The survival of patients with Hodgkin's disease has dramati-
cally improved over the past 30 years because of advances
in treatment. However, concern for the risk of long-term
complications has resulted in a number of trials to evaluate
reduction of therapy. The consequences of these trials on
recurrence, development of long-term complications, and
survival remain unknown. One major consequence of suc-
cessful treatment of Hodgkin's disease is the develop-
mant of second malignant neoplasms. We sought to determine
the factors most important for development of second tu-
mors in pathologically staged and treated Hodgkin's disease
patients followed for long intervals to provide background
information for future clinical trials and guidelines for rou-
tine patient follow-up. Between April 1988 and December
1988, 794 patients with laparotomy staged PS IA-IIIB Hodg-
kin's disease were treated with radiation therapy (RT) alone
or combined radiation therapy and chemotherapy (CT).
There were 8,500 person-years of follow-up (average of 10.7
person-years per patient). Age and gender-specific incidence
rates were multiplied by corresponding person-years of ob-
servation to obtain expected numbers of events. Observed
to expected results were calculated by type of treatment,
age at treatment, sex, and time after Hodgkin's disease. Ab-
solute (excess) risk was expressed as number of excess
cases per 10,000 person-years. Seventy-two patients have
developed a second malignant neoplasm. Eight patients de-
veloped acute leukemia, 10 had non-Hodgkin's lymphoma
(NHL), and 53 patients developed solid tumors at a median
time of 5 years, 7.25 years, and 12.2 years, respectively, after
Hodgkin's disease. One patient developed multiple myeloma
16.5 years after Hodgkin's disease. The relative risk (RR) of
developing a second malignancy was 5.6. The absolute ex-
cess risk per 10,000 person-years (AR) of developing a sec-
ond malignancy was 69.6 (7.0% excess risk per person per
decade of follow-up). The highest RR occurred for the de-
velopment of leukemia (RR = 66.2), however because of the
low expected risk, the AR was only 9.3. The RR of solid
tumors after Hodgkin's disease was lower (4.7); however,
the AR was greater (49) than for acute leukemia. Among the
solid tumors, breast, gastrointestinal, lung, and soft tissue
cancers had the highest absolute excess risks. The risk for
developing breast cancer after Hodgkin's disease was great-
est in women who were under the age of 25 at treatment.
The most significant risk factor for the development of both
leukemia and solid tumors was the combined use of radia-
tion therapy and chemotherapy. The RR following RT alone
was 4.1 (AR = 51.1); for RT + CT (initially or at relapse) the
RR was 9.75 (P < 0.05, nonoverlapping confidence limits,
AR = 123.9). Survival following development of a second
malignancy was poor in patients with leukemia, gastrointes-
tinal tumors, lung cancer, and sarcoma. Survival from other
malignancies including NHL and breast cancer was more
encouraging. Second malignant neoplasms are a major
cause of late morbidity and mortality following treatment
for Hodgkin's disease. The most significant risk factor for the
development of second tumors is the extent of treatment
for Hodgkin's disease. Recommendations are presented for
both prevention and early detection of these tumors.

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are low. For example, the increased observed to expected ratio for developing a second solid cancer is of much lower magnitude than the ratio for acute leukemia or NHL. However, because of a high background risk, the absolute excess risk (AR), per 10,000 person-years of developing a solid tumor is greater than the absolute excess risk of developing acute leukemia or NHL after treatment for Hodgkin’s disease.

The current study evaluates 794 uniformly staged and treated patients seen at a single institution from 1969 to 1988. All patients underwent a diagnostic staging laparotomy and splenectomy, and all were treated with RT with or without combination chemotherapy. Patients who did not undergo surgical staging were excluded because the follow-up is much shorter for this group than for laparotomy-staged patients, reflecting the decrease in the use of this diagnostic procedure in more recent years. Risk factors are presented for both pediatric and adult patients; these patients were treated on the same protocols. The study presents RR and AR data 15 years after treatment for Hodgkin’s disease. Survival data is shown for patients who developed second tumors.

MATERIALS AND METHODS

Between April 1969 and December 1988, 794 patients with laparotomy staged (PS) IA-IIIB Hodgkin’s disease were seen at the Joint Center for Radiation Therapy and treated at the New England Deaconess Hospital, Beth Israel Hospital, Brigham and Women’s Hospital, Children’s Hospital, or the Dana-Farber Cancer Institute. The median age at treatment was 24 years (range, 3 to 69 years). Histologic classification for all patients was confirmed by hematopathologists at the treating hospital. All patients underwent clinical staging with history and physical examination, chest radiography, complete blood counts and chemistries, and lymphangiography and/or computerized tomography of the abdomen and pelvis. All patients underwent surgical staging with a bone marrow biopsy (either before or at the time of staging laparotomy), and a staging laparotomy with splenectomy, liver biopsy, and evaluation of para-aortic, pelvic, and iliac lymph nodes. Surviving patients had a minimum follow-up time of 5 1/2 years and a median follow-up time of 11 years.

Patients in this study were initially treated with RT alone or combined radiation therapy and chemotherapy (CMT). Sixty-two percent of patients were treated with RT alone without relapse. Nineteen percent of patients received initial RT and were subsequently treated with chemotherapy for recurrent disease (RT-R-CT). The remaining 20% of patients received initial CMT. Fifty-six percent of patients were male. Nineteen percent of patients were 16 years of age or younger at diagnosis, 68% were age 17 to 39, and 13% were age 40 or older. Seventy-seven percent of patients had PS I-II and 23% had PS III Hodgkin’s disease (Table 1).

Patients in this study received RT to either the involved nodes only (n = 3), or to mantle (n = 44), mantle and paraaortic (n = 604, [MPA]), pelvic and paraaortic (n = 26), or total nodal (n = 117, [TNI]) fields. All patients underwent treatment simulation and received RT on 4-6 MV linear accelerators for mantle and pelvic fields, and 6-15 MV linear accelerators for paraaortic fields. The doses to the mantle field ranged from 3,500 to 4,000 cGy with a boost to bulk disease for a total of 4,000 to 4,400 cGy; paraaortic and pelvic fields were treated to 3,000 to 4,000 cGy. Daily fractions ranged from 150 to 200 cGy, 5 days per week. Technical factors included the use of individualized divergent blocks, equal treatment from anterior and posterior fields, and the addition of a posterior cervical spine block at 3,000 cGy and a larynx block at 2,000 cGy.34,35 None of the patients were treated with posterior thoracic spine blocks.

Initial chemotherapy included MOPP in 139 patients (88%), ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) in 10 patients (6%), alternating or hybrid MOPP/ABVD chemotherapy in 3 patients (2%), CHIVPP chemotherapy in 5 patients (3%), and COPP (cyclophosphamide substituted for mechlorethamine) chemotherapy in one patient (1%). Treatment at first relapse included MOPP in 92 patients (65%), ABVD in 17 patients (12%), alternating or hybrid MOPP/ABVD chemotherapy in 8 patients (5%), combined MOPP and involved field RT in 10 patients (7%), RT alone in 7 patients (5%), EVA (doxorubicin, VP-16, vinblastine) in 5 patients (3%), CHIVPP in 6 patients (4%), and single agent chemotherapy in 2 patients (1%). Of the patients who received combination chemotherapy (initially or for relapse) 85% received MOPP or CHIVPP.

A total of 794 patients were analyzed in this report. There were a total of 72 events and 8,500 person-years of follow-up for the second tumor analysis (average of 10.7 person-years per patient). Patients were analyzed by sex, age at diagnosis, and treