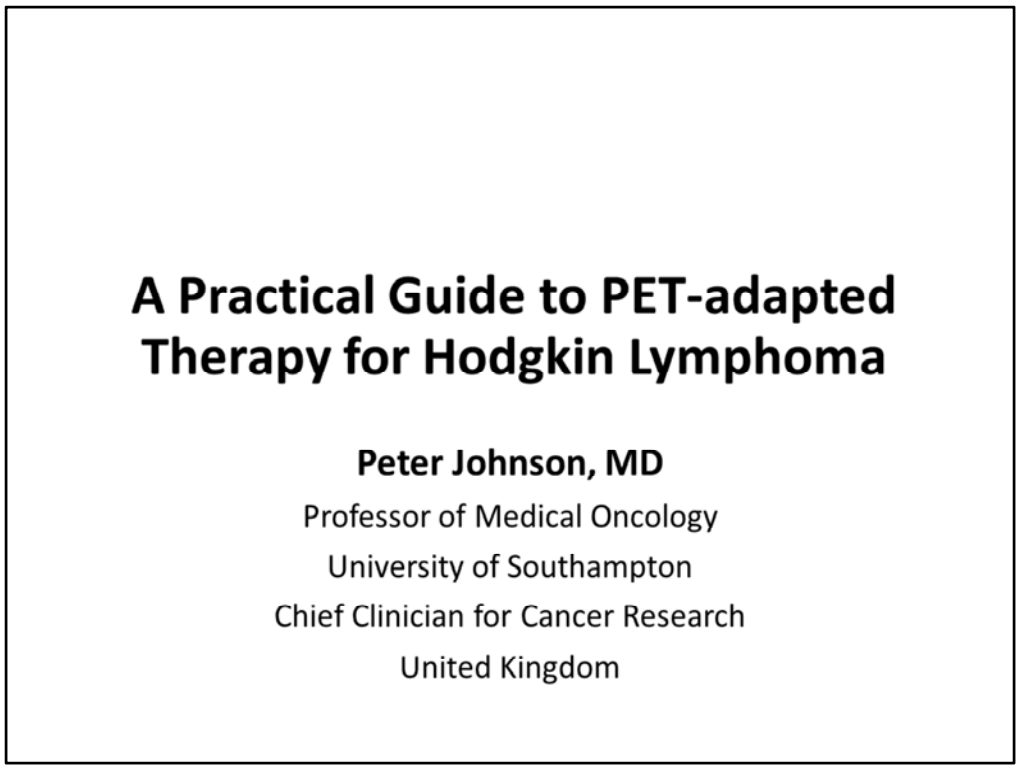
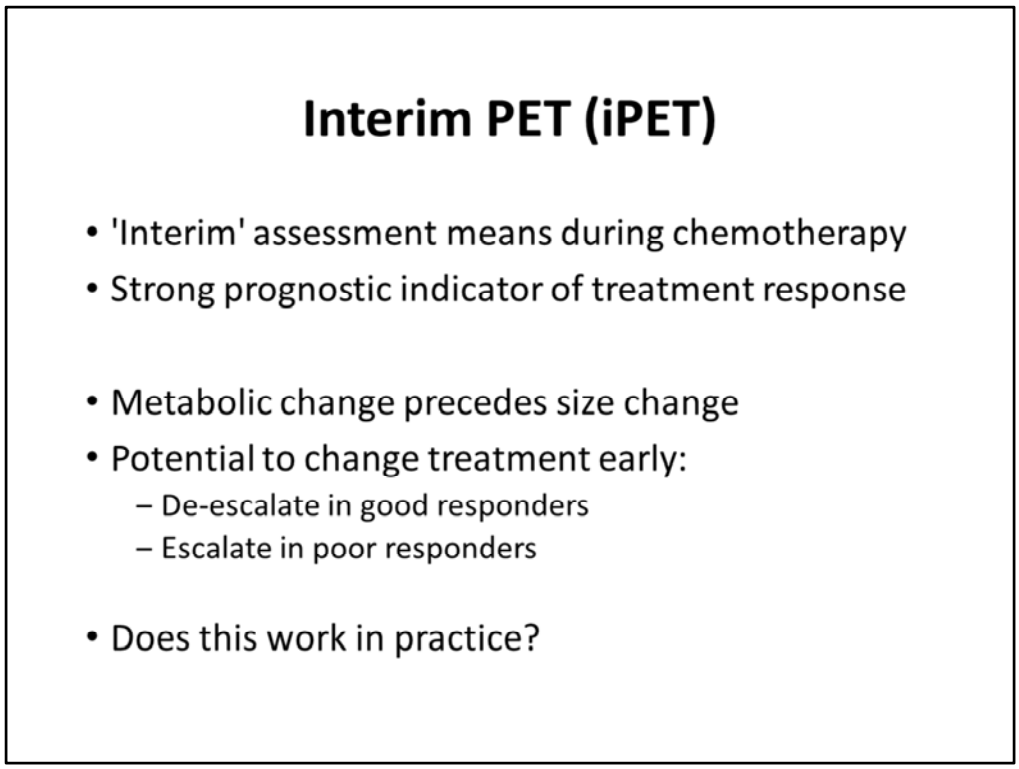
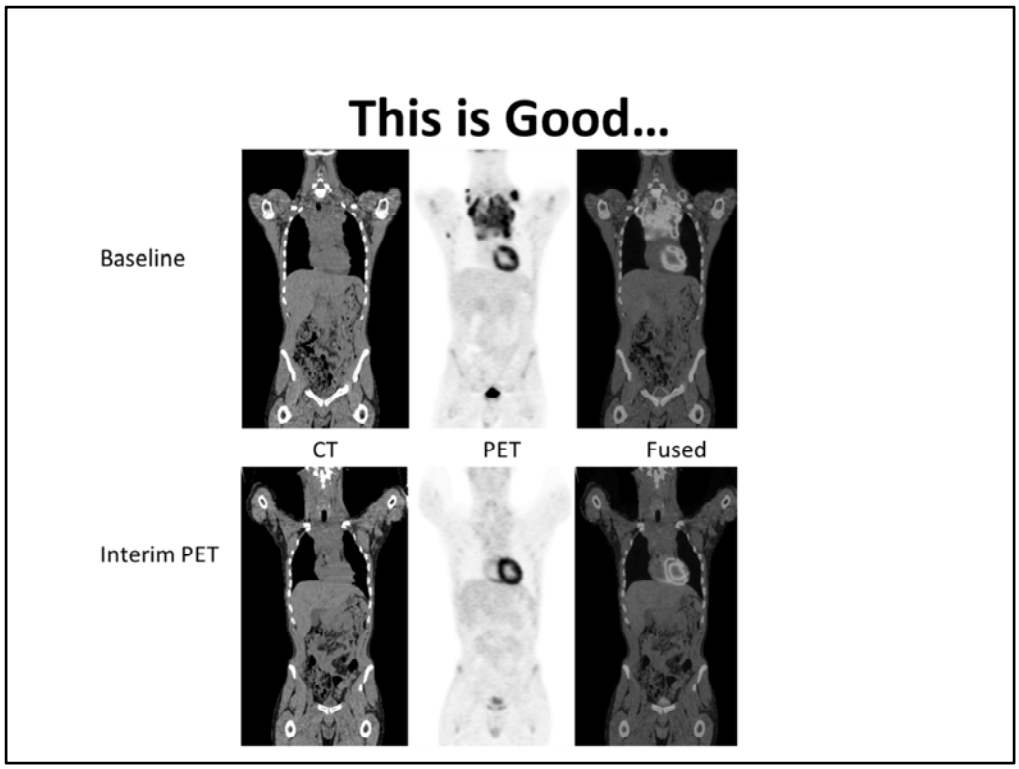
A Practical Guide to PET-adapted Therapy for Hodgkin Lymphoma



