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How should we treat early unfavourable Hodgkin Lymphoma?

Dr Osborne: Hello, I'm Dr Wendy Osborne and as I said, I'm from Newcastle in the UK and I'm delighted to spend the next 30 minutes or so talking about early unfavourable Hodgkin Lymphoma because this is somewhere where we have lots of different treatment options. And it's really about understanding the risk benefit and trying to individualise care for our patients. I will be presenting a reasonable amount of clinical trial information, so, Astrid and I thought it would be helpful to address any questions at the end, but please send them throughout the talk so that we've got time for discussion. So, we all see this in our MDT quite regularly, don't we? We see young people presenting with quite extensive early disease. And our concerns about these patients is the impact of radiotherapy for them. And so, I want to really think about when, what data we have in the situations where we are trying to avoid radiotherapy. And I think it highlights why Lymphoma is such a multidisciplinary specialty, why we can't make decisions about our patients with Hodgkin Lymphoma without our clinical oncologists in the room, because we need to have careful discussion. So, this is a 24-year-old student I met last year or two years ago now, and he presented biopsy-proven Hodgkin Lymphoma, and this was his staging PET scan. So, I think even before we start, often some of my trainees will have a discussion about why we would call somebody unfavourable. And as a note, I think it's interesting that now the German Hodgkin's study group are using the term intermediate rather than unfavourable, which I have to say I do like because we're putting on patient clinic letters, we're discussing with them, although, they have early disease, we're using that term unfavourable and it isn't very well received often. So, I'm now using early-intermediate for many of these patients. We know that there are risk factors that put them into this intermediate group. And we know that the EORTC has slightly different risk factors to the German Hodgkin's study group. So, if you are over 50, then you are automatically considered unfavourable in the EORTC, whereas if you have extra nodal disease, then you are considered unfavourable in the German Hodgkin's study group. And then, the only other difference is slightly different number of lymph node involved. So, if you are considered unfavourable with EORTC trial data, then it's slightly worse disease in the sense that it's four or more lymph node sites, whereas it's three or more lymph node sites. And I think that this is important that we just highlight this because if we are following treatment approaches, depending on different trials, we do need to understand how our patients have been classified to make sure that they would be translated into the outcome from a certain clinical trial. And I have to say that we just have these data in our MDT so that we look up all of the risk factors rather than trying to remember them or remembering them incorrectly. So, I think that there are lots of different ways we can treat these patients. And the top two were the ways that over a decade ago, or a bit less, I would always use, and these were not PET-directed or PET-guided approaches, it was before we had PET scanning as standard of care. So, we always used to, a few years ago, follow the four-plus-30 approach if they were unfavourable and then, the Germans went on to do the HD14 study. And the HD14 study, they call it the two-plus-two approach, so, patients were given two BEACOPPS and then, two ABVDs and then 30 Gy radiotherapy. And if we look at their HD14 study, they showed that when they randomised patients to receive either the standard four-plus-30 approach

