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My name is Martin Hutchings. I am a hemato-oncologist from Copenhagen, Denmark, and I am delighted to be able to show to you some highlights from a talk I had the opportunity to give at the 9th International Symposium of Hodgkin Lymphoma in Cologne, Germany. The talk is about challenges in applying PET for early-stage Hodgkin lymphoma, and the objectives of the presentation was to describe what I find to be a large and probably underestimated impact of PET/CT on the staging and stage migration in Hodgkin lymphoma and in early stage Hodgkin lymphoma in particular; and also to address the value of PET/CT to predict outcome early during chemotherapy in early stage disease; and to address the selection of patients for less intensive chemotherapy and therapy in general based on the results of early interim PET/CT results, and this by reviewing the results of some recently published trials that I will be showing you.

But first, the stage migration. I believe 15-20% of all patients with early stage disease are, by the use of PET/CT, allocated to advanced stage. So in other words, patients that used with conventional staging to be in early stage and treated as early stage patients are now regarded as advanced-stage patients. So, this means that we are looking today, in 2013, at a different group of patients than we did before. This means an increased risk of overtreatment because in fact you are dealing now with a better group than you used to, and overtreatment is already a big problem in Hodgkin lymphoma, so this needs to be addressed properly, and also it means that we may find it difficult to compare present-day trials with trials of past eras. So in other words, PET/CT should be accompanied by more refined and tailored treatment strategies to avoid this overtreatment which is a risk and also perhaps by relevant modifications to the staging system in order to enhance the benefit of this staging by PET/CT which is certainly more accurate than what we had before.

A number of studies have been performed and published investigating the prognostic value of an early interim PET/CT scan done during chemotherapy for Hodgkin lymphoma. Many of the studies published focused mainly on advanced-stage patients, so it had been difficult to conclude anything firmly on the prognostic value of PET in early stage disease. Some of the studies published did include smaller numbers of early stage patients, but with very few events, it is difficult to say anything about the prognostic, particularly of those patients with an early interim positive PET. Certainly, patients with an early PET which is negative fare very, very well, but that is general for

the group as a whole. But some recently published studies, one from South America by the authors Cerci and colleagues, and also a larger retrospective study by Zinzani and colleagues from Italy show that indeed there is both, as expected, a very good negative predictive value of early PET but also a value of a positive PET showing a poorer prognosis than outpatients who reach a negative PET early during treatment.

I also showed results from a study that we conducted in Denmark along with colleagues in the US, Poland, and Italy. It is a recently completed a study of 126 Hodgkin lymphoma patients that we scanned already after a single cycle of chemotherapy. The majority of patients were also scanned after 2 cycles, but I did not report any results about those scans. But looking at the scans performed after 1 cycle of chemotherapy, the patients who turned PET negative, and particularly those in early stage disease, fared very well. Indeed, patients with early stage disease and a negative early PET after 1 cycle of chemotherapy did not experience any progressions at all, whereas those still with positive PET findings after this single cycle of chemotherapy had a 2-year progression-free survival of 50%, so that is a clear difference.

Now in the end, I will focus a little bit on the results of some trials that have been published recently using early interim PET to direct treatment for those patients. A number of trials are either ongoing, two trials have recently been published, and most of the trials ongoing focus on the role of PET, the possibility of an early interim PET which is negative to select patients who might not need radiotherapy for early stage disease. As you probably know, the standard treatment for early stage Hodgkin lymphoma is combined modality treatment beginning with a short course of chemotherapy followed by radiotherapy to the initially involved nodes. Well, radiotherapy has serious long-term side effects, so it is desired to select patients who might be cured well with chemotherapy alone and without radiotherapy. We are looking at the results of two recently published trials, one is the European H10 trial and the other one is the UK RAPID trial. They are somewhat different in the respect that the EORTC/LYSA/FIL trial, that is the H10 trial, has only been observed for a median of 13 months. So, this is indeed a very preliminary interim analysis, whereas the UK RAPID trial has a median observation time of 3 years. But that regarded, the results from these two trials are strikingly similar. There seems to be a slight loss of efficacy if you omit radiotherapy to the early PET-negative patients, but this reduction is counted in single digit percentages of around 3%, 4%, 5%, 6% in terms of progression-free survival. Nevertheless, even though these trials show strikingly similar results, the conclusions from the authors are quite different. Indeed the H10 trial was closed early due to futility, and the RAPID trial is reported as a positive trial, and I think this can lead to many interesting discussions, but the most important conclusion here is that we need

really to observe these study results for longer before we can draw any firm conclusions about these trials.

In the meantime, we have a running and recruiting German study called the HD16 study which is a quite simple layout, patients in this study, and they will reach a total of 1,400, patients randomized upfront to either a standard arm which is the German standard treatment for early favorable disease, 2 cycles of ABVD followed by radiotherapy, or an experimental arm where also patients receive 2 cycles of ABVD, but only those who are PET positive after chemotherapy will receive radiotherapy. This is a non-inferiority trial just as the RAPID trial and the H10, but we do not have the results from this trial which is ongoing.

To sum it all up, I talked about stage migration. There is a marked stage migration due to PET/CT in early stage Hodgkin lymphoma, around 15% of patients in early stage according to conventional imaging methods allocated to advanced stages due to PET/CT, and this has important implications for the treatment of individual patients and also for our ability to compare present-day study results with previous trials. It should really be taken into account when we look at studies and when we treat individual patients. I have talked to you about the value of early interim PET in early stage Hodgkin lymphoma, a value which has not really been recognized until quite recently. We have had a lot of knowledge about the value of interim PET in advanced-stage disease, but recent data suggest that indeed the prognostic value of PET is present in early stage disease as well, and I have talked to you about the recently published results from completed trials to using early interim PET to direct treatment in early stage Hodgkin lymphoma, and we concluded that we need more studies and we need more observation time in order to draw any firm conclusions about this.