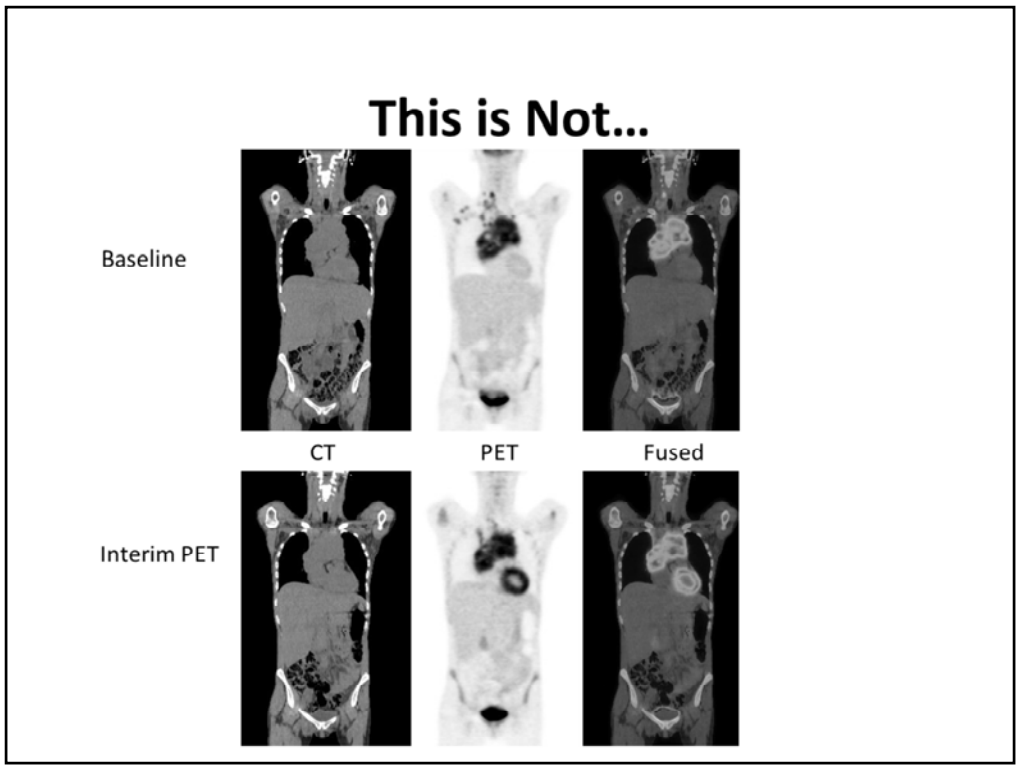
Hello. My name is Peter Johnson. I am a Professor of Medical Oncology in Southampton in the UK and I am speaking today on behalf of *Managing Hodgkin Lymphoma*, and particularly, I am going to talk about the use of interim PET scanning as a means of adapting therapy for Hodgkin disease.