versus their two-plus-two approach, both including radiotherapy, that there was an improvement in outcome in terms of progression-free survival with the more intensive arm. So, it was a 6% improvement and this took a five-year PFS up to 95%. And so, this is, you know, this is impressive for early unfavourable, early-intermediate disease. And they didn't see any longer-term problems in terms of treatment-related mortality or secondary malignancy, but there was more acute toxicity. And I have to say that when these data were presented at ASH a few years ago, it didn't really change our practise in the UK. And I think that was because we still had to give the patients not only BEACOPP, in the UK, as you may know, we use escalated BEACOPP dac. We replaced the procarbazine with dacarbazine to try and limit toxicity and fertility toxicity, we've audited it. It looks as if our outcomes are similar so this is our standard in most centres, but we didn't really take up the HD14 approach. Now, the big change has happened certainly in my practise, since HD17 has been published. So, what the German study group did in HD17 was randomise patients to the standard arm which now was a two-plus-two plus radiotherapy. So HD14, the best outcome from their most recent trial to a PET-guided arm. So, they randomised the patients that would get two-plus-two, so two BEACOPPS, two ABVDs and then, they would have a PET scan. And if that PET scan was negative, then these patients in the PET-guided arm would not have radiotherapy. They were looking for a non-inferiority, it was a non-inferiority design. And what they showed was that if patients were PET negative at the end of treatment, at the end of all four cycles, then there was no-inferiority of emitting radiotherapy. And this is the first study that we have seen in Hodgkin Lymphoma and early Hodgkin, where the removal of radiotherapy did not cause a detriment to the progression-free survival, because we know in all of the other studies, RAPID, H10, HD16, that if you took away the radiotherapy, you may lose some of that PFS benefit. Now, in some patients that may have been the right thing to do because of the risk of radiotherapy toxicity, but I think that HD17 gave us this opportunity for some patients to omit the radiotherapy. And in early unfavourable patients, we often want to do this because of the extensive radiotherapy sites, the heart involvement, the breast involvement. So, it's something certainly that we considered. Now, as in many Hodgkin trials, there was a debate about what should be considered as a positive scan in terms of Deauville score. And in many de-escalation studies there was more caution. So, in this study a Deauville score of 3 was considered a positive score. However, as the Germans have extrapolated from their other study groups, it appeared as if it was only the Deauville score of 4 and 5 where there was a difference in outcome. And they have extrapolated that, really, we should be considering only a Deauville score of 4 and 5 as positive as we now do in all of our standards Hodgkin management. So, if patients obtained a Deauville score of 3 or less then their five-year progression-free survival was at 98% and only 9% of patients required escalation to radiotherapy. So, this is of real interest when we compare our other treatment options for patients, I'm going to come back and talk about this at the end, as to where the pros and cons would be in using an HD17 two-plus-two approach with a PET4 and avoiding radiotherapy in up to 90% of patients. So, prior to HD17, we have been following an H10 EORTC approach. So, if you remember, that will be slightly different characterization of what will be considered unfavourable to four or more nodal sites and over the age of 50. But the PET-guided H10 was such a helpful trial in these groups of patients. And just a reminder, please send in any questions this is a discussion point, and we're very happy to discuss this at the end. So, if you think about the H10 trial design. The top half of this trial design is for the favourable patients. So, I just want to focus on the bottom half, the unfavourable patients. So, patients were randomised to receive a standard of care so, that will be a total of 4 ABVDs and radiotherapy. They did have a PET scan, but in the standard of care arm that wasn't acted upon because the standard of care at the time was four-plus-30. They were randomised also to be in the experimental arm. And in the experimental arm, patients were given two cycles of ABVD. And if they were PET negative, then, they continued a further four cycles of ABVD. It was before the RATHL trial data were published so, the bleo was not removed so that they had a total of six cycles of ABVD and no radiotherapy. Whereas if they were PET positive, then, they were escalated to two cycles of escalated BEACOPP and they got radiotherapy. So, if we look at the outcomes for these patients in the unfavourable group, the patients who had radiotherapy and this is just focusing on PET negative patients, so, negative after the two cycles of ABVD, those patients who had radiotherapy had a PFS at five-years and 92%. So, that really matches reasonably well with the data

