Hodgkin's disease: Complications of therapy and excess mortality

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Summary

Background: The long-term survival of patients treated for Hodgkin's disease permits careful evaluation of long-term complications and excess mortality.

Patients and methods: Between 1960 and 1995, 2498 patients who were treated for Hodgkin's disease at Stanford University were evaluated. Survival, freedom from relapse, and important complications of therapy (cardiac disease and secondary cancers) were analyzed, and risk of mortality from all causes was calculated utilizing absolute excess risk calculations.

Results: The risk of death from Hodgkin's disease is 17% at 15 years of follow-up and increases only slightly thereafter. The risk of death from other causes is also 17% at 15 years, but increases sharply thereafter. The major causes of mortality (other than Hodgkin's disease) are secondary cancers and cardiac disease. Second cancers with significant increase in risk include leukemia (acute nonlymphocytic), non-Hodgkin's lymphoma, lung/pleural cancer, breast cancer, melanoma, soft tissue and bone sarcomas, stomach cancer, salivary gland tumors, thyroid cancer, and pancreatic cancer. The absolute excess risk of death from causes other than Hodgkin's disease increases during each five-year follow-up interval for at least 25 years. However, the absolute excess risk of death during similar follow-up periods is less for patients treated in more recent years (1980-1995) than in the prior treatment era (1962-1980).

Conclusions: Mortality for causes other than Hodgkin's disease is important in the long-term follow-up of patients. Causes of death are often treatment related. Changes in treatment programs can reduce the long-term excess risk of death from complications of therapy.

Key words: cardiac, complications, Hodgkin's disease, mortality, secondary cancers

Introduction

The long patient survival that can be achieved after treatment for Hodgkin's disease has permitted a careful evaluation of long-term complications and excess mortality. Since 1960, nearly 2500 patients have received definitive treatment for Hodgkin's disease at Stanford. They have been followed regularly after the completion of treatment in order to detect recurrent Hodgkin's disease and to identify complications of therapy. This paper summarizes the important events that may lead to compromised survival in these patients.

Patients and methods

Between 1960 and 1995, 2498 patients were treated for Hodgkin's disease at Stanford. Treatments included radiation therapy, chemotherapy with a variety of drug combinations (e.g., MOPP, PAVe, ABVD, VBM, Stanford V), and combined modality therapy. Staging during the period 1968-1990 often included laparotomy and splenectomy.

Patients were followed at regular intervals after the completion of treatment in order to detect recurrent Hodgkin's disease and to identify complications of therapy. This paper summarizes the important events that may lead to compromised survival in these patients.

Absolute excess risk was calculated as follows:

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\text{Absolute excess risk} = \frac{\text{observed events} - \text{expected events}}{\text{person years of follow-up}} \times 10000
\]

This expresses the absolute (excess) risk per 10000 patient years. The absolute risk divided by 10 represents the percentage likelihood of an event per decade of follow-up for an individual patient.

Results

Figure 1 displays the actuarial risk of death from Hodgkin's disease or other causes for the cohort of patients treated between 1960 and 1995. Death from Hodgkin's disease is rare after more than 10 years of follow-up. Beyond 15 years, the risk of death from other causes begins to exceed the risk of death from Hodgkin's disease. Table 1 lists the causes of deaths in 754 patients. Among causes other than Hodgkin's disease, two-thirds are from second cancers (21%) or cardiovascular disease (16%).

Second cancers

The major categories of second cancers after treatment for Hodgkin's disease include leukemia, non-Hodgkin's lymphoma, and solid tumors. Table 2 displays the risk for
Chemotherapy programs that included alkylating agents and procarbazine (e.g., MOPP and MOPP-like combination) are largely reflective of patients who were treated with combined modality therapy or salvage therapy (< 1%). The risk after treatment with radiation therapy alone is exceedingly small after treatment with radiation therapy alone. The absolute risk for developing solid tumors is much lower than secondary leukemias or non-Hodgkin's lymphomas, and the risk for development of leukemia as a complication of therapy should decline concurrently.

The secondary non-Hodgkin's lymphomas that develop after treatment for Hodgkin's disease are usually B-cell lymphomas, and the most common histologic type is diffuse large cell. Most series report that the risk for developing secondary non-Hodgkin's lymphoma is independent of the type of initial therapy. There are similar risks for primary radiation therapy, combined modality therapy, and chemotherapy alone. This suggests that secondary non-Hodgkin's lymphoma may be related to the underlying immunosuppression that contributed to the initial development of Hodgkin's disease, leaving the host at high risk for developing a non-Hodgkin's lymphoma later. In addition, patients with Hodgkin's disease who present with the lymphocyte-predominant subtype may actually have a B-cell lymphoma rather than Hodgkin's disease. Patients with lymphocyte-predominant histology are reported to have a higher risk for developing intermediate- or high-grade B-cell lymphoma than patients with other histologic subtypes of Hodgkin's disease.

Secondary solid tumors have a much longer latent period than secondary leukemias or non-Hodgkin's lymphomas. In addition, although the relative risk for developing solid tumors is substantially less than for development of leukemia or non-Hodgkin's lymphomas, solid tumors are more prevalent in the general population and the absolute risk for developing solid tumors is much higher than for either leukemia or non-Hodgkin's lymphoma (Table 2). The types of solid tumors that have been demonstrated to have increased risk among the Stanford cohort include those listed in Table 3. In addition, when all genitourinary sites are combined, the risk of second cancer in those sites is significantly increased, and a recent analysis has shown that the risk for pancreas cancer also is elevated significantly.