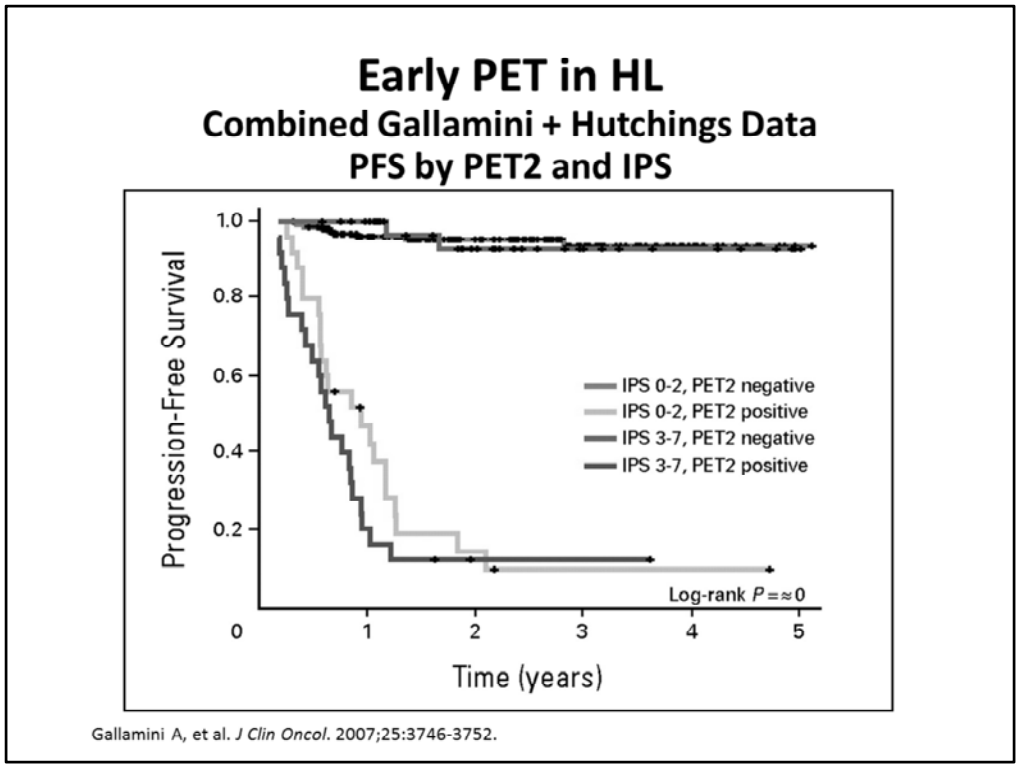
What do we mean by interim PET scanning? This means the assessment of a response to treatment during the chemotherapy. This is usually carried out after 1 or 2 cycles of standard chemotherapy and compared to the baseline PET scan, and there is good historical data to suggest that the outcome of the interim PET scan is a good indicator and early indicator of the response to systemic treatment. Traditionally, we have used FDG PET and we have seen the changes in metabolism in glucose metabolism within a mass of lymphoma precedes the change in size that you can see on conventional cross-section imaging. And what this does is it gives us the opportunity to change treatment earlier on than would otherwise be the case. So for people who are responding well, we can deescalate treatment, remove agents or modalities of treatment, thereby avoiding some of the long-term side effects, and for people in whom the response is inadequate, we can potentially escalate or add in different agents in order to try and improve the therapeutic effect. So, this is a means of personalizing treatment of Hodgkin lymphoma by getting an early readout of how well the chemotherapy that we are using is working. The question then is, does this work in practice?



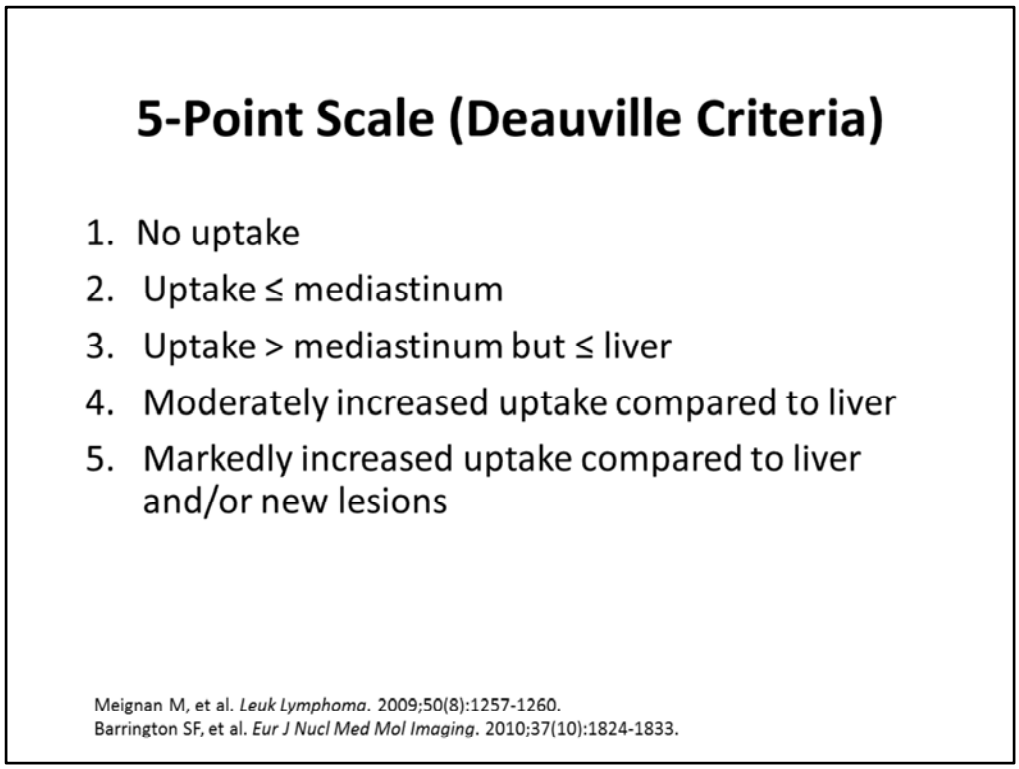
So, to look at some pairs of PET scans which have been carried out to see the sort of thing that we are talking about, this is the kind of illustration. So, in the top panel we see here on the left-hand side a conventional CT image, in the middle a conventional FDG PET gamma-camera image, and the fused image on the right. And you can see in the top panel, this is the patient with extensive involvement of the mediastinum by FDG-avid Hodgkin disease with nodes in the supraclavicular fossa on both sides of the mediastinum. If we look at the lower panel now, what we can see is that, although there is a residual mass within the mediastinum still visible on the cross-section imaging, this is entirely non-FDG avid. This is metabolically inert. So, this is an excellent response to treatment.



