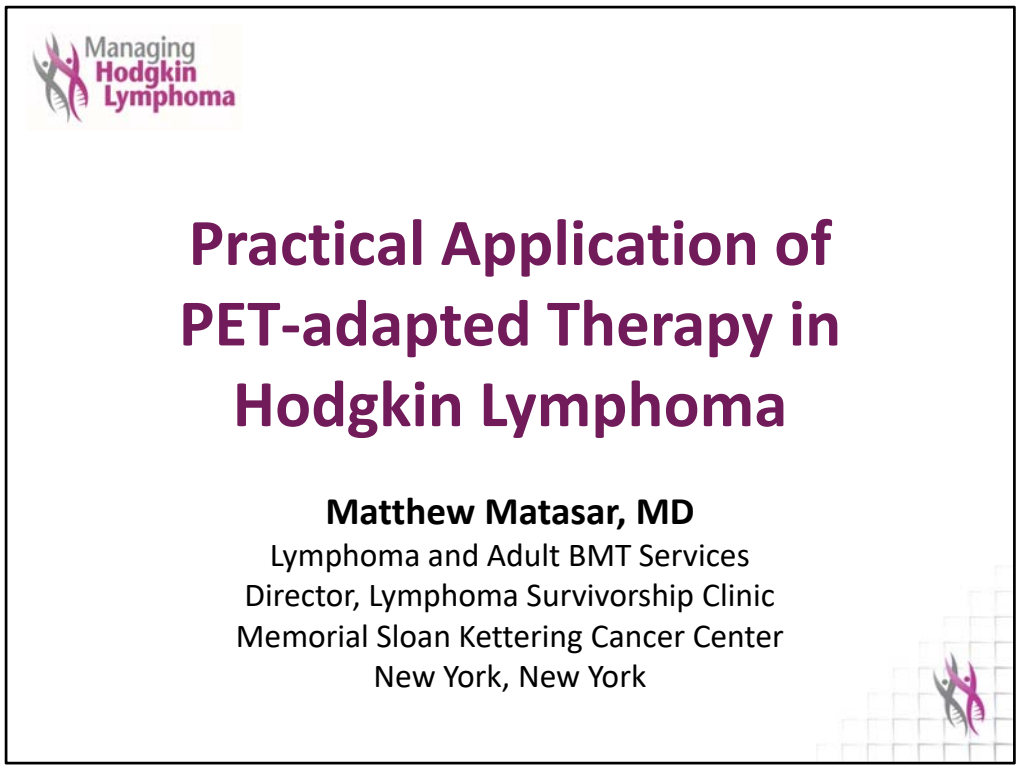
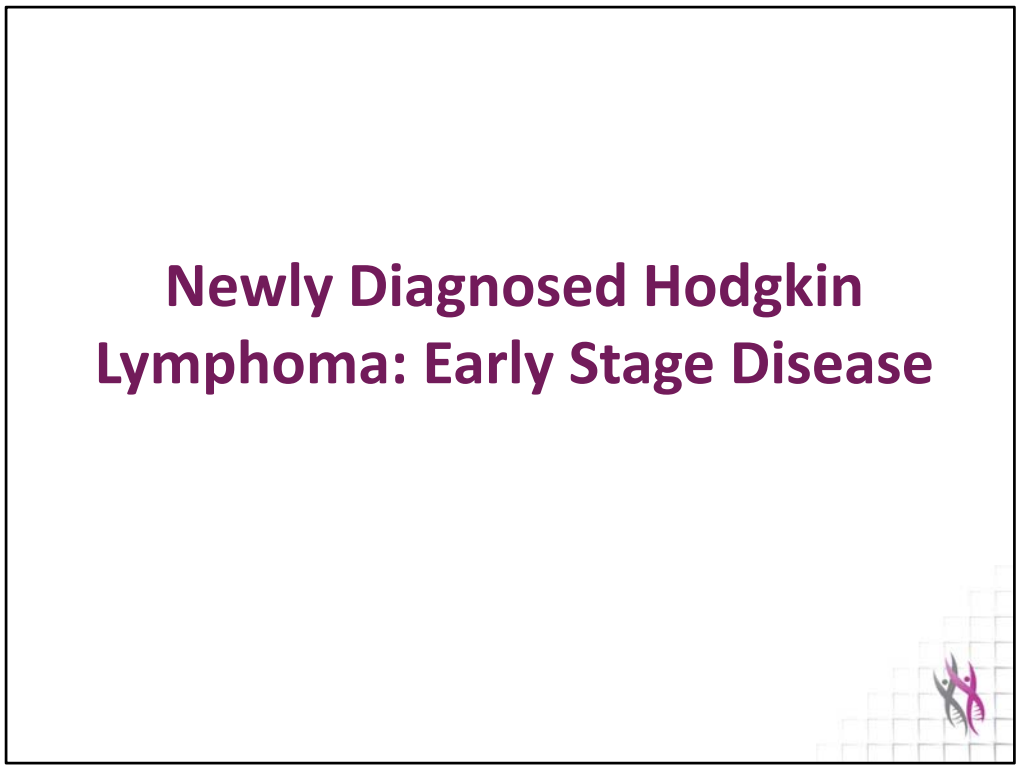


Hi everyone. My name is Dr. Matthew Matasar. I am an attending physician at Memorial Sloan Kettering Cancer Center, a member of our lymphoma and adult bone marrow transplant services. I am looking forward to speaking with you about the role of PET response in PET-adaptive therapy in the management of classical Hodgkin lymphoma. Let's begin.

Roadmap

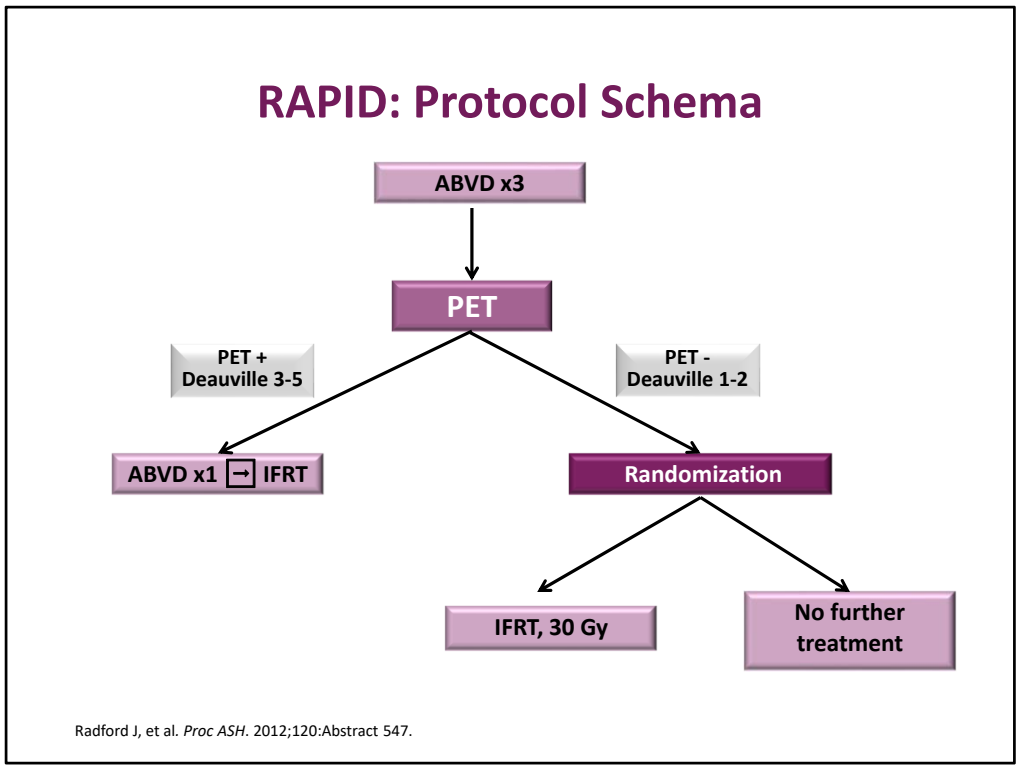
- Newly diagnosed Hodgkin lymphoma
  - Early stage
  - Advanced stage
- Relapsed Hodgkin lymphoma

Over this next stretch of time, I'm going to be speaking about data in both newly diagnosed patients with classical Hodgkin lymphoma, both early stage and advanced stage disease, as well as patients with relapsed Hodgkin lymphoma focusing specifically on the role for PET in guiding therapeutic decision-making for patients with Hodgkin's.