The most common type of second cancer after treatment for Hodgkin's disease is lung cancer. Both radiation therapy and chemotherapy have been implicated in lung cancer induction. Recent series have demonstrated a very strong linkage between smoking and secondary lung cancer in patients treated for Hodgkin's disease. This information is important to share with patients who continue to smoke after treatment for Hodgkin's disease.

Among women, the most important second solid tumor risk is for breast cancer. The latent period is

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**Table 1. Causes of death among 2498 patients treated for Hodgkin's disease.**

<table>
<thead>
<tr>
<th>Cause</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin's disease</td>
<td>333</td>
<td>44</td>
</tr>
<tr>
<td>Other cancers</td>
<td>160</td>
<td>21</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>117</td>
<td>16</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Infection</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>Accidental</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Hematologic</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Other, multiple</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>754</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Secondary cancer risk among patients treated for Hodgkin's disease.**

<table>
<thead>
<tr>
<th></th>
<th>O/E</th>
<th>RR</th>
<th>Absolute risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia (AML)</td>
<td>38/1.0</td>
<td>37.7</td>
<td>18.4</td>
</tr>
<tr>
<td>Non-Hodgkin's</td>
<td>(35/0.24)</td>
<td>(144.1)</td>
<td>(17.3)</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>126/29.4</td>
<td>4.3</td>
<td>48.8</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>104/16.6</td>
<td>6.3</td>
<td>43.5</td>
</tr>
</tbody>
</table>

* Excess cases per 10000 patients per year.
Abbreviations: O/E - observed risk; RR - relative risk.
From ref. [2].
often 15 years or longer. The relative risk for young women (teenagers or younger) is exceedingly high. The risk decreases with patient age and is elevated only slightly for women who are 30 years or older at the time of treatment for Hodgkin's disease. Breast cancer risk appears to be related primarily to radiation treatment, with little evidence that it is increased among patients treated with chemotherapy alone [14].

**Cardiac disease**

Radiation-induced cardiac disease can have a variety of manifestations, including acute pericarditis, delayed pericarditis (acute or chronic), pancarditis, coronary artery disease, and functional valvular/conduction defects. In the Stanford series, approximately one-half of cardiac deaths are due to myocardial infarction and one-half due to other cardiac causes [15]. For the entire population of patients treated at Stanford, the relative risk from death from cardiac causes was 3.1, with an absolute (excess) risk of 28.0. As shown in Table 4, the risk was greater for men than for women and was clearly associated with mediastinal irradiation. It appears, however, that there is a radiation-dose effect on cardiac complications, with few deaths occurring when mediastinal radiation doses were 30 Gy or lower. In addition, patients treated more recently, with efforts to provide more cardiac protection and employ lower daily doses of radiation, are at decreased risk for cardiac mortality.

The value of screening studies in detecting cardiac abnormalities in patients treated for Hodgkin's disease is unclear. Currently, at Stanford, we are conducting a large study supported by the National Cancer Institute looking at the efficacy of screening with stress echocardiography and thallium radioisotope exercise scans.

**Excess mortality**

As noted in Table 1, a substantial excess risk of mortality in patients treated for Hodgkin's disease may be attributable to second cancers and cardiac diseases. An absolute excess risk of death from all causes (exclusive of Hodgkin's disease) can be calculated as an indicator of iatrogenic mortality. Tables 5 and 6 demonstrate a comparison of excess deaths for patients with early- and advanced-stage Hodgkin's disease treated during the period 1962–1980 versus 1980–1996. For patients with stage I–II disease, there was a clear decrease in the excess risk of death during each five-year follow-up interval. This may be attributable largely to the changes in radiation therapy techniques noted earlier, and perhaps also to the use of careful combined-modality therapy in selected patients, such as those with large mediastinal masses. Patients with stage III-IV disease clearly had decreased treatment-related mortality during the first 10 years of their follow-up. There may be an increase in treatment-related mortality between 10 and 15 years of follow-up; however, this may be due, in part, to the much lower risk of death from Hodgkin's disease in the more recently treated cohort.
Discussion

It is clear that patients who have been treated for Hodgkin's disease, despite being cured of their malignancy, may develop iatrogenic complications that lead to premature mortality. These risks have been appreciated for more than a decade, and many centers and clinical trial groups have instituted changes in treatment programs in order to minimize these risks. This is an important area of contemporary clinical research in Hodgkin's disease.

Important questions remain regarding long-term effects. Although there are abundant data detailing the long-term risks of radiation therapy, there are few data bearing on the long-term excess risk of death for patients treated with chemotherapy alone. Although many series include several hundred patients treated with radiotherapy alone, with median follow-ups in excess of 10 years, there are no similar data for treatment with chemotherapy alone [3, 6, 11, 16].

Another important issue relates to the dose effect in radiation therapy. Specifically, is there any safe dose of radiation, especially as it is employed in combined modality therapy programs, such that the risk for secondary solid tumors or cardiac disease will not be increased? This is an important issue, since radiation remains the most effective single agent for the treatment of Hodgkin's disease.

Finally, how can we assure long-term follow-up of our patients? In the United States, changes in health care management have decreased the ability of oncologists (both medical and radiation) to continue to follow their patients after the completion of therapy. Current research to identify less morbid treatment programs may be compromised by our inability to follow these patients and assess outcome.

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