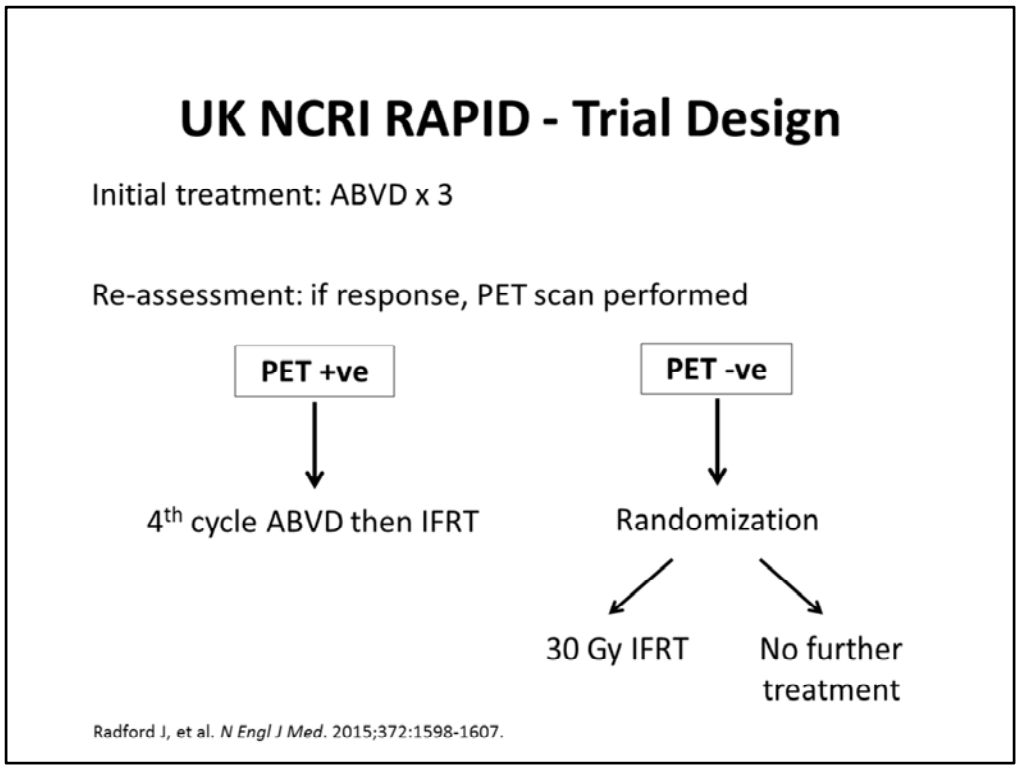
We can now contrast that with the patient with the same format again, at the top here we have the baseline scan showing FDG-avid nodes on both sides of the mediastinum and on the right side of the neck, but when we look at the panel at the bottom, following 2 cycles of chemotherapy, unfortunately in this case, we can see that the mediastinal lymph nodes remain FDG avid, indicating an inadequate response to the treatment. So, this is a bad prognostic feature.