that we got from HD14 and HD17, so, a percentage in the early 90%, but it's encouraging that the patients who didn't have radiotherapy also achieved a five-year PFS of 90% nearly, with six cycles of chemotherapy. So, if we knew that a patient was going to be PET negative at the start of treatment, and we wanted to avoid radiotherapy, then, this would feel like a very good option, giving them six cycles of chemo, we would usually remove the bleo because we know that from the RATHL data. But the problem is that we do not know upfront who is going to be PET negative on the iPET2. And then, if we look at the PET positive patients, so, if you look at the bottom half of this trial, the patients who were PET positive, remember they were escalated to BEACOPP and they got radiotherapy. Now, if they were escalated and got radiotherapy, yes, they did well, 91% five-year PFS. But look at those patients who weren't escalated, their PFS dropped to 77% and they still had to have the radiotherapy. So, we know that if patients are PET positive, that the outcomes are not good unless they are escalated in terms of chemo and they all have radiotherapy. So, if we compare this to the five-year HD17, the five-year PFS for those 9% of patients who are Deauville score of 4 at the end, theirs was 82%. So, it's this trying to predict upfront who we are going to know is going to do badly with less intensive chemo. And really, I think that we could spend a long time talking about the predictive value of certain tools in Hodgkin Lymphoma, because this has to be the answer. If we know that we can cure a patient with ABVD, we wouldn't want to give them BEACOPP or radiotherapy, but we just don't know upfront. So, this is just an interesting presentation from ASH a few years ago, where they looked at these high-risk unfavourable patients, early unfavourable, treated on both the H10 approach and the AHL2011. So, just to remind you about AHL2011. So, this is an advanced Hodgkin trial. And remember that in some advanced Hodgkin trials, they did treat some early unfavourable patients. In fact, in RATHL, there were 40% of RATHL and advanced Hodgkin trial which had to be patients in. So, in AHL2011, patients in the experimental arm were given two escalated BEACOPPS and if they were PET negative, now, the PET negative threshold was slightly... Well, the PET positive threshold was slightly higher than we would normally, it's almost like a Deauville score of 4 and a half equivalent, it was 140% of liver, but if they were PET positive, these patients stayed on BEACOPP for six cycles. And if they were PET negative, then, they were reduced down to four cycles of ABVD. And they showed in this trial with a slightly different Deauville score cut-off for the iPET2, that actually you can de-escalate patients safely with good outcomes. And they also have longer term fertility data showing that this is an option. And I have to say for some of my advanced patients in whom I'm trying to preserve fertility, I have been occasionally using this approach. But what they showed when they're comparing these favourable patients within both studies was that actually both approaches gave us similar PFS. So, both the H10 and the AHL2011, the groups weren't perfectly matched more severe in AHL2011, but they did show that patients with a higher metabolic tumour volume with a cut-off of 155 mils and a higher IPS were associated with an inferior outcome with an H10 approach. And I do think that although we haven't got the answers yet, we have to start to understand predictive factors to help us with these clinical decisions within our MDT. So, if we come back to where we are now with our options. So, I think that, personally, I have sort of discounted these top two options purely because they're not using a PET-guided approach and I think that we can benefit from a PET-guided approach. I think that we have this good outcome from the patients who have escalated BEACOPP upfront from the German HD17 trial, and that PET scan after four. And then, we also know that H10, if we know they're going to be PET negative, do very well. And if they're PET positive, they will do well if you escalate them to BEACOPP and give radiotherapy, but it's not such a good option if we want to keep them on chemotherapy, and because we know that six cycles of chemotherapy from the RATHL trial for those patients who are PET2 positive, the progression-free survival is only about 66% for these. So, we can't really compare, all of these studies did have different patient populations and different PET assessments, but I do find it quite helpful just to think about what we can talk to our patients about when making these decisions and what we need to think about in our MDT. So, if we look at HD17, a hundred percent of the patients in this trial were early unfavourable as per the German definition of unfavourable. They didn't do a PET2, it was a PET4 and 9% of patients were a PET4. It was slightly different in the presentation EAL compared to the publication but if you look at the publication, the PET4s was about 9%. You've got a 9 out of 10 chance that you could avoid radiotherapy for your patients. If patients are PET negative at the end of their two escalated

