these pregnancies in the event that cfDNA testing becomes the primary screening tool for fetuses affected by trisomy 21 in the future.

Norton et al. used a targeted approach to cfDNA testing by the sequencing of specific chromosomal regions. Other providers use different technical and bioinformatic approaches, which may deliver variation in specific aspects of test performance. However, the general principles remain the same in considering cfDNA testing, and the study by Norton et al. adds to the evidence showing good efficacy of such analysis in all women seeking screening for trisomy 21. Indeed, well-conducted studies, such as this one, improve our understanding of the performance of cfDNA testing, including sensitivity and specificity, the incidence of discordant results, and overall failure rates.

However, test uptake, economic aspects, and clinical utility will depend on local cultural and societal factors, including attitudes with respect to disability, laws around termination of pregnancy, and the existing health care structure. The availability of existing screening programs, in particular the expertise required for measurement of nuchal translucency, will also influence implementation in publicly funded maternity services. For these reasons, it is not possible to generalize regarding implementation strategies, although it is clear that the performance of cfDNA testing for trisomy 21 is superior to traditional approaches in unselected pregnancies. However, its use in screening for other chromosomal abnormalities, particularly the sex-chromosome aneuploidies and microdeletion and duplication syndromes, requires further validation before clinical implementation, especially in view of the contribution of maternal sex-chromosome anomalies to discordant results and the rarity of other chromosomal imbalances.

The views expressed in this editorial are those of the author and do not necessarily reflect those of the National Health Service, the National Institute for Health Research, or the Department of Health in the United Kingdom.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the UCL Institute of Child Health and the Great Ormond Street Hospital for Children NHS Foundation Trust — both in London.

This article was published on April 1, 2015, at NEJM.org.


DOI: 10.1056/NEJMe1502441
Copyright © 2015 Massachusetts Medical Society.

Controversies in the Treatment of Early-Stage Hodgkin’s Lymphoma

Dan L. Longo, M.D., and James O. Armitage, M.D.

Hodgkin’s lymphoma affects about 8000 patients a year in the United States, and with available therapies, about 7000 of them will be cured. Although room for improvement still exists, recent clinical research has focused on determining how little therapy can be given to maintain the current high cure rates. The focus on cutting back therapy to the bare minimum is related to well-defined,
treatment-related late toxic effects. The life-threatening or fatal toxic effects of radiation therapy include second cancers (including cancers of the breast, skin, thyroid, lung, and stomach) and premature coronary-artery disease. Life-threatening or fatal toxic effects of chemotherapy are less frequent and include pulmonary fibrosis caused by bleomycin and secondary acute leukemia and lung cancer caused by alkylating agents; the risk is greatly enhanced when these agents are used together with radiation therapy.

With regard to the relative risks of death associated with each therapeutic method, data from a National Cancer Institute study are informative. The study involved randomly assigning patients with pathologically staged early-stage Hodgkin’s disease to receive radiation therapy or alkylating agent–based chemotherapy. The primary results of this study were reported.\(^1\) Now, with a median of 27 years of follow-up, the survival rates among the patients in the two study groups who had complete remission and never had a relapse can be used as a measure of the late fatal toxic effects of therapy. The 30-year survival rate in first remission is 91% for patients treated with chemotherapy and 76% for those treated with radiation therapy. This difference is significant. The causes of death in the radiation-therapy group are mainly second cancers and premature coronary-artery disease.

Radiation therapists argue that efforts have been made to alter the delivery of radiation therapy and that these changes make its use much safer. We hope they are correct; however, long-term follow-up has not yet occurred. Even if the current delivery of radiation therapy is safer than earlier methods, it is unlikely to have fewer late effects than no radiation therapy at all.

In the face of the disparity in late toxic effects between the methods of treatment, one might guess that the direction of research would be to determine whether radiation therapy can be eliminated without an adverse effect on survival, just as it has been eliminated in the treatment of children with early-stage Hodgkin’s lymphoma, in whom the toxic effects of radiation are even greater. However, most of the published work on early-stage Hodgkin’s lymphoma in recent years has had the aim of reducing the number of cycles of chemotherapy while continuing to use radiation therapy at the lowest possible dose. This approach yields a high cure rate.\(^2\)

More recently, efforts have been made to individualize treatment courses by adjusting treatment on the basis of the speed of response to therapy — so-called response-adapted therapy. In this issue of the Journal, Radford and colleagues\(^3\) report the 5-year results of a treatment program in which patients with stage IA or stage IIA Hodgkin’s lymphoma and no large mass undergo positron-emission tomographic (PET) scanning after three cycles of chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). The authors wanted a stringent definition of complete remission and defined it as a score of 1 or 2 on the Deauville 5-point scale (i.e., uptake equal to or lower than that in the normal mediastinal blood pool).\(^4\) If the PET scan was negative, patients were randomly assigned to receive involved-field radiation therapy or no further therapy. Patients who had positive PET findings received a fourth cycle of chemotherapy and involved-field radiation therapy.

The study was designed as a noninferiority study. On the basis of a substantial body of previous work, it was expected that patients who received chemotherapy plus radiotherapy would have a progression-free survival rate that was 10 percentage points better than that of patients receiving chemotherapy alone, an advantage that has not translated into improved overall survival in part because of later deaths related to the treatment. The investigators designed the study with the goal of detecting a noninferiority margin of 10 percentage points. After the study was approved and embarked on, the investigators decided to put the noninferiority margin to a vote at an international meeting. Attendees voted that the margin should be reduced to 7 percentage points, a number that has no basis in experimental treatment results. If the 10-percentage-point margin doesn’t lead to a survival advantage, why would a 7-percentage-point margin be a better choice?

In any case, with the bar for noninferiority set more stringently, the study went on. Among the 571 patients who underwent PET scanning, 75% had negative PET findings after three cycles of chemotherapy. The 3-year progression-free survival rate was 94.6% among those who received radiation therapy and 90.8% among those who received no further therapy, a difference of approximately 4 percentage points. Given the number of patients, the 95% confidence limits for the difference included the absence of further therapy

More recently, efforts have been made to individualize treatment courses by adjusting treatment on the basis of the speed of response to therapy — so-called response-adapted therapy. In this issue of the Journal, Radford and colleagues\(^3\) report the 5-year results of a treatment program in which patients with stage IA or stage IIA Hodgkin’s lymphoma and no large mass undergo positron-emission tomographic (PET) scanning after three cycles of chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). The authors wanted a stringent definition of complete remission and defined it as a score of 1 or 2 on the Deauville 5-point scale (i.e., uptake equal to or lower than that in the normal mediastinal blood pool).\(^4\) If the PET scan was negative, patients were randomly assigned to receive involved-field radiation therapy or no further therapy. Patients who had positive PET findings received a fourth cycle of chemotherapy and involved-field radiation therapy.

The study was designed as a noninferiority study. On the basis of a substantial body of previous work, it was expected that patients who received chemotherapy plus radiotherapy would have a progression-free survival rate that was 10 percentage points better than that of patients receiving chemotherapy alone, an advantage that has not translated into improved overall survival in part because of later deaths related to the treatment. The investigators designed the study with the goal of detecting a noninferiority margin of 10 percentage points. After the study was approved and embarked on, the investigators decided to put the noninferiority margin to a vote at an international meeting. Attendees voted that the margin should be reduced to 7 percentage points, a number that has no basis in experimental treatment results. If the 10-percentage-point margin doesn’t lead to a survival advantage, why would a 7-percentage-point margin be a better choice?

In any case, with the bar for noninferiority set more stringently, the study went on. Among the 571 patients who underwent PET scanning, 75% had negative PET findings after three cycles of chemotherapy. The 3-year progression-free survival rate was 94.6% among those who received radiation therapy and 90.8% among those who received no further therapy, a difference of approximately 4 percentage points. Given the number of patients, the 95% confidence limits for the difference included the absence of further therapy.
being 1.3 percentage points better and 8.8 percentage points worse. Because 8.8 is more than 7, the noninferiority margin was exceeded. Given these and other data, it seems that patients with favorable prognostic characteristics who have early-stage Hodgkin's lymphoma in remission after chemotherapy alone are slightly more likely to have a relapse without radiotherapy.5,6

Several issues influence the interpretation of the results. First, the patients did not undergo a baseline PET scan; thus, some patients may have actually had more advanced disease. Second, the authors considered a score of 3 to indicate a positive PET finding — yet data from other studies suggest that in patients with Hodgkin's and other lymphomas, scores of 2 and 3 are similar in outcome.7-9 Third, the key measurement of efficacy is overall survival, and 5 years of follow-up is not sufficient to capture the treatment-related fatalities, which increase 10 to 30 years after treatment. Because Hodgkin's lymphoma often occurs in young adults, late fatal toxic effects still foreshorten the lives of the affected patients.

What are we to conclude from this study? Clearly, both treatment strategies work. Patients who have negative PET findings after three cycles of chemotherapy are cured approximately 9 times out of 10. Is a 4-percentage-point difference in the rate of relapse worth the added risk of using radiation therapy? Should 100 patients be exposed to radiation therapy to keep 4 from relapsing with no evidence of long-term survival benefit? The patient should be involved in making that decision after being fully informed of the risks and the benefits. Some patients will elect to minimize the long-term risks and expect that they are among the 90% of patients who have already been cured by the chemotherapy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Department of Internal Medicine, Division of Hematology–Oncology, University of Nebraska Medical Center, Omaha (J.O.A.).


DOI: 10.1056/NEJMe1502888
Copyright © 2015 Massachusetts Medical Society.