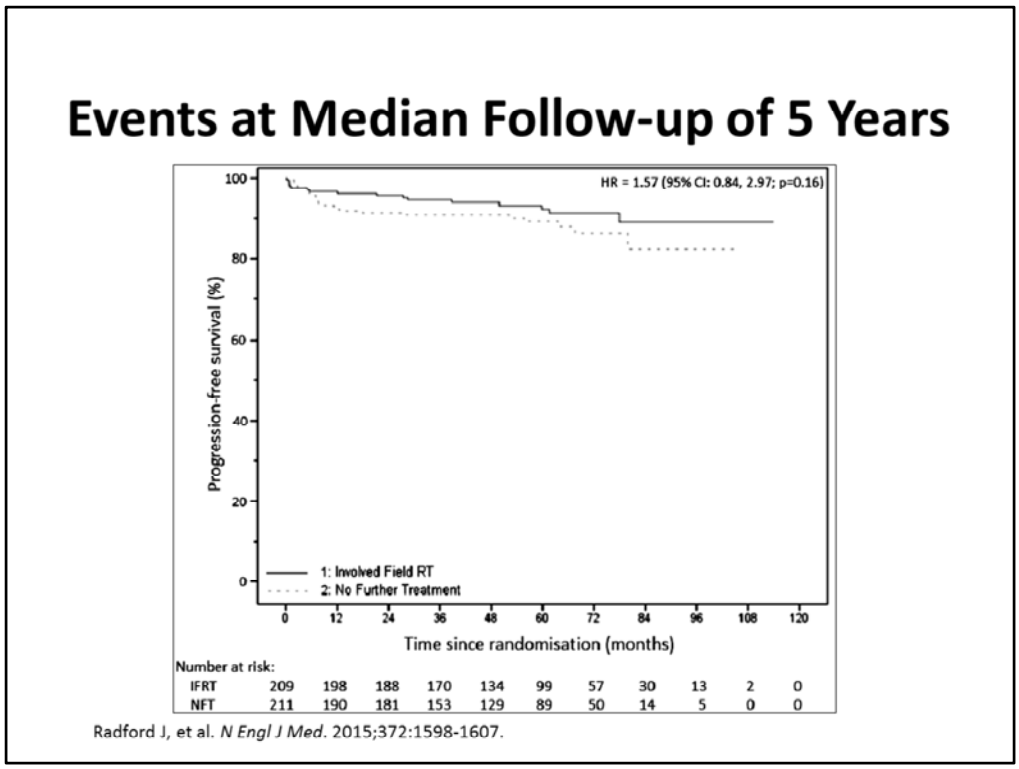
If we look at a series of patients analyzed retrospectively, one of the best known publications is shown here. This is a paper published nearly 10 years ago now in the *Journal of Clinical Oncology*, looking at the progression-free survival from cohort of patients treated with ABVD chemotherapy looking at their outcomes by the interim PET scan carried out after 2 cycles. What we can see is that if patients have become PET-2 negative, they have an extremely good progression-free survival in the series of the order of 95%, and this was regardless of the baseline prognostic features. The IPS score, the baseline prognostic score, is a measure of how severe the Hodgkin disease is, and even those with a high baseline IPS score, if they had a negative interim PET scan, the gray line here, did very well indeed. Conversely, the patients who retained a positive PET scan after 2 cycles of ABVD, even if they had low-risk disease, as shown by the yellow line, still had a very poor outcome with a progression-free survival of well below 20% in this retrospective series. So, a number of studies have been carried out to test whether this information can be used in the prospective allocation of treatment. It is very important to emphasize in talking about interim PET that reproducibility has historically been a big issue for this modality. Because what you are given to read is an image from a gamma camera, there is a degree of subjectivity which comes into the interpretation of the uptake of the signal.



So, in order to get around this and to try and formalize the reporting of scans, the so-called 5-point scale, the Deauville criteria, were devised, and those are shown on this slide. Whereby a score of 1 shows no uptake, which would be like the slide that we showed a couple of images ago. A score of 2 is uptake within nodes but at a lower level of uptake than the mediastinal blood pool. A score of 3 has an uptake higher than the mediastinum but less than or equal to that of the liver. A score of 4 is uptake more than that of the liver, and 5 is much more than the liver and/or the presence of new lesions. This scale has proven to be very reproducible across a variety of nuclear medicine physicians and people reading scans in multicenter trials. So, this is a very important part of the use of interim PET is to use standardized criteria for the reporting.