BEACOPPS, 2 ABVDs, then, their five-year PFS is 95%, so, pretty impressive. However, if they're PET4 positive that PFS has dropped down to 82%. And it's because of this drop down to 82% and also, because I've seen patients in clinic who have early disease, but a really low diaphragmatic node and a really high disease. And the radiotherapy doctors I work with say if we want to give radiotherapy to this patient, I accept that it is a only a 1 in 10 chance from the data, but we'd have to give a massive field of radiotherapy. It would be really toxic. So, it's because of this that I actually do still include an iPET2 in my patients who I follow HD17. And the reason for this is because there is an occasional patient that if they are still positive at iPET2, I then want to weigh-up the risk and benefit of keeping them on a BEACOPP approach as per HD18, the advanced Hodgkin trial. So, they would need six cycles compared to just dropping them down to ABVD and accepting that they might be in that risk group where they need radiotherapy. So, that's my practise. We've just published our British Society of Haematology Hodgkin Guidelines last month. And we've kept in the flow diagram I'm about to show you. In that we haven't included that iPET2, purely because that wasn't done in the trial, but I have to say it is my practise. So, I think HD17, these are the data you can discuss with the patient. H10, as you can see here in the unfavourable arm, they were all early unfavourable. Now, 1 in 5 of these patients are going to be PET positive. So, if you are using this approach, we have to be prepared for the fact that the patients who are PET positive will end up getting two ABVDs, two escalated BEACOPP and radiotherapy. Now, their outcomes will be good 91%, but they will have had that toxicity of the radiotherapy and I've talked about why I'm concerned about this in some patients due to the site of disease. And if you don't escalate them and you keep them on this standard chemo and radiotherapy, then, there's 77% PFS, so again, that drops down. And all patients, if they are PET positive have to have radiotherapy following this approach. Now, this approach is fantastic. Look, if they're PET negative and you just want to give them chemo alone, their PFS is 90%, so it's good. But the problem with H10 is we don't know upfront who is going to be PET negative. So really, the chemotherapy arm of H10 is very similar to the RATHL approach. The only thing is they haven't dropped the Bleomycin. So, again RATHL, which did have 42% of early unfavourable patients in, 16% chance of being iPET2 positive and again, if they're PET negative the PFS is acceptable, 84%, it's still 10% lower than HD17. But if they're PET positive, it drops down despite escalation to four cycles of escalated BEACOPP to 68%. Now, not much radiotherapy was used in RATHL, again a good option if patients we know are going to be PET negative, but that's what we don't know upfront. And then, finally, not many patients early unfavourable in HD18, but I've put this in here to show you that the outcomes for HD18, even if they're PET positive, requiring six cycles of escalated BEACOPP is still excellent at 88%. And remember if they're PET negative, it allows us to drop down to a total of four cycles of escalated BEACOPP and their PFS is 95%. So, this would be often my standard approach for patients with advanced Hodgkin. And then, I talked about the AHL2011 trial, more because it's starting to give us maybe some predictive information, but again, not many patients with early unfavourable and not many patients having radiotherapy. So, it's looking at all of these data that we devised our local sort of Northeast map, and it looks a bit complex, but the first thing we do in the MDT when a patient with early Hodgkin is put up on the screen with the PET scan, the first thing I do is look at my clinical oncology colleagues. And if they say that they are happy to give radiotherapy, and we know that we have patients, you know, a 52-year-old for example, who's therefore classed as unfavourable, but they've got sites of disease that is not going to cause any radiotherapy concerns or many radiotherapy concerns, then, we will follow the H10 approach because that will give a good outcome, whether they're PET positive or PET negative with that radiotherapy. But we also have these patients who we really want to avoid radiotherapy. They're less fit, but we can't give them escalated BEACOPP upfront. And for the patients who are less fit that we are wanting to still avoid radiotherapy, then, we start them on ABVD, and we will aim to give them if they're iPET2 negative 4 ABVD. So, still following an H10 approach. Now obviously, if their scan is positive after two, it does change some of the risk and discussion. So, although, they may have been borderline fit for BEACOPP, and we didn't want to start BEACOPP, it may be that when they're iPET2 positive, we feel actually the risk of the disease is more of a concern to us than the toxicity of the escalated BEACOPP. So, it may be that we do decide to escalate them. But if they're, for example, over the age of 60, I wouldn't give escalated BEACOPP over 60 and we really want to avoid radiotherapy, then, we would continue on a

