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Stephen D. Smith and John W. Sweetenham

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Studying Survival in Hodgkin’s Lymphoma: All for One, or One for All? Why Methodology Matters

STEPHEN D. SMITH, JOHN W. SWEETENHAM

Cleveland Clinic Foundation, Department of Hematologic Oncology and Blood Disorders, Cleveland, Ohio, USA

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The paradigm of therapy for Hodgkin’s lymphoma (HL) in the past half century has transformed from nihilism to optimism, and more recently, idealism—in the recognition that successful treatment need not impart a heavy cost. Successive cooperative group trials, testing approaches aiming to minimize treatment-related toxicities while maintaining cure rates, report a steady improvement in survival outcomes (reviewed by Bartlett [1]). Brenner et al. [2] provide insight on this phenomenon from a different vantage point, employing a projection-based model using Surveillance, Epidemiology, and End Results (SEER) data to estimate the survival rate of future HL patients. Their model is first applied to historical cohorts, where it outperforms other methods for estimating outcomes, and is then used to project the survival of HL patients diagnosed in 2006–2010. Stated goals of the study are to provide more timely and useful survival figures in HL, given that published registry data may lag years behind therapeutic improvements.

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The model projects that patients diagnosed with HL in 2006–2010 will achieve higher 5- and 10-year survival rates than ever before, especially for adults aged 45–54 (and with the possible exception of adults aged >75, who represent a minute fraction of HL patients). The model, which assumes positive trends for prior years in the SEER data, seems somewhat self-fulfilling. It might be expected to project improvements in many cancers, because survival even for lethal forms has improved in past decades [3]. And, although the authors suggest reasons for optimism based on their findings, the incremental improvements in survival projected in this report are modest in the context of historical gains in HL. Likely of greater relevance to the typical young, curable HL patient is the impact of treatment on fertility, organ function, and development of secondary cancers, and how to reduce their risk for such late effects. As shown in a report on nearly 2,500 HL patients treated at Stanford, mortality in the long-term (15 years after therapy) has more to do with late treatment effects like cardiac disease and second malignancies than recurrent HL [4]. The authors acknowledge the late effects of therapy, and note that their 10-year projection would include few deaths from such causes. Secondary solid tumors attributable to radiotherapy, for example, occur after a latency of 5–10 years and show a continual increase in risk [5]. Chemotherapy alone has been shown to produce equivalent survival to strategies involving radiotherapy in diverse groups of patients with early and advanced stage HL [6–8], suggesting...
that the use of radiotherapy will continue to decline. The trend away from radiation therapy will probably accelerate if early data concerning the utility of functional imaging to assess residual masses after chemotherapy are confirmed [9].

A notable finding in the study of Brenner et al. [2] is the relatively large gain projected for 45- to 54-year-olds diagnosed with HL in 2006–2010 (10-year survival rate, 83.6%). This should be interpreted cautiously because it may in part be an artifact of superior diagnostic techniques over the last 20 years. For example, lymphocyte-depleted HL is generally thought to have been overdiagnosed in historical groups, with most cases likely representing aggressive non-Hodgkin’s lymphoma [10]. Diagnosed in older patients and carrying a worse prognosis, the removal of lymphocyte-depleted HL cases from among 45- to 54-year-olds diagnosed with HL in the modern era may artificially improve survival figures. Albeit a rare entity, the case of lymphocyte-depleted HL illustrates a limit to comparing cohorts diagnosed in different eras.

The author’s “all for one” population-based approach otherwise provides survival estimates in line with those expected from modern clinical trials. However, their report comes at a time when individual patient features, rooted in disease biology and response, carry increasing weight in trials of HL therapy. Favorable survival projections in HL derived from population-based studies are not likely to help patients or oncologists make informed treatment decisions, because they are unable to dissect the competing risks that contribute to excessive late mortality in this population. Prospective randomized clinical trials remain the only reliable way to assess the effectiveness of new treatments for this disease. Very long-term follow-up should be incorporated into all new trials to ensure that the true benefit of novel therapies is understood and to generalize results, “one for all.”

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REFERENCES
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