Let's start with patients that have newly diagnosed classical Hodgkin lymphoma identified at early stage. What is the role for PET in guiding decision-making?

Practical Application of PET-adapted Therapy in Hodgkin Lymphoma



Some of the key data that we'll be looking at are focusing on recent clinical trials that help us better understand how to use functional imaging in managing our patients. One important study for patients with early stage classical Hodgkin lymphoma is the study that's known as the RAPID trial, aptly named because it focuses on the ability of delivering a rapid or foreshortened course of chemotherapy for select patients. In this study, patients with early stage, more favorable classical Hodgkin lymphoma were identified and received three cycles of traditional chemotherapy in the form of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and subsequently underwent restaging imaging with an ^{18}F-FDG PET scan. Based upon the response by PET after these three months of three cycles of ABVD chemotherapy, next steps in the patient care were determined. For patients who had a PET-negative response, here PET-negative is defined as a score of either Deauville 1 or Deauville 2. I will be speaking more about Deauville scoring later on in this talk. Patients who had a PET-negative response by those relatively stringent criteria, subsequently were randomized while they are being told that's all the treatment you need or receiving what we'd say consolidative radiation therapy with a dose of 30 Gy to the involved field where the disease was initially. There is also what to do with patients if their PET was still positive at this point. These patients went on to receive additional treatment in the form of a fourth month of chemotherapy and radiation, but I want to focus on the PET-negative arm here for this discussion.

FDG-PET Assessment
Deauville Criteria or 5-point Score

Score	FDG-PET / CT scan result
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately more than liver uptake, at any site
5	Markedly increased uptake at any site or new sites of disease

Score of 1 or 2 = PET negative

Reminding us what the Deauville scoring is all about, we know that a score of 1, 2, 3, 4, 5 represent these different findings on a PET scan. Traditionally, a score of 1 or 2 is always defined as negative, and a score of 4 or 5 is always defined as positive. Various studies decide what to do with a Deauville 3 which is some sort of an in-between result. Here in the RAPID trial given that they were giving quite minimized therapy, they selected the most stringent PET results which is only a Deauville 1 or 2.

RAPID: Eligibility

- Histologically confirmed classical Hodgkin lymphoma
- Stages IA or IIA by CT scan (no baseline PET)
- No mediastinal bulk or B symptoms
- No previous treatment
- Written informed consent

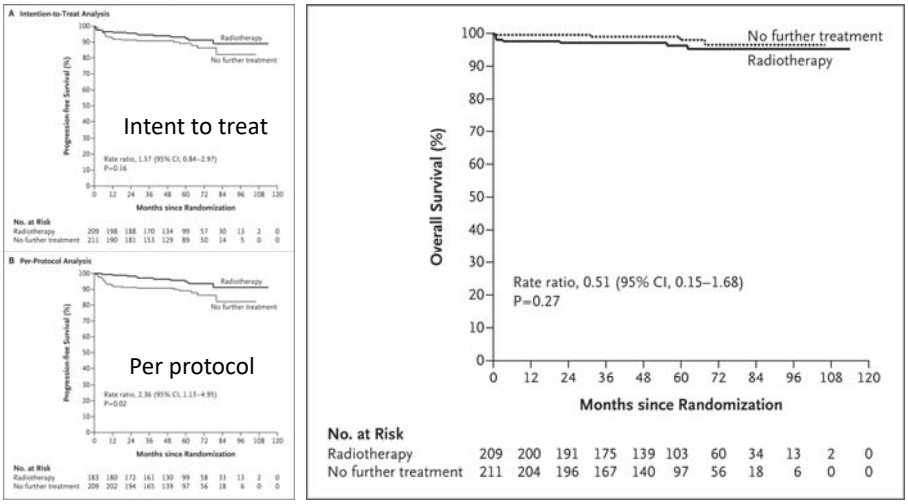
Radford J, et al. *Proc ASH*. 2012;120:Abstract 547.

Eligibility for this trial, we are looking at histologically-confirmed classical Hodgkin lymphoma, early stage disease by CT. Interestingly baseline PETs were not mandated or are always available. Patients could neither have bulky disease nor the so called B symptoms of drenching night sweats, unexplained fever or weight loss greater than 10% of body weight without alternate explanation. Had to be previously untreated and had to agree to the study.

Practical Application of PET-adapted Therapy in Hodgkin Lymphoma

RAPID: Results in PET-negative Patients

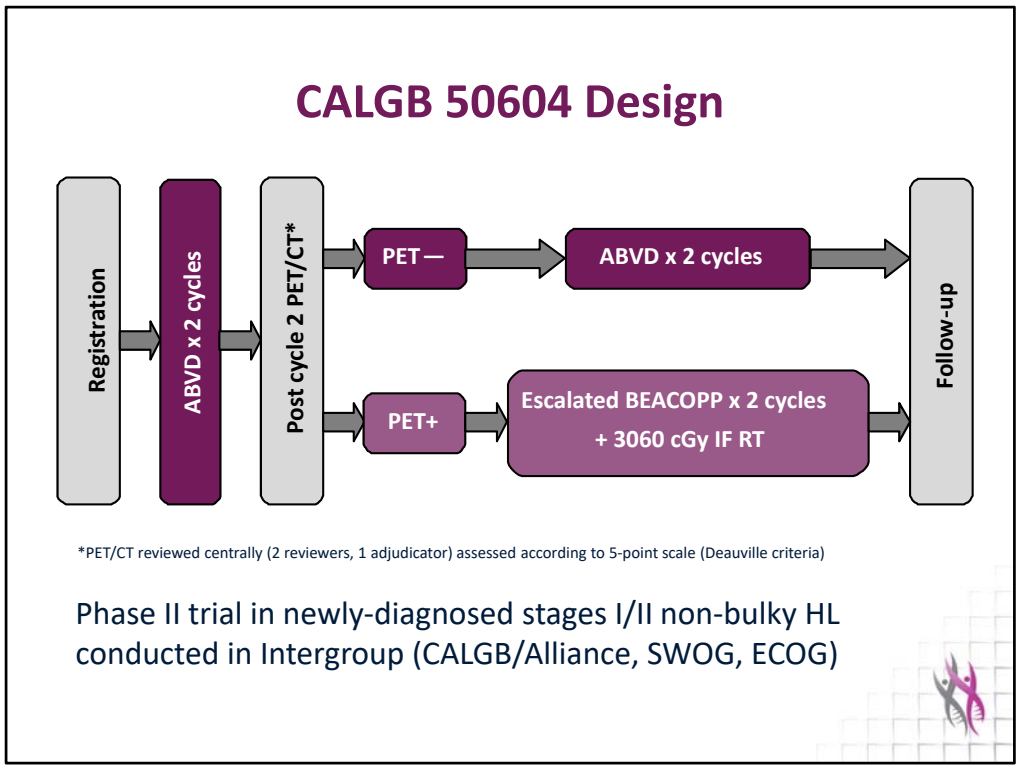
PFS **OS**



Radford J, et al. *N Engl J Med.* 2015;372:1598-1607.