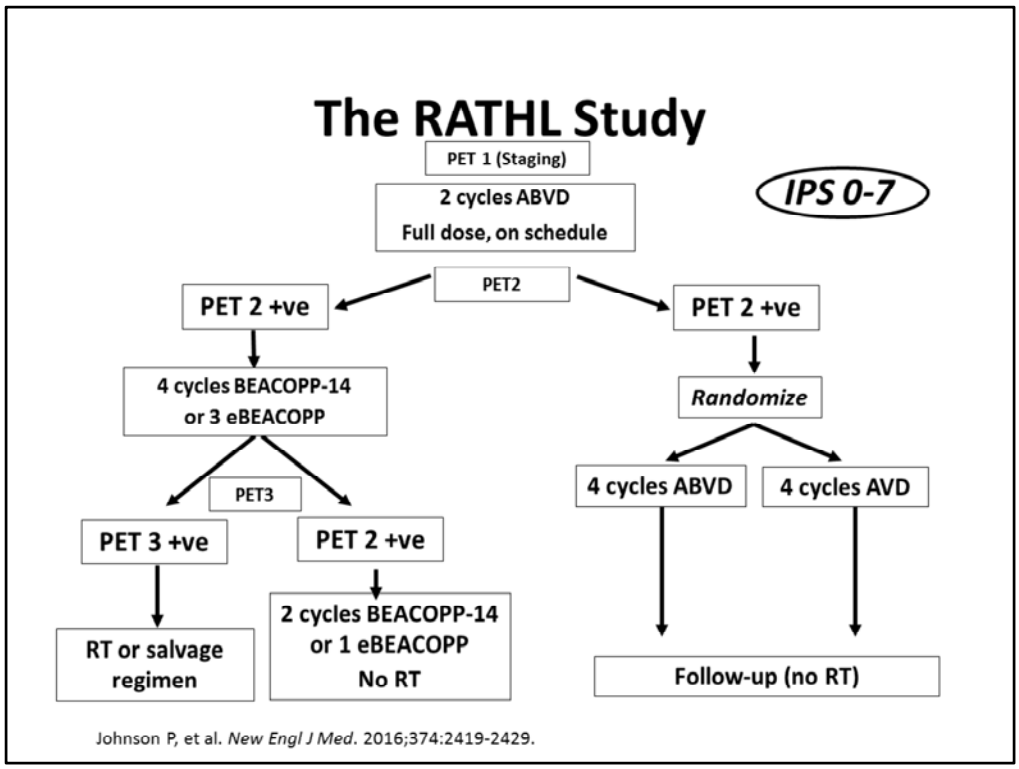


So, we designed a trial in the UK for early-stage Hodgkin lymphoma called the RAPID study, and the trial design is shown here. Patients with early-stage disease, that is stage 1 or 2A disease without bulky disease in the mediastinum and with a limited number of sites of involvement, were given 3 cycles of ABVD chemotherapy and then they had a PET scan performed at that point in order to make an early assessment of the response. This trial was started some time ago, so unfortunately, we did not have the resources at that time to do baseline PET scans, we just did an interim PET scan. The patients who were PET positive went on to receive a fourth cycle of ABVD and involved-field radiotherapy to the sites of original involvement, which is standard chemotherapy and standard combined modality treatment for early Hodgkin's. The patients who had a negative PET scan after 3 cycles were randomized to have consolidation radiotherapy to the involved field as previously specified, 30 Gy, or to have no further treatment, to stop at that point. The idea of this question was to see whether you could use a negative PET scan to deescalate the treatment by removing consolidation radiotherapy.

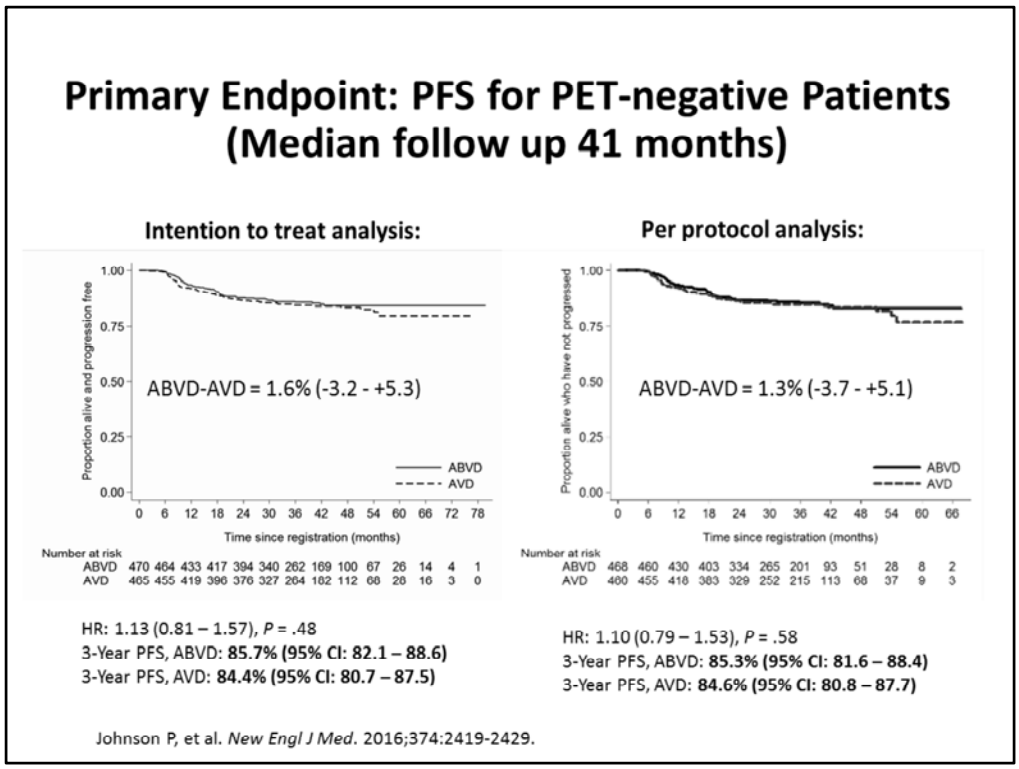


Radford J, et al. *N Engl J Med*. 2015;372:1598-1607.

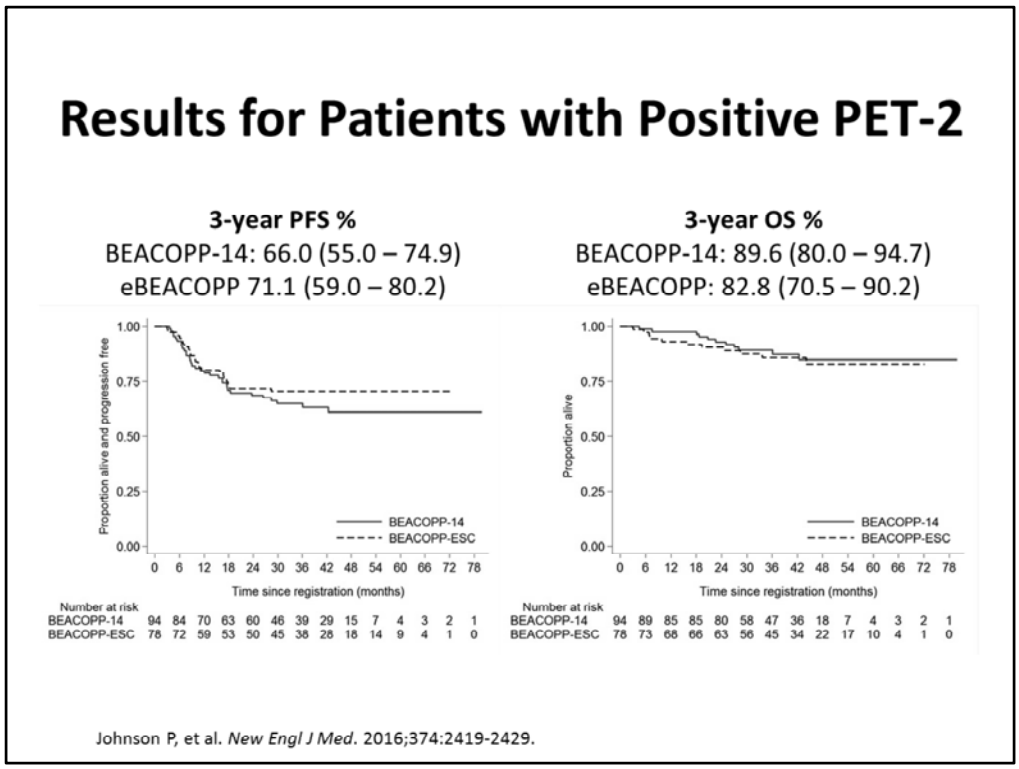
To summarize results very briefly, what we found was that there was a slight increase in events in tumor progression with a median follow-up of 5 years, but this was at a very low level. You can see here the hazard ratio is 1.57, and the confidence intervals lie only just outside the limits of what we have preset as equivalence. And certainly, if you look at overall survival, there is no difference at all between these two groups of patients, showing that if you omit radiotherapy in patients with a negative PET scan after 3 cycles of ABVD, the very small increase in the risk of recurrence is offset by the ability of salvage treatment to restore their overall survival to that of the population who received radiotherapy. So, this is potentially one means of using interim PET to distinguish who does and does not need consolidation radiotherapy, and that is an attractive idea for younger patients in particular for whom the late effects of radiotherapy would be good to avoid.