chemotherapy approach. And we would drop the Bleomycin as per RATHL. So, it's that first question, planning for radiotherapy, yes, H10, aiming to avoid radiotherapy for patient less fit, H10, again going down extended chemo. But if we've got a younger, fitter patient that we are aiming to avoid radiotherapy in, like the patient I started to show you at the start, we are now using this HD17 approach. We are starting them on two cycles of escalated BEACOPP. As I said, I would use escalated BEACOPP dac. I do do a PET scan after two, just to give me that option if I want to keep them on BEACOPP as an HD18 approach. But if that PET scan is negative, or if I still don't want to keep them on HD18, then, I will de-escalate two cycles of ABVD, then do a PET4. And if that PET4 is negative, which overall only 9% should be positive, then, I will avoid radiotherapy. And that should give me a PFS of over 90%. Sorry, I'll just move that slide forward. So just coming back to this patient, we talked to him about the options. We talked to him about starting off with ABVD and escalating as per H10, we talked about the risks of radiotherapy and he elected for HD17. I did do a scan after two and he was in a Deauville 3. So, he de-escalated to 2 ABVDs, no radiotherapy and he remains in a complete metabolic response. So, just to summarise, the clinical oncology opinion in our MDT is essential. And I really feel that we should not be making any decisions about, well, many of our Lymphoma patients without our clinical oncology colleagues. If they accept the toxicity of the radiotherapy, looking at individual patient risk factors, as well as sites of disease, then, I would follow an H10 approach for my patients with early unfavourable or also called early-intermediate Hodgkin Lymphoma. However, if they really don't want to give radiotherapy, I will look and assess how fit the patient is. And if I feel that the patient is fit, I will start with escalated BEACOPP dac. And my practise with escalated BEACOPP dac is I would never give it over the age of 60, I rarely give it over the age of 50 and I am cautious over the age of 50, but under 50, I do give escalated BEACOPP dac, a lot of these patients are younger, between 40 and 50, I watch them really closely and sometimes admit them. But when I'm seeing them, I can explain that they have a two-plus-two approach, if they achieve PET negativity at the end, their five-year PFS is 95% and there's a 9 out of 10-chance they won't need radiotherapy. If they're not fit enough for an HD17 approach, then, I will start them on H10 and we know that 22% of patients were positive and they have a less good outcome. But the patients who are negative, which is 70, 77, 78%, their five-year PFS with 6 ABVDs is 90%. So, if they're PET negative, everything is good, I do drop the bleo. And then finally, if we don't want to think about escalating them or give them any radiotherapy, we talk about the RATHL approach, which as you know, is very similar to H10. And just to say that 16% of those patients did need to be escalated. And those patients who were PET positive, they were escalated to escalated BEACOPP but despite that their three-year PFS is only 68%. Whereas if they are PET negative again, the three-year PFS is acceptable at 84%. And really the goal will be to understand upfront which patients will become PET negative, which patients we could just manage with chemotherapy, ABVD alone, and trying to understand these predictive values so that we can really select and personalise the treatment options for our patients with early-intermediate Hodgkin Lymphoma. Thank you very much.

Dr Pavlovsky: Okay. Thank you, Wendy. You went through all the options we have and thank you very much. So, I think this is a big effort different comparative groups are trying to balance between toxicity and the PFS in this group of patients, right? So, we have two different worries here to under-treat and to over-treat, right? I think this is the way we're going. First of all, I think you clarified this, but I think it's worth just saying it again, the German group used a different definition of a negative PET CT, including the Deauville score 3 as a positive PET. So, in your opinion, we are ready to incorporate the German approach, but defining a negative PET CT as Deauville score 1, 2 and 3, right?

Dr Osborne: Yeah, I agree. They did as many de-escalation studies did, initially be more cautious with the scoring. So, did consider they did this in HD15 as well, a Deauville score of 3 to be positive. However, when these data were published, they clearly showed that it was the Deauville scores 4 and 5 who had an inferior outcome, even though that wasn't the cut-off of the randomization. So, having seen that in longer follow-up from HD15 and also in our own practise, which we have audited. And also, if you look at the trial designs and all of the future trials such as HD21, the Deauville score of 4 and 5 as now I'm happy to consider that looking at the data as a positive scan. And it could actually be, that may be too cautious. So, we know that a Deauville

score of 5 is bad and is disease in most situations. We know that for many of our patients with Lymphoma that even with further treatment, they do badly. If you looked at the AHL2011, the fact that they were happy if patients were above liver so, Deauville 4, but less than 140% above liver. The French have considered that to be a negative scan. And I do think now that it's possible. I don't want to start using different Deauville score cut-offs because I think that then we can't compare the data, but I think we've all seen these patients who have a Deauville score of 4, which turns out to not be disease. So, I am happy to only escalate my patients, even in those German trial designs, if they have a Deauville score of 4 or 5. And also, with many of my patients with Hodgkin's, if I'm seeing Deauville score, I always try and get biopsies if we're worried about them relapsing, I'll always go for a biopsy, because I'm really cautious about those Deauville 4s, because we've got good data that there's often false positives with the Deauville 4s.