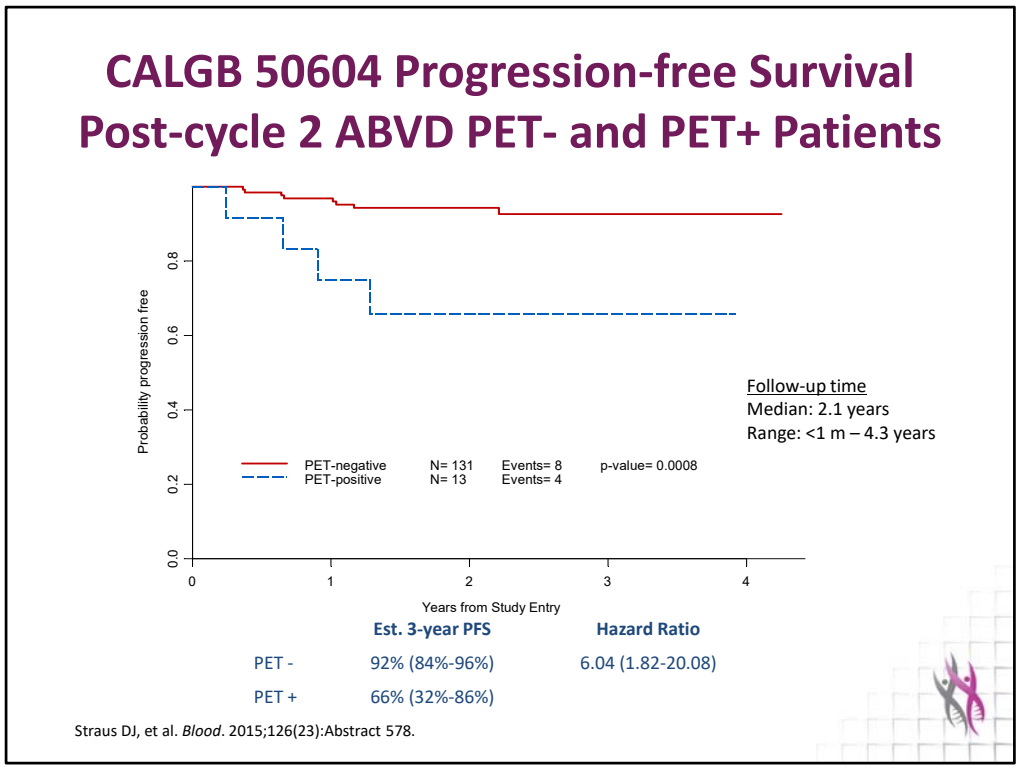
What we see is that in the PET-negative patients, the results were outstanding whether or not consolidative radiation therapy was administered. From the upper left here, in the intent to treat progression-free survival curve, you see that there is no statistically significant difference in progression-free survival whether or not consolidative therapy was given. Most importantly in terms of overall survival, there is absolutely no difference in terms of a statistical measurement between the survival of patients whether or not they receive radiation therapy. This is important, because it gives us justification for minimizing the exposure of patients to radiation treatment that can have both short- and long-term consequences for their wellbeing, justifying three months of therapy alone in a select group of patients.

Practical Application of PET-adapted Therapy in Hodgkin Lymphoma



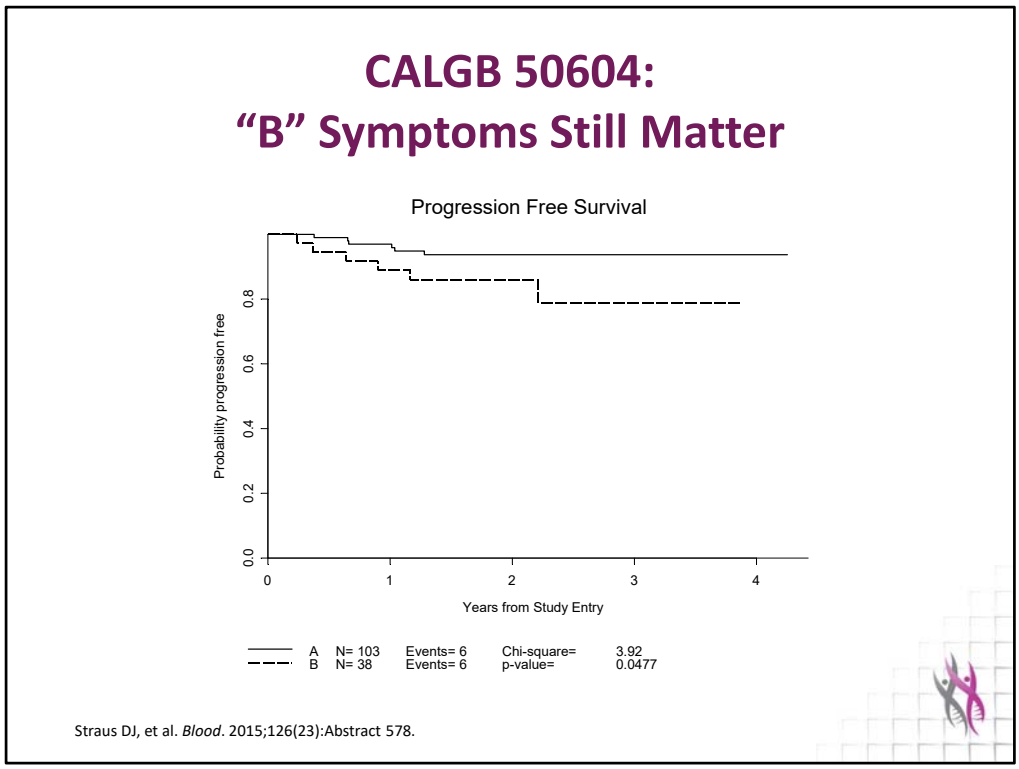
Here is a second study with a slightly different design but also giving quite important data to us as practicing clinicians looking to manage our patients. In the CALGB study, the patients were started by receiving two months of ABVD and then having an interim PET or a PET-2. Patients who had a PET-negative response at that time went on to receive two more months for a total of four cycles of ABVD without radiation therapy. Importantly for the CALGB study, PET-negative is defined as Deauville 1, 2 or 3, meaning that fewer patients will be classified at being PET-positive and fewer patients will thus be exposed to escalated therapy including radiation treatment.

Practical Application of PET-adapted Therapy in Hodgkin Lymphoma



Shown here is the results for our patients who are either PET-negative at the two-month mark or PET-positive at the two-month mark. You see that for the PET-negative curve, despite the fact that they did not go on to receive consolidative radiotherapy, results are quite outstanding at a relatively early median follow-up time for progression-free survival. PET-positive patients with escalated treatment to a more intensified chemotherapy regimen in escalated BEACOPP with radiation therapy having a progression-free survival of 60% is quite favorable, better than you would expect with ABVD completion alone with or without radiation treatment suggesting that there may be a role for intensification in this patient population when they have an adverse PET at the end of two months of ABVD.

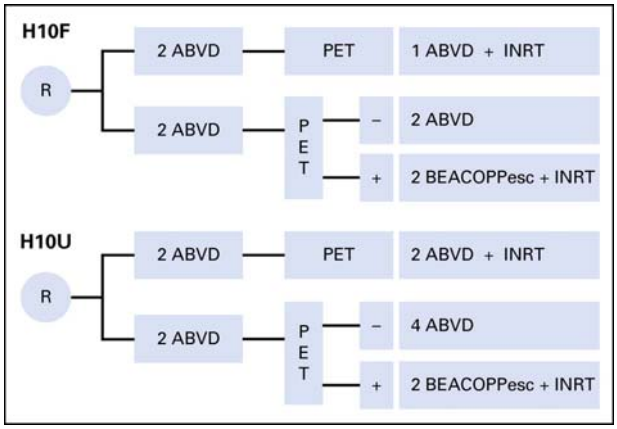
Practical Application of PET-adapted Therapy in Hodgkin Lymphoma



Something important for us to remember is that there is a nice set of data from the CALGB study showing that the presence of B symptoms at the time of diagnosis, even in the modern era, remains prognostically adverse; and it's important for us to remember that such patients really should not receive ultra-minimized therapy. The standard at Memorial is for such patients to really receive full-course therapy as if they were to have advanced stage disease.