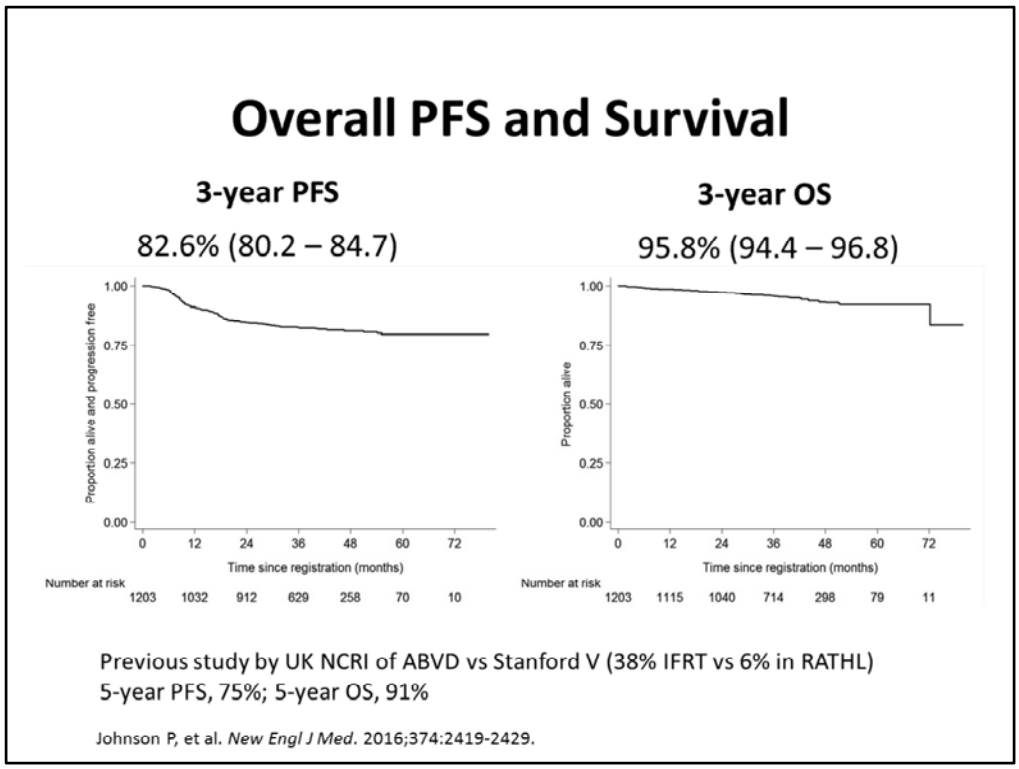
If we go on to think about advanced disease, the study I am going to talk about now is the international RATHL study, which we recently published in *The New England Journal of Medicine*. This took patients with advanced Hodgkin lymphoma of any prognostic score. We carried out a baseline PET scan and then administered 2 cycles of ABVD at full dose and on schedule, regardless of the blood count, before carrying out a second PET scan. The patients who had a positive PET scan went on to have escalation of their therapy using one of the BEACOPP regimens, either BEACOPP 14 which is a 2-weekly schedule using growth factors, or escalated BEACOPP, which is a 3-weekly schedule. And they had either 4 or 3 cycles of that before a further PET scan to see whether the sites of residual metabolic involvement had resolved. If they had, then they went on to receive 1 or 2 more cycles of BEACOPP but no consolidation radiotherapy. If they still remained involved, if the third PET scan was positive, then they either had local radiotherapy if it was localized disease or went on to systemic salvage therapy. The patients who had a negative PET scan after 2 cycles of ABVD were randomized between continuing standard ABVD chemotherapy for a further 4 cycles or deescalating by the omission of bleomycin for the last 4 cycles so that they just received AVD. And once again, the patients with a negative interim PET scan were recommended not to receive consolidation radiotherapy, again a departure from previous practice where around a third to a half of patients had received consolidation radiotherapy in studies like this.