Dr Pavlovsky: And then, another important thing, most of these trials are trying to avoid radiotherapy, right? So, but then at the same time we have publications coming on saying that today's radiotherapy is totally different from what we used to see decades ago so, maybe we shouldn't be so worried about radiotherapy. So, what is your thought on this?

Dr Osborne: Yeah, I mean, I think that's a really good point. And I think that, particularly, when we are thinking about, for example, the RAPID trial where patients have favourable Lymphoma, early favourable Hodgkin and small volume disease, and we are looking at trying to avoid radiotherapy in them, that these patients did have a 7% inferior PFS. That is very true when I speak to my clinical oncology colleagues and they say, look at the site, we can give very focused radiotherapy with less toxicity than the previously. I think that is true. I think that with these early unfavourable patients, they often still, no matter how your radiotherapy techniques are, they still have a wide field and you can see the cardiac involvement and the extent of the radiotherapy fields. But I am not qualified to comment on these radiotherapy fields so, I'll look at a scan and say, yes, that looks like a nightmare. I don't think it looks like a good idea. But that is why I will always listen to my clinical oncology colleagues, because I think that they are the ones, they'll be able to look and see about the coronary artery involvement. Sometimes they'll go and look as if they're doing a planning scan and say, actually, from first look, it may not be as bad as we thought. But I think with some of this extensive widespread mediastinal disease, no matter what newer techniques we have, the clinical oncologists say, I really do not want to give radiotherapy. So, even though we I'm fully agree with you, that the toxicity of further chemotherapy should not be ignored, this were the risk-benefit and clear individualised thought about what's going to cause the patient most harm whilst trying to get the best disease control.

Dr Pavlovsky: And while we're on this topic and trying to see that your opinion on your colleagues, when you are going to do radiation, can you comment on what doses you're using and also, on patients who are PET positive, interim PET positive in whom you will continue and then radiate. Do you radiate only areas who are positive in interim PET or do you do radiation to basal hypermetabolic lesions?

Dr Osborne: So, this really does depend on individual patients. And we actually have a Hodgkin review meeting now with our clinical oncologist, just focusing on these specific questions. Because, for example, we know that in these early trials, these are all patients who had involved node radiotherapy, their whole site or involved site radiotherapy depending on the trial design so that everything was encompass able. But if we are thinking about an advanced Hodgkin patient and we have these patients who we might be for following RATHL, for example, and we have these patients who are IPET2 positive and at the end of treatment, they may be fully in a complete metabolic response. So, they were iPET2 positive, they were escalated to BEACOPP and then, their six-week PET is clear. We don't actually know whether giving radiotherapy to that iPET2 site is of definite benefit. So, we don't know that and many centres do, some centres don't. We also don't know whether we should involve just the sites of PET positivity or the whole sites of involved field. And really, it depends on the risks to the patient in a data-free zone. And so, if it looks as if it's going to cause a lot of toxicity doing whole initial sites of disease, then, my clinical oncology colleagues may say, I'm just going to do the sites of PET positivity. So, I think that there are definite standards on these early patients' trial designs

where standard radiotherapy doses and fields are used. I think when we are consolidating treatment, consolidation of bulk if they're PET negative, we don't tend to do that, if we're following RATHL, we trust the PET scan. At the end of treatment, we certainly do for HD18 escalated BEACOPP patients, but there are some centres that still do consolidate bulk. So, I think that that area is still a lot of uncertainty. We've obviously seen some data to suggest we don't need to consolidate bulk, but in terms of fields and dose, then, that would be my clinical oncologist with discussion and me, but they definitely lead on those decisions.

Dr Pavlovsky: Okay, so that was the next question, but I think you answered it and it was that even though we've had all of these trials showing the importance of an interim negative PET CT, we are still a bit concern about patients who have bulk disease at diagnosis. So, I think you already sort of mentioned that, but would you like to make any comments, whether in spite of a having an interim negative PET CT bulk disease has to be irradiated.