Practical Application of PET-adapted Therapy in Hodgkin Lymphoma

EORTC H10 Trial in Early Stage Hodgkin Lymphoma

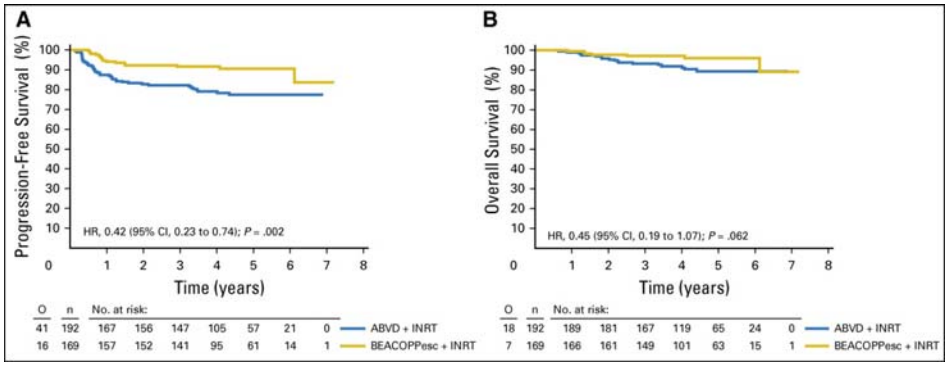


André MPE, et al. *J Clin Oncol.* 2017;35:1786-1794.

The third trial that I would like to talk about for early stage Hodgkin lymphoma is the set of trials known as the H10 trials which put patients into either favorable or unfavorable risk strata. Again, two months of ABVD chemotherapy were administered for patients that were randomized to the experimental approach. If they were PET-negative they went on to receive chemotherapy alone without radiation therapy. The PET-positive patients were escalated to the intensified escalated BEACOPP approach and all would go on to receive radiation.

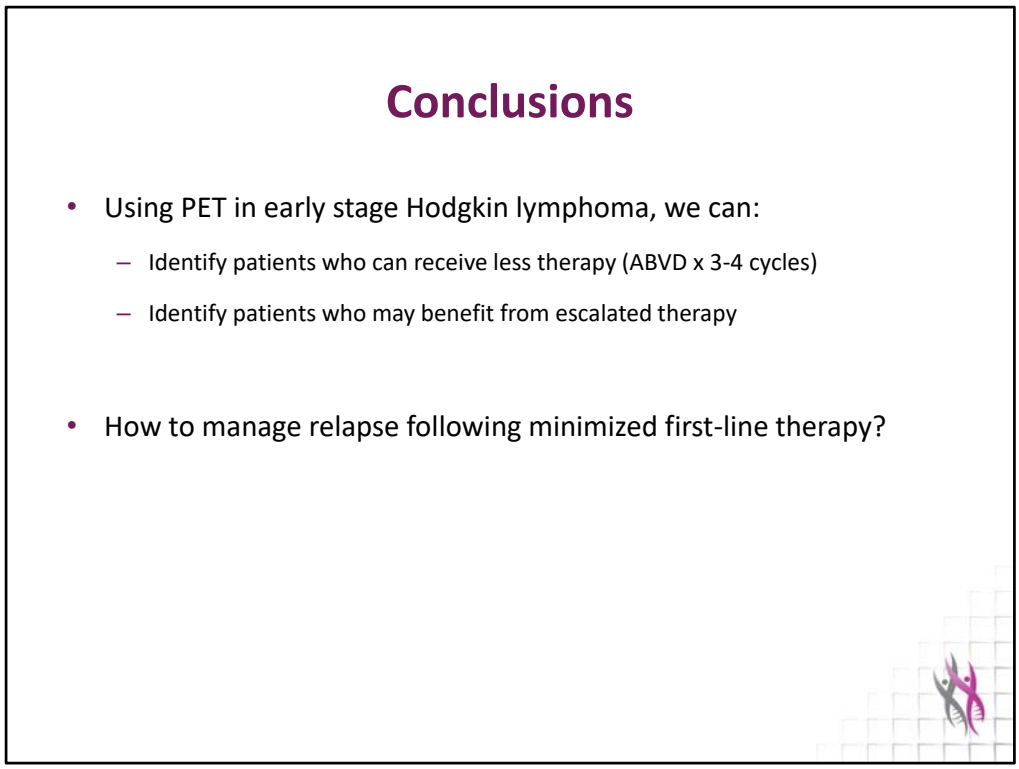
Practical Application of PET-adapted Therapy in Hodgkin Lymphoma

H10 Results: Interim PET+ Patients

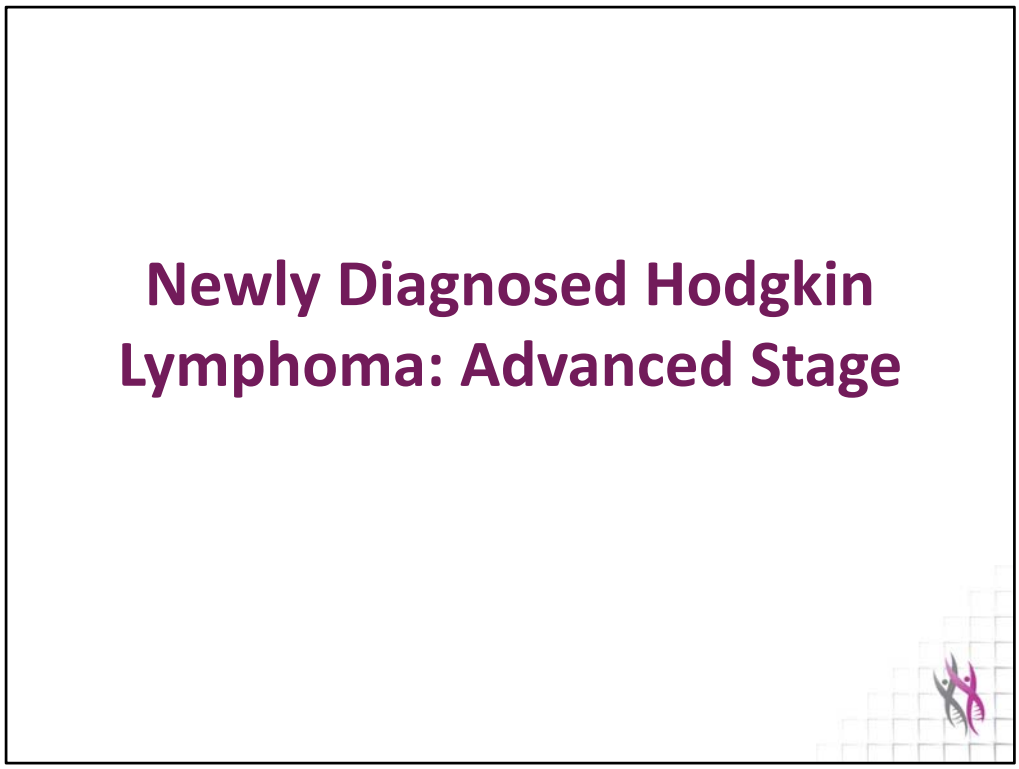


André MPE, et al. *J Clin Oncol.* 2017;35:1786-1794.

Looking at the interim PET-positive patients, patients who were escalated to BEACOPP as opposed to completing ABVD, we see that the use of a more intensified chemotherapy approach for such patients was associated with improvement in progression-free survival quite dramatically. Even here there is a trend towards overall survival benefits with a *P*-value of 0.06, not yet achieving statistical significance but approaching it, and many of us expected these results to continue to diverge as the data set matures, meaning that there may be a true survival benefit for escalated therapy for patients with an adverse PET at the end of two cycles of ABVD chemotherapy, in people with early stage disease.

