patients without disease relapse ($P<.0001$).

Given the larger number of events in the total cohort, we were able to separately analyze the patients who had received and had not received RT after the postchemotherapy PET-CT scan. In the patients who had not received RT (n=59; 18 events), FFP was highly associated with the Deauville score and STV reduction on univariate and multivariate analysis ($P<.0001$, for all). Likewise, among the patients who received RT (n=143; 4 events), FFP was significantly associated with the Deauville score ($P=.002$) and STV reduction ($P=.0004$) on univariate analysis. However, a multivariate analysis could not be performed for this subset owing to the small number of events. No difference was found in the RT dose between the patients with a small versus large STV reduction (mean 30.5 Gy vs 30.2 Gy; $P=.54$). The STV reduction was not associated with the presence of bulky disease at diagnosis ($P=.8$); thus, it was not a surrogate for bulky disease but instead was a distinct predictor of outcome.

Discussion

In the present cohort of early-stage HL patients, the relative reduction in tumor size during chemotherapy was a highly significant predictor of outcome, independent of the Deauville score. Furthermore, a model incorporating STV reduction and Deauville score was more predictive of progression than the Deauville score alone. Our findings suggest that a

composite measure, incorporating CT and FDG-PET data, more accurately risk stratifies patients than the use of either measure alone. Thus, although PET has become the accepted modality to assess disease response, CT maintains significant value.

Previously published data support the conclusion that STV reduction is important prognostically. In a report by the Cancer and Leukemia Group B (CALGB), 88 patients with nonbulky, stage I to II HL were treated with 6 cycles of doxorubicin, vinblastine, and gemcitabine and were evaluated by PET-CT after 2 cycles. Progression-free survival was associated with the Deauville score and with the change in tumor size, reported as the percentage of change in the sum of the products of the perpendicular diameters (9). Consistent with the present study, the investigators found that a composite measure, incorporating the Deauville score and tumor size reduction measured on CT scan, better predicted outcome than either test alone. In their cohort, the best cutoff value for the percentage of change in the sum of the products of the perpendicular diameters was a decrease of 65%, identical to the cutoff value we identified.

Another study addressed 105 HL patients, all of whom had negative PET scan findings at the end of treatment (chemotherapy with or without RT). Patients with a residual CT mass experienced significantly worse FFP. A larger residual mass correlated with lower FFP in a continuous fashion (P=.007). When the size of the mass was dichotomized as a maximum diameter <4 cm versus ≥4 cm, the FFP was 82% versus 50%, respectively (P=.029) (10).

Finally, in the German Hodgkin Study Group HD15 trial of advanced-stage HL treated with BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, Oncovin, procarbazine, prednisone), those patients with a residual mass after chemotherapy that measured >2.5 cm on CT scan were assessed using PET. RT was given if this PET scan revealed FDG-avidity of the mass. In the PET-positive patients, the relative reduction in the size of the CT mass was predictive of outcome. The rate of relapse was 5.3% in patients with a reduction in diameter of >40% compared with 23.1% in those with a reduction in diameter of ≤40%. This difference in outcomes was observed despite administration of RT. Likewise, in our study, a small reduction in STV was associated with a worse outcome, even in patients who received RT after PET-CT scanning. With the caveat of a small number of events, these results suggest that RT might not overcome the negative prognostic effect of a suboptimal reduction in the STV. In our cohort, no difference was found in the RT dose used for patients with a small versus large STV reduction. The role of radiation dose escalation in patients with a small STV reduction warrants future investigation.

The cited studies used the diameter to measure the tumor size. We elected to assess the tumor volume, rather than the diameter, because it is a more accurate indicator of the total disease burden. However, this approach has limitations. First, the interobserver variability in STV versus diameter measurements could be greater. However, our findings reached such strong statistical significance that interobserver differences in the STV measurements would not be expected to influence the overall conclusions. A second limitation is that STV measurements take longer to perform. Thus, although our work demonstrated the principle that the reduction in tumor volume is an important prognostic factor, an interesting future direction will be to operationalize this finding for daily clinical practice.