Dr Osborne: Yeah. So, I have to say my practise is that we don't irradiate bulk. And I think that we've got some data presented in the last couple of years, ICML ASH suggesting that there is no negative outcome from not doing that. However, the numbers are quite small and you could argue whether statistically it was significant in terms of the numbers needed to treat. My practise is that I don't routinely irradiate bulk in my advanced Hodgkin patients, whether they've had a RATHL approach or an HD18 approach. For patients that are iPET2 positive with a RATHL approach, then, we may sometimes consolidate those patients. And just finally, patients are iPET2 with an HD18 approach, so, these are patients who start on escalated BEACOPP, if they're iPET2 positive, they'll need six-cycles of escalated BEACOPP. We don't give them radiotherapy if they are negative at the end, because I think that we've got good data from the German trials that we don't need to do that. And their PFS is still excellent.

Dr Pavlovsky: And then we have these are very rare cases, but I think there are cases that we need to discuss a lot and are for those patients, regardless which approach you chose, but who are interim PET negative. And then, at the end of therapy, they're interim PET positive. So, can we rescue these patients with radiotherapy or does this mean we have to go onto salvage therapy?

Dr Osborne: Yeah, again really good. If there is... obviously, I'm really worried about these patients, is it a false negative iPET? We know that we're doing these scans very early. We know the earlier we do the scans, the less sensitive they are, I would tend to give radiotherapy if there's sites of PET positivity at the end, unless, it's extensive disease, because I don't feel that we've lost anything. Obviously, I would re-scan them depending on my concern, I might do it earlier. So, normal practise would be to do a scan three months after radiotherapy because of the prolonged uptake. However, if I'm clinically worried, I might do it at six weeks and that's not because of worrying about the uptake in the site of radiotherapy. It's looking for progression outside of radiotherapy field. So, I do tend to give radiotherapy hoping you might still manage to salvage some patients, but I'd be watching them really closely. And then, obviously trying to get a biopsy. If they've got too much PET positivity outside of field, these patients, I would again try biopsy, but I think we would be moving to chemo and an auto at that point.

Dr Pavlovsky: Okay, and then, you also mentioned something very important. That is our inability to predict which patients will be PET2 positive. And also, I think I would have to add to that, which patients were PET2 negative will eventually relapse, we also don't know that. So, you mentioned, and we had an excellent lecture just a couple of days ago with Sally Barrington, talking to us about a total metabolic tumour volume. And you mentioned one of the trials. So, are we ready to incorporate this in clinical trials? I'm sorry, not in clinical trials, in our everyday clinic?

Dr Osborne: So, I don't think we're ready yet. I think that there needs to be standardised measurement and assessment on how total metabolic tumour volume is measured. So, there are different segmentation techniques trying to get a standardisation so that we can again compare across trials. I think that I'm glad that you had a talk from Sally Barrington. She is so fantastic in her knowledge of this area. And I think that I

definitely feel that we understand more about predictive outcomes than we used to. And we are, I think all of us trying to look at possible models to pick out predictive features upfront because it's so-so important. I think in clinical practise no, I think that we know that total metabolic tumour volume, if there's lots of bulky disease, I'm much more likely to go in with a more intensive approach in terms of chemotherapy. But I don't think it's yet changing practise in terms of data.

Dr Pavlovsky: Okay, we have time for one last question. I think, in the last years, in the last decades, we have seen a big advance in the treatment of relapse refractory Hodgkin Lymphoma patients with incorporation of new drugs. So, how do you see the incorporation of new drugs upfront in this group of patients?

Dr Osborne: Well, I think it's a really exciting time at the moment. And I think we were all excited at ASH this year when you looked at that flat-line from Pamela Allen, when pembrolizumab was used in combination with AVD and I think that maybe having been nervous about bringing checkpoints upfront, I think this looks really encouraging. So, what I'm hoping is that by allowing the introduction of immunotherapy for some patients, it will allow us maybe less toxicity from the chemotherapy that we have to give with that. So, that's my hope that we can try remove some of the toxicity of intensive chemo, wide-field radiotherapy in the future by using more targeted therapy.

Dr Pavlovsky: Okay, so, thank you very much, Wendy. I think this has been great because this is a proportion of patients in which we have so many different options and we have so many to think about. So, thank you very much for joining us today and I don't know if you have any other comments you want to add?

Dr Osborne: No, I just don't. Thank you for inviting me. I always enjoy talking about Hodgkin Lymphoma and it's lovely to chat with you, Astrid.

Dr Pavlovsky: Okay, thank you very much. And thank you to all the participants.

Dr Osborne: Thank you.