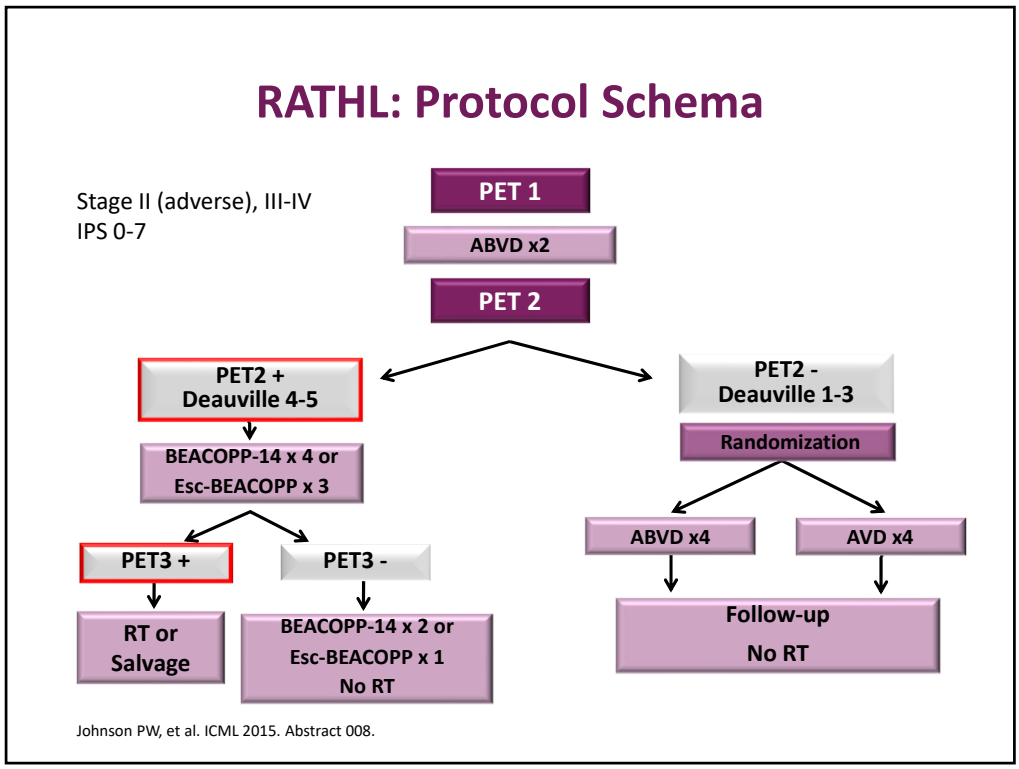


In conclusion for early stage Hodgkin lymphoma that is newly diagnosed, we can use PET in a couple of ways. Number 1, we can use it to identify patients who may be able to receive less therapy, meaning chemotherapy alone three or four cycles of ABVD and exclude radiation therapy safely. We may be able to identify patients who may benefit from a more intensified approach despite having an early stage Hodgkin lymphoma diagnosis that is traditionally associated with excellent overall outcomes. One challenge that we in the lymphoma community are going to face over these next years is what to do with patients who receive minimized therapy as their first-line treatment and then go on to experience a relapse. Traditionally, relapsed classical Hodgkin lymphoma is managed with intensified chemotherapy approaches and autologous stem cell transplantation. One wonders whether all patients who relapsed after minimized first-line therapy really require such as an intensive second approach, and this is the question that we in the research community are actively trying to answer in the present tense.



Going on to advanced stage classical Hodgkin lymphoma. What do we know about the role for PET scan in guiding decision-making?

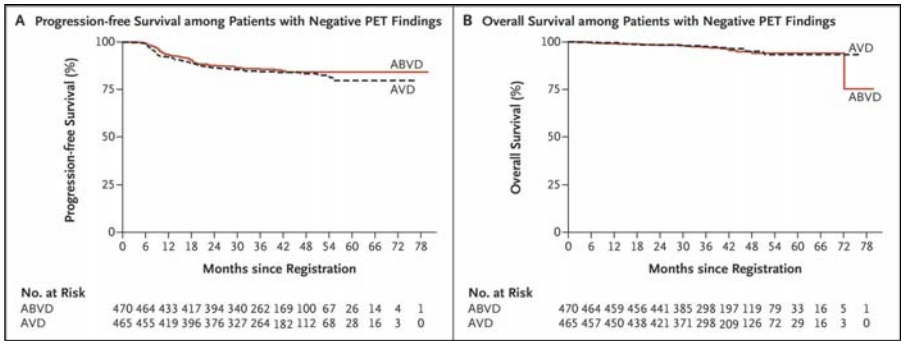
Practical Application of PET-adapted Therapy in Hodgkin Lymphoma



First, I'd like to call attention to the so-called RATHL trial which was recently reported in the *New England Journal of Medicine*. This is a very important study, both in and of itself, as well contextualizing further decision-making in cross-trial comparisons as treatments continue to evolve. Here, patients receive two months of ABVD chemotherapy for advanced stage disease and underwent PET re-imaging, PET-2. Patients who had a negative PET-2 here defined with a more broad criteria again of a Deauville 1, 2 or 3 score were subsequently randomized to complete the six months of ABVD chemotherapy as with the standard or to deescalate, exclude bleomycin from the next four cycles and give AVD (ABVD minus the B) for four months and then follow up those patients subsequently. Essentially asking the question of, if you have an interim PET that is negative, can you exclude bleomycin and thus minimize the risk of bleomycin pulmonary toxicity which is one of the most feared complications of ABVD chemotherapy.

Practical Application of PET-adapted Therapy in Hodgkin Lymphoma

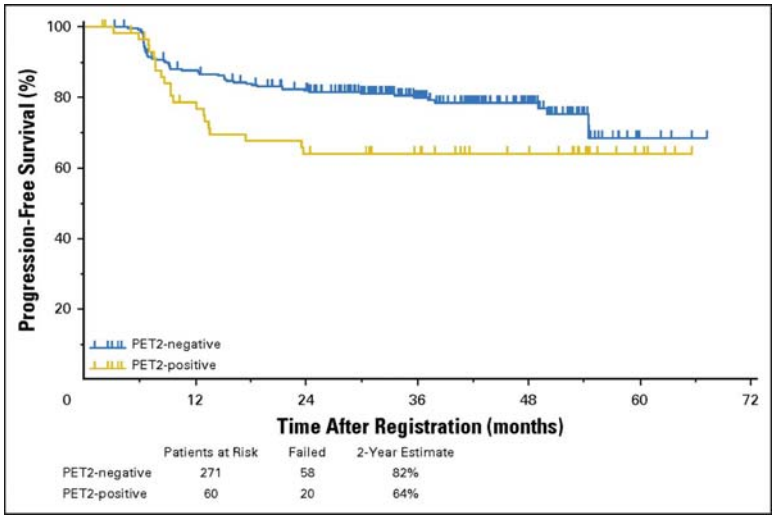
RATHL Trial Results: Progression-free and Overall Survival



Johnson P, et al. *N Engl J Med.* 2016;374:2419-2429.