The strengths of our work included the large number of patients and analyses of all PET-CT scans by the same researchers. A limitation, inherent to any study of a highly curable condition, is the small number of events. Thus, these results should be viewed as proof of concept and validation of previous findings. Prospective testing in ongoing clinical trials is encouraged to confirm these data.

Conclusions

Although PET has assumed a central role in response assessment in HL, CT provides additional value and should not be abandoned. A composite measurement, incorporating functional and anatomic data, yielded the most accurate risk stratification. Therefore, PET and CT scans should be performed for all patients before and after chemotherapy to enhance the prediction of outcome. An area of active study is the de-escalation or intensification of therapy according to the disease response as measured by PET. Incorporation of CT data might improve response assessment and enable better patient selection for such individualized treatment strategies.

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Summary

In a cohort of 202 patients with early-stage classical Hodgkin lymphoma, the relative reduction in tumor size during chemotherapy was highly predictive of outcome, independent of the Deauville score. A model incorporating soft tissue volume reduction and the postchemotherapy Deauville score was more predictive of freedom from progression than the Deauville score alone. Our findings suggest that a composite measure, incorporating CT and PET data, more accurately risk stratifies patients than either study used alone.

Table 1

Patient, disease, and treatment characteristics

Characteristic	Value
Age at diagnosis (y)	
Median	32
Range	18–90
Female sex (n)	116 (57)
White race (n)	146 (72)
Stage (n)	
I	29 (14)
II	173 (86)
B symptoms (n)	54 (27)
Bulky disease (n)	60 (30)
Extranodal disease (n)	11 (5)
ABVD or ABVD-like chemotherapy (n)	194 (96)
Chemotherapy cycles (n)	
2	14 (7)
3	3 (1)
4	81 (40)
5	4 (2)
6	100 (50)
RT given as part of upfront therapy (n)	143 (71)
Radiation dose (Gy)	
Median	30.6
Range	20–42.2

Data in parentheses are percentages.

Table 2

FDG-PET-CT parameters

Variable	n (%) or median (range)
Final PET-CT Deauville score	
1–2	105 (52)
3	61 (30)
4	21 (10)
5	15 (7)
Final PET-CT soft tissue volume (cm^3)	14 (0–714)
Final PET-CT maximum SUV	2 (1–20)
Final PET-CT metabolic tumor volume (cm^3)	0 (0–648)
Final PET-CT total lesion glycolysis	0 (0–4497)
Reduction in soft tissue volume (%)	91 (−10 to 100)
Reduction in maximum SUV (%)	82 (−120 to 97)
Reduction in metabolic tumor volume (%)	100 (20–100)
Reduction in total lesion glycolysis (%)	100 (26–100)

Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; PET = positron emission tomography; SUV = standardized uptake value.

Table 3

Patient outcomes according to Deauville score

Deauville score	Patients (n)	Events (n)	2-y FFP (%; 95% CI)	HR (95% CI)	*P* value
1–2	105	1	99 (97–100)	Reference	Reference
3	61	4	95 (89–100)	6.96 (0.78–62.3)	.08
4	21	4	86 (72–100)	21.4 (2.39–192)	.006
5	15	13	13 (0–48)	258 (33.0–2012)	<.0001

Abbreviations: CI = confidence interval; FFP = freedom from progression; HR = hazard ratio.

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2018 July 05.

Table 4

C-indexes for FDG-PET-CT parameters in the Deauville 1–4 subset

Parameter	C-index	Bias-corrected C-index
Deauville score (1–3 vs 4)	0.67	0.66
Final MTV	0.59	0.55
Final TLG	0.58	0.54
Final STV	0.64	0.61
Final SUV_{max}	0.73	0.72
MTV reduction	0.40	0.63
TLG reduction	0.41	0.61
STV reduction	0.71	0.70
SUV_{max} reduction	0.70	0.68
STV reduction dichotomized (≤65% vs >65%)	0.69	0.70
Deauville Score (1–3 vs 4) plus STV reduction dichotomized (≤65% vs >65%)	0.83	0.82

Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; MTV = metabolic tumor volume; PET =positron emission tomography; STV = soft tissue volume; SUV_{max} = maximum standardized uptake value; TLG = total lesion glycolysis.