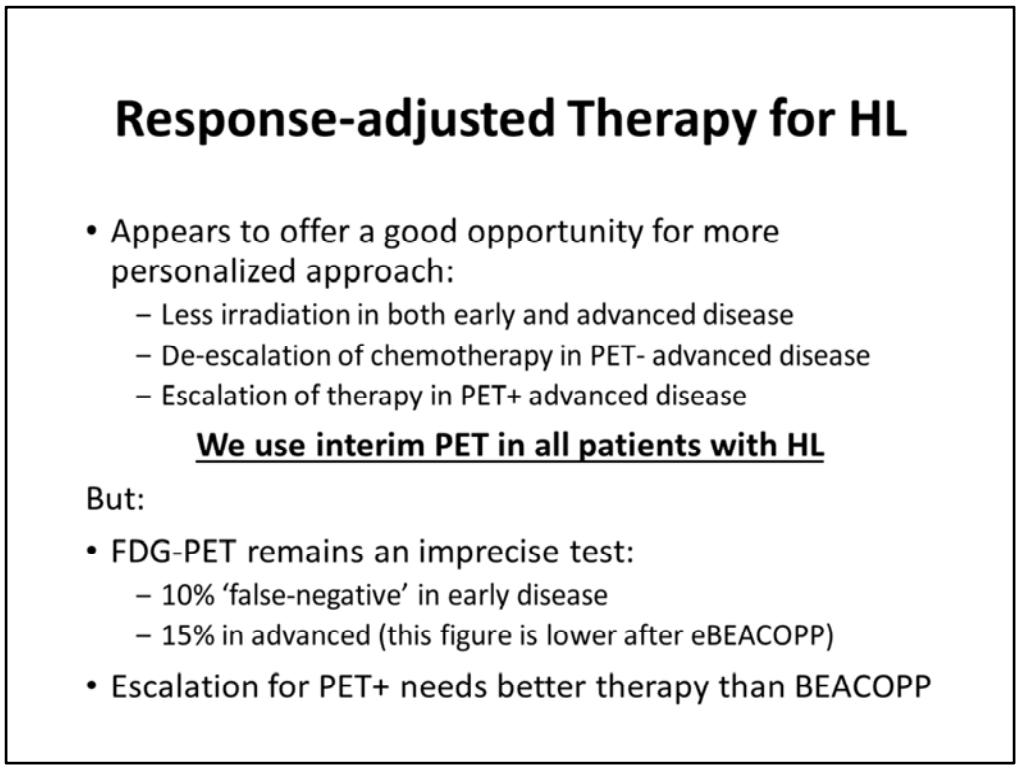
So, the primary endpoint of this study was the progression-free survival for the PET negative patients who were randomized to continue or to omit the bleomycin. What we found was that there was no difference in terms of progression-free survival whether or not you continue bleomycin after negative interim PET scan, as exemplified by the progression-free survival curve shown here. So, extremely good progression-free survival whether or not patients continued with bleomycin, and you can see the figures at the bottom of this slide showing a 3-year progression-free survival of around 85% in both these groups. So, this suggests that the negative interim PET scan allows you to consider deescalating the therapy.



The patients who had a positive interim PET scan went on to have escalated therapy with BEACOPP. Now, this was not randomized against continuing ABVD because the patients did not feel that would be an ethical choice given the progression-free survival curves that I showed you earlier from the 10 years ago *Journal of Clinical Oncology* article where the progression-free survival for interim PET positive patients was below 20%. The interesting thing in this series is that by escalating to BEACOPP we see a progression-free survival of around 65% to 70% for these groups, with an overall survival of around 85%. So, this looks like an improvement on the historical data, although again it is important to emphasize that this was not a randomized comparison.



If we look at the overall progression-free and overall survival in the trial as a whole in the RATHL study, we can see that our 3-year progression-free survival, taken this modulated approach to deescalation or escalation on the basis of the PET scan, has come in at just under 83%, and our 3-year overall survival is just under 96%. We can compare this to the previous study carried out in the UK group comparing ABVD and Stanford V where we used a great deal more involved-field radiotherapy; 40% of patients in that study had involved-field radiotherapy as compared to only 6% in the RATHL study. The 5-year progression-free survival in that previous study was 75%, and the 5-year overall survival 91%. So, this suggests that our current study with this modulated approach based on interim PET has produced results at least as good as those we have seen previously, and we cautiously think that they may actually be a bit better, but this is with a great deal of less treatment, less consolidation radiotherapy, and less use of bleomycin.



So, in conclusion, we feel that response-adjusted therapy for Hodgkin disease does offer us a good opportunity for a more personalized approach to treatment. It has allowed us to drop radiation in both early and advanced disease in the majority of patients, and it has allowed us to deescalate the chemotherapy for patients with advanced disease who have a negative interim PET scan. Those who have a positive interim PET scan appear to benefit by the escalation therapy to a more intensive regimen. So, our current practice is to use interim PET for all patients with Hodgkin lymphoma in order to make an early assessment of the response and to modulate treatment accordingly. It is important to emphasize, however, there are some caveats about this data. Firstly, this is still an imprecise test. We have a 10-15% false negative rate, that is to say patients have a negative interim PET scan but still develop progressive Hodgkin lymphoma. The false negative rate is lower in early-stage disease, it is about 10%, and it is about 15% in advanced disease. It goes down, interestingly, if you have more intensive treatment prior to the PET scan, so the false negative rate after escalated BEACOPP is much lower. We also need to find better treatments for escalation for those who are PET positive at the interim than BEACOPP. So, although we have two-thirds of patients progression free after escalating after a positive PET scan, we still feel there is considerable room for improvement on that figure as well. So taken overall, we think this is a useful introduction to the treatment of Hodgkin lymphoma using an interim PET scan to modulate treatment, but we still clearly have some research questions to answer. Thank you very much for your attention.