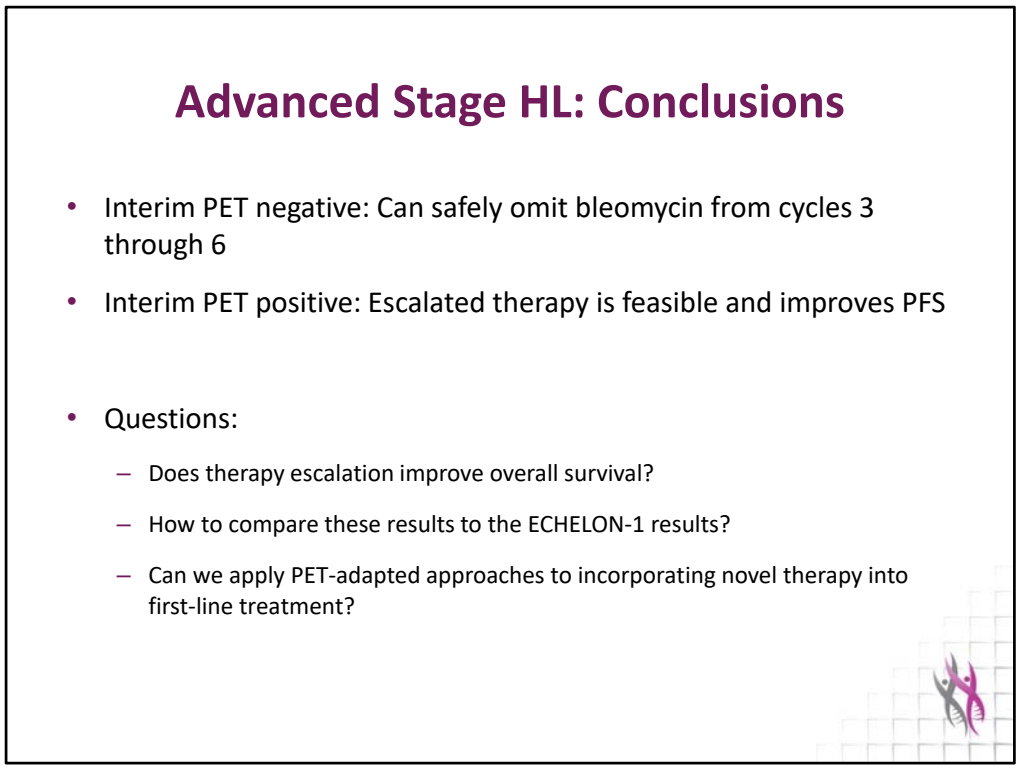
The answer from RATHL is, yes, you can exclude bleomycin safely if you achieve a Deauville 1 through 3 PET-negative interim PET scan. We see here that there is a minimal difference in progression-free survival and absolutely no difference in overall survival justifying this, and this truly has been practiced changing data and is a standard of care right now for advanced stage Hodgkin lymphoma.

SWOG S0816 Trial in Advanced Stage HL: Results

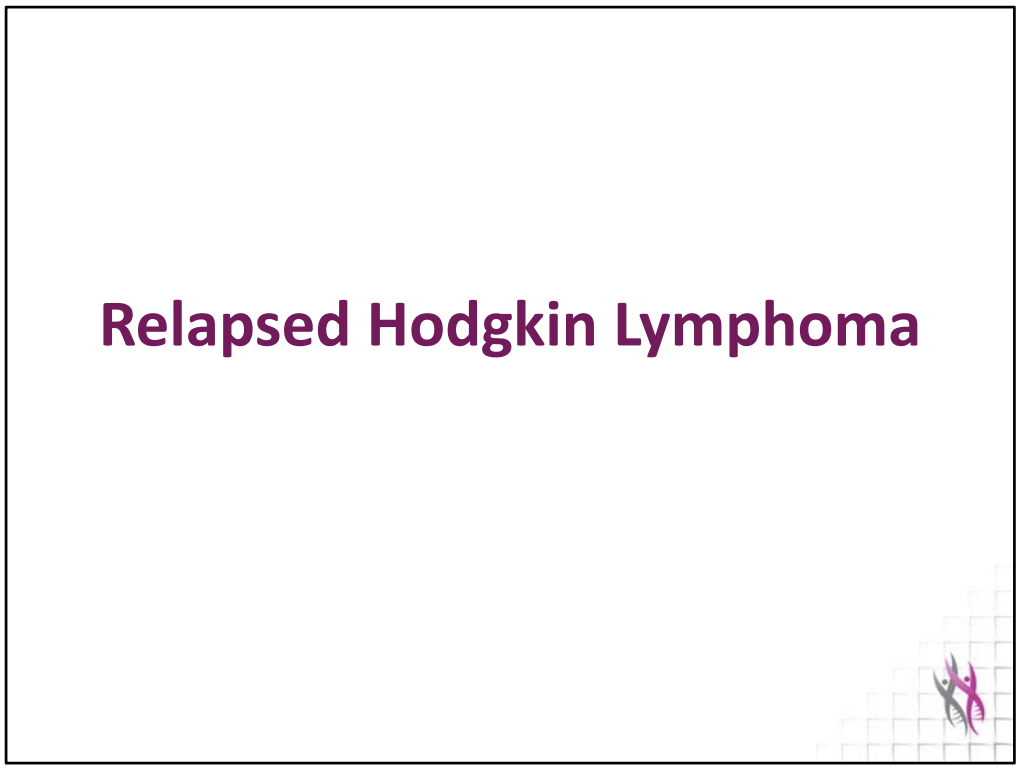


Press OW, et al. *J Clin Oncol.* 2016;34(17):2020-2027.

That is the de-escalation approach. Do we have any data regarding escalation of therapy for PET-positive patients? There are data from the RATHL trials, well that I've not shown here, but I want to look more carefully at the SWOG data. This is the trial that looked at PET-2 and was designed to analyze the role for intensification to escalated BEACOPP and see whether you can intensify treatment exposure in this group of patients and alter subsequent outcomes. We know from historical data that progression-free survival rates of patients who were interim PET-2 positive and go on to complete the ABVD chemotherapy alone are quite poor, some estimates in the 20% to 40% range in terms of progression-free survival at three years. Here in the SWOG data, we see that intensification of these patients to escalated BEACOPP to complete chemotherapy achieves a progression-free survival, approximately 60%. This is quite attractive and gives reasonable substantiation for the consideration of escalated BEACOPP in select patients. It is important to remember that escalated BEACOPP is toxic therapy. It is challenging treatment. It cannot be safely administered to elderly patients, and it is associated with a number of both short- and long-term risks, including but not limited to severe myelosuppression, gonadotoxicity and so on, as well a small but real rate of treatment-related MDS or AML. This is a decision that we do not make lightly, but knowing that a PET-2-positive patient has a very high risk of relapse and subsequent exposure to second-line therapy and stem cell transplant, the ability to avoid such second line approaches with intensification of first-line treatment is attractive.



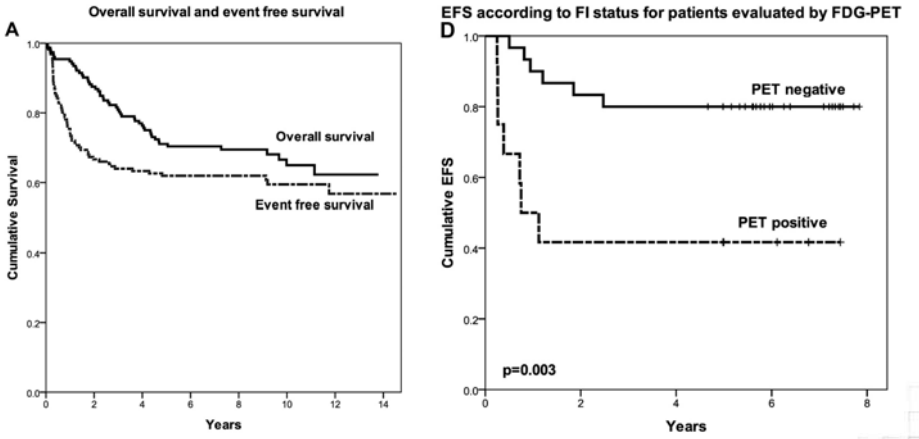
In summary, patients who are interim PET-negative after two cycles of AVD can go on to complete AVD chemotherapy with the omission of bleomycin, and patients who were PET-2 positive, it is a reasonable consideration to escalate appropriate patients to escalated BEACOPP to overcome this adverse finding. There are a lot of questions that we are going to face moving forward in how to best treat advanced stage Hodgkin lymphoma in the era of PET-adaptive therapy. Number 1, we need to better understand the long-term impact of escalated therapy. We see that it improves progression-free survival, it is important for us to be confident that we are actually changing the natural history of the illness with the intensification and not merely delaying the inevitable. Overall survival data are still maturing in these studies and are very important just to characterize this intervention. We have new data regarding a normal chemotherapy regimen with replacement of bleomycin with brentuximab vedotin. This is the so-called ECHELON-1 trial. We see that the substitution of bleomycin for brentuximab vedotin does improve to a very modest degree progression-free survival with no differences in overall survival. Some of that benefit is associated with or attributable to bleomycin pulmonary toxicity. This study was designed and conducted pre-RATHL, and whether the results are as meaningful in the era where we are using PET scans to minimize bleomycin exposure and thus bleomycin pulmonary toxicity is still more in question for us as a community to better understand. Lastly as we continue to develop novel first-line therapies, whether it's inclusion of brentuximab or other treatments such as checkpoint inhibitors, how can we best leverage the importance in the biological insight of PET response and PET-adaptive therapy as we design these next-generation regimens.



