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Milestones in Hodgkin Lymphoma: The Discovery and Evolution of Radiation Therapy in the Management of Hodgkin Lymphoma

Hello, my name is Richard Hoppe. I am a professor of radiation oncology at Stanford, and I will be speaking about the role of radiation therapy in Hodgkin's lymphoma, specifically its evolution in Hodgkin lymphoma management.

It is actually quite an interesting story. It was more than a century ago in 1902 that William Allen Pusey, who was actually a dermatologist in Chicago, experimenting with the newly discovered x-rays that Roentgen had discovered just within the previous decade and testing them in a variety of different diseases used them to treat a young boy who had Hodgkin's lymphoma and the young boy had significant lymphadenopathy on the left side of his neck and Pusey treated him with the x-rays and he marveled at the response that this young boy experienced.

In fact, he said that the effect of the rays on the patient were almost magical, and radiation therapy was used in this way for treating patients with Hodgkin lymphoma over the next couple of decades, that is treating small fields, seeing responses, but inevitably, the disease would come back in the same place or in other locations in the body. The treatment was palliative, but there were responses. Some of the early radiologists who were involved in these studies proposed that perhaps more comprehensive radiation treating larger areas at higher dosage might be effective, but the technology to accomplish that simply was not there at that time.

It was not until the early 1920s that higher energy x-ray apparatus became available. William Coolidge who was working for GE developed a deeper penetrating radiation device, and this began to be used in the late 1920s and into the 1930s. In 1931, a Swiss radiologist, René Gilbert, was the first to report using this more deeply penetrating x-ray treatments with larger fields of treatment, treating not only the involved areas but also to include areas that were not obviously involved, and he showed some very promising results in a small group of patients who had survived for 5 years after his treatment which was unheard of at that time. This was an inevitably failed disease. Then, later in 1950s, Vera Peters who was at the Princess Margaret Hospital in Toronto reviewed the experience of her mentor, Gordon Richards, who had treated patients between 1920 and 1950 at the Princess Margaret Hospital, and he had applied that principle of treating

uninvolved areas as well as the involved sites to roughly half of the patients that he treated, and Vera looked at those data, and she found that firstly, the 5-year survival in the patients he had treated was about 50% which was really quite good, but more interestingly perhaps was the fact that the survival of the patients who had been treated to the unaffected areas as well as the involved areas was significantly better than the survival of patients who were treated just to the involved sites of disease.

So, this is a very important observation, but still, although there was deep x-ray treatment available, the technology of the day still did not permit very safe treatment to very large areas and this really required some new therapeutic developments which occurred in the second half of the 20th century, the development of what we call megavoltage x-ray therapy, and this was in several different forms.

First of all, there was the development of the Cobalt-60 unit and the first Eldorado Cobalt unit was installed at the hospital in London, Ontario in 1951, and then in the UK, they were the first to develop a medical linear accelerator. The Metropolitan-Vickers Company installed an accelerator at the Hammersmith Hospital in 1953, and at Stanford, a different technology was used for developing a Klystron-driven medical linear accelerator that was developed by Henry Kaplan in the Department of Radiology and Ed Ginston in the Department of Physics. And these devices permitted treatment to very large fields without seriously damaging the more superficial tissues such as the skin, and this opened up the possibility for really much more aggressive radiation treatment for Hodgkin's disease, and at Stanford, Henry Kaplan was one of the main proponents of this more aggressive therapy, and using the medical linear accelerator that he had helped develop, he began to treat patients with fields that encompassed basically all of the lymphatics in the body and designed new concepts and treatment of large fields, for example, the mantle field that includes all the lymph nodes about the diaphragm, the inverted Y for treating lymph nodes below the diaphragm, and putting these together in combinations that he referred to as total lymphoid irradiation or subtotal lymphoid irradiation, and he treated a group of patients in this manner and found a remarkably excellent outcome with about 80% 5-year survival.

He compared this retrospectively to a group of patients who had been treated palliatively before the era of the medical linear accelerator, and of course, all of those patients did poorly, and his conclusion was that the more aggressive treatment should be the treatment of choice. Now, just at about this time, he recruited to Stanford Saul Rosenberg to join him in the lymphoma program. Saul Rosenberg is a medical oncologist, and Dr. Rosenberg looked at the data and said to Kaplan, "Well, that looks very good, but I think we need to prove it," and that challenge led to the initiation of the Stanford randomized trials with the treatment of Hodgkin disease which were among

the first clinical randomized trials for any type of cancer. And early on, these trials focused on the use of radiation therapy, for example, the very first clinical trial, which was called the L1 trial, randomized patients with any of this histology of lymphoma who had stage 1 or 2 disease to treatment with involved-field radiation or total lymphoid irradiation, and before long, it was realized that the patients who were treated more aggressively truly had the better outcomes, and that treatment then became standard for patients with stage 1 or 2 disease until the late 1980s or early 1990s.

At about that time, chemotherapy was being developed that was very effective also for treating the disease, MOPP chemotherapy, ABVD chemotherapy, and these chemotherapies at first were employed primarily for patients with advanced disease, but it was appreciated that even patients with early stage disease would respond to chemotherapy treatment. In addition, as 20-30 years of experience with radiation treatment was observed, it was noted that there were some late complications related to that treatment, potential cardiac effects of the radiation, and potential secondary cancers related to the radiation, and so there was a movement to incorporate chemotherapy earlier in the course of disease and incorporated then to patients who had stage 1 or 2 involvement.

That led to a series of clinical trials both at Stanford and cooperative groups around the world, the EORTC, the BNLI, the German Hodgkin Study Group which was organized in 1978. Trials looking at different combinations of chemotherapy and radiation for patients with early stage disease. Ultimately, those large fields got much smaller, and we went from total lymphoid irradiation back to involved-field radiation, and in the current era, we are using even smaller fields referred to as involved site radiation or involved node radiation, and this has really required a new advance in technology of radiation therapy. What we do now is a far cry from the way that radiation therapy was designed and delivered by Henry Kaplan. We do advanced types of simulation procedures using CT imaging and fusing, or CT imaging with PET scan, functional imaging. We do three-dimensional treatment planning. We have techniques such as deep inspiration breath hold and advanced technologies of treatment delivery such as IMRT, intensity modulated radiation therapy, or volumetric modulated arc therapy where we can focus the dose of radiation very conformally in the area that is treated. However, there is a much lower dose of radiation that is distributed to adjacent tissues and that volume of low-dose treatment can be quite significant. Perhaps a more advanced means for delivering radiation dose would be to use proton therapy. Protons are different than x-rays or photons. The conventional treatment with x-rays and photons, the radiation beam enters the patient and then gradually falls off in dose as it gets deeper into the body but goes through the body completely. So, if you treat a tumor that's halfway through the depth of the body, there will be treatment to the

tumor, but the radiation dose passes beyond that tumor. Protons are positively charged particle, and when protons is used for radiation, the entry dose is lower than is required with an equivalent dose of x-rays. Because the dose remains stable and actually increases a bit with depth due to a phenomenon called the spread-out Bragg Peak, and then the dose drops off to virtually zero after the depth of the tumor is reached so that there is no dose distribution beyond the depth of the tumor.

Using all of these technologies, we can now give radiation very much more safely than it had been given in the past, and this leads us to the opportunity to combine this minimal radiation approach with minimal chemotherapy approaches in early stage disease to really achieve the goal of high cure rates for these patients, and yet having very limited effects on the long-term outcome of their general health and with very little in the way of late complications and risks. Thank you.