Let's turn our attention now to the management of relapsed classical Hodgkin lymphoma and see what, if any, role we have here for the use of PET to guide decision-making.

Practical Application of PET-adapted Therapy in Hodgkin Lymphoma

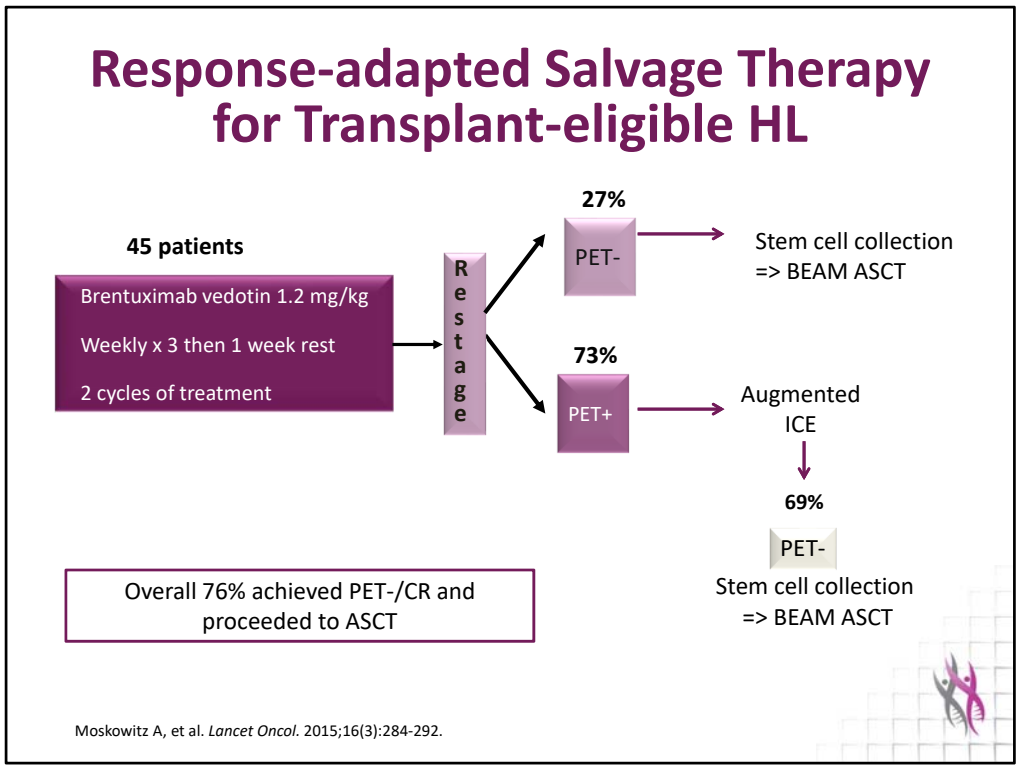
Impact of Pre-transplant PET in Relapsed HL



Moskowitz A, et al. *Blood.* 2010;116:4934-4937.

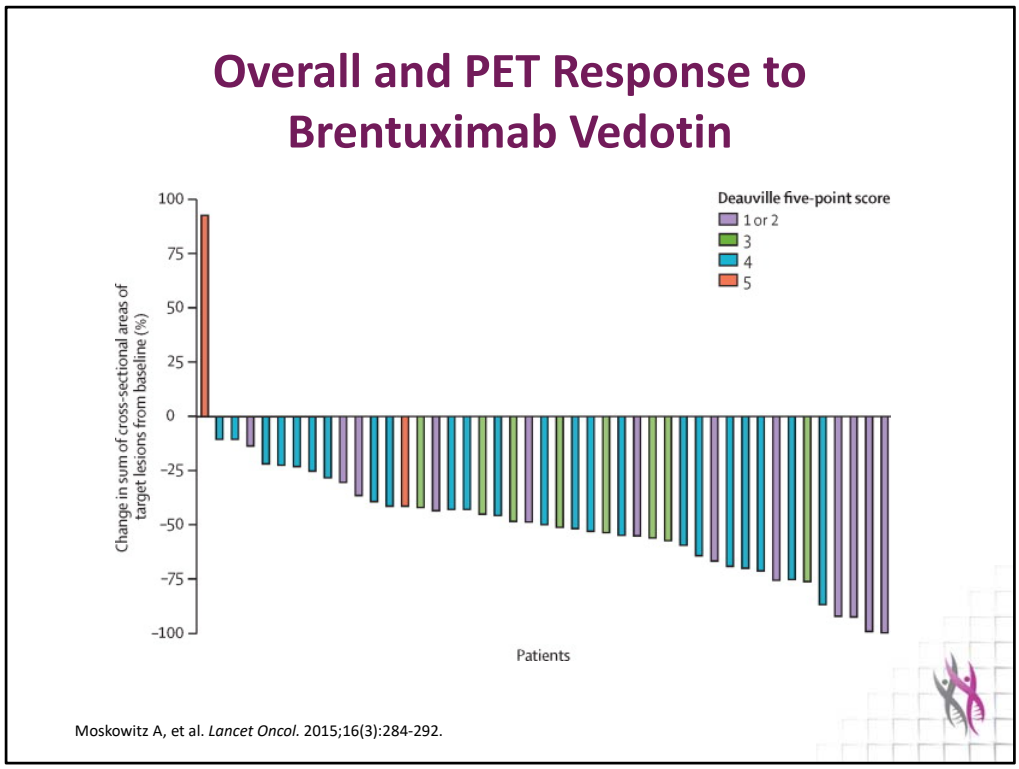
First, we have very important data to show us that the quality of the response to so-called salvage therapy, as measured by functional imaging with PET scan, is very powerfully predictive of cure rates and outcomes after a consolidative stem cell transplant. Both in terms of overall survival and event-free survival, we see that patients who are PET-negative go into a transplant do much better than patients who are PET-positive going into a transplant.

Practical Application of PET-adapted Therapy in Hodgkin Lymphoma



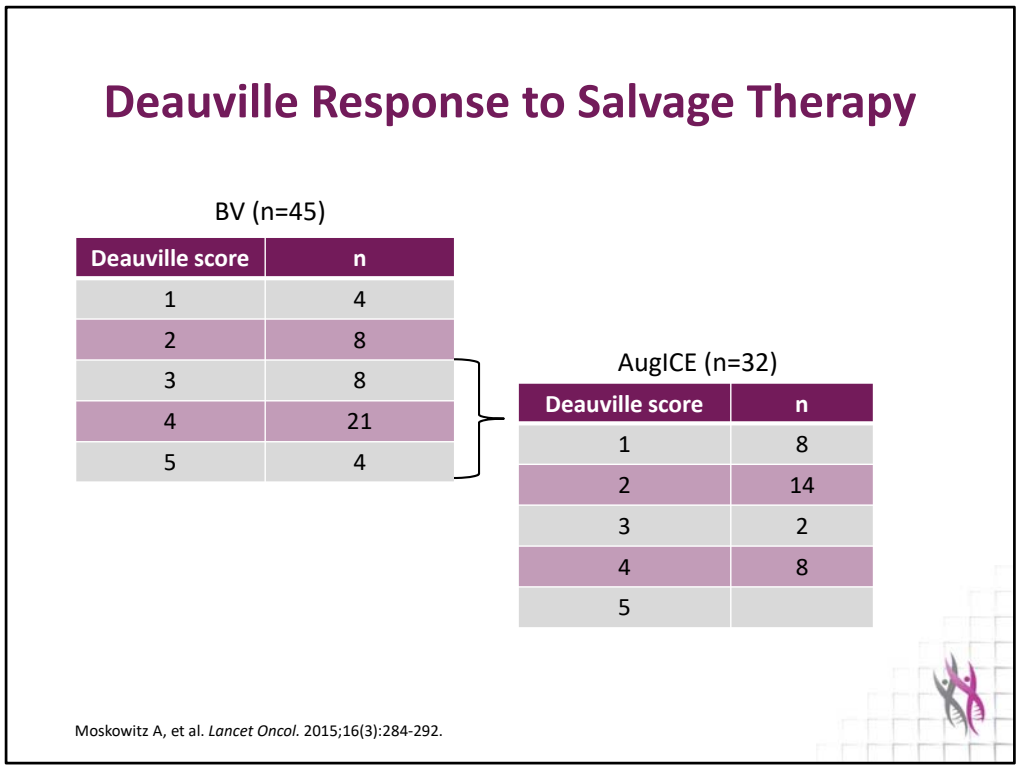
With that in mind, can we use this understanding to guide the design of less toxic and more rational salvage therapeutic approaches? One approach, that my colleague Alison Moskowitz has taken on, is to try to use a staged approach for second-line therapy for classical Hodgkin lymphoma, where brentuximab vedotin is given as monotherapy for two months (two cycles of intensified dosing schedule of brentuximab vedotin) then the patients undergo restaging PET scan. If the patients who are PET-negative lead to Deauville 1 or 2 go directly to stem cell collection and consolidative autologous stem cell transplant. Whereas patients who have a Deauville 3, 4 or 5 go on to receive a more traditional cytotoxic approach. Here is the regimen that we will prefer in these patients. It is a program we call augmented ICE, that is the ICE chemotherapy program with dose-intensification of etoposide and ifosfamide. Be that as it may, it's second-line cytotoxic therapy to try to achieve a PET-negative response prior to transplant. Overall, this two-step approach was able to achieve a PET-negative complete response either after the brentuximab alone or after ICE, and 27%, approximately one in four, were able to go directly to transplant without needing second-line cytotoxic therapy.

Practical Application of PET-adapted Therapy in Hodgkin Lymphoma



Brentuximab vedotin in the second line is very potent treatment with the majority of patients having some clinical benefit in terms of response to the agents. Shown here is the waterfall plot with an overlay of PET responses showing where the Deauville 1 or 2 fallout versus the 3, 4 and 5.

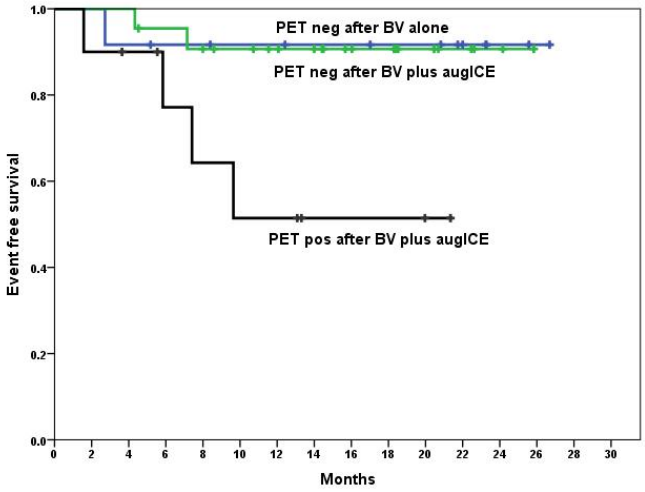
Practical Application of PET-adapted Therapy in Hodgkin Lymphoma



Forty-five patients were treated with brentuximab vedotin, and you see here the distribution of their Deauville scores. For the 3 through 5, they went on to get augmented ICE followed by a repeat PET afterwards. You see here that the majority achieved a Deauville score of 1 or 2 after ICE, even after not achieving satisfactory response to brentuximab monotherapy.

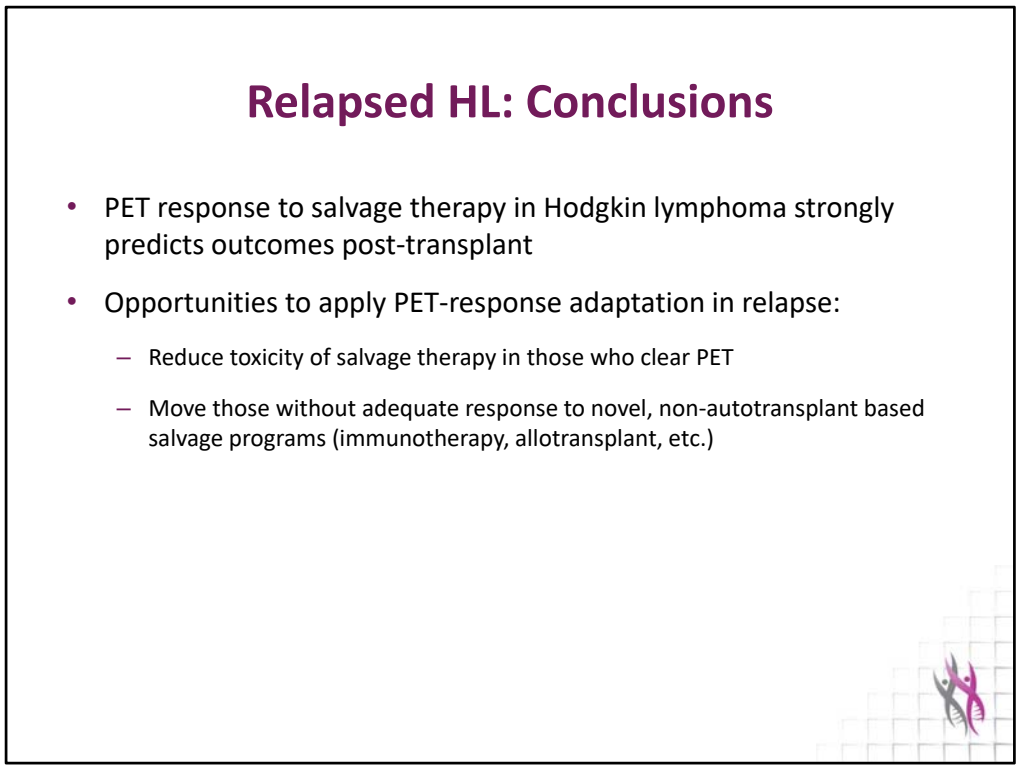
Practical Application of PET-adapted Therapy in Hodgkin Lymphoma

EFS According to Treatment and PET Status



Moskowitz A, et al. *Lancet Oncol.* 2015;16(3):284-292.

Regardless of what it took to get them there, if they were PET-negative after brentuximab alone or PET-negative after brentuximab plus augmented ICE, it did not matter in terms of the event-free survival after transplant. What matters is achieving the complete response, not the selection of therapy to get you there, and this has been a theme that we've seen across the salvage Hodgkin lymphoma literature, but it holds up even now in the modern era of using targeted therapy and immunotherapy in the treatment of Hodgkin's disease.



In conclusion, as we saw in the treatment of newly diagnosed classical Hodgkin lymphoma, you can use PET response to guide the selection of appropriate salvage treatments. A strategy such as a staged approach of using brentuximab alone, rather than using standard cytotoxic regimen as the first salvage approach, can allow us to minimize the exposure of patients to additional cytotoxic and thus toxic treatment.
There are opportunities moving forward here that are important for us to consider as a community. Number 1, can we go on and further reduce the toxicity of salvage approaches in those who do have a PET-negative response to treatments?
On the flip side for patients who do not achieve an adequate PET response, to salvage whether it is targeted therapy or cytotoxic therapy, should we be taking those patients to transplant or should they be shunted down other therapeutic pathways; such as moving them on to checkpoint inhibitor therapy, immunotherapy or other approaches, rather than taking them through a traditional autotransplant.

Thank you very much for viewing this activity with me today, and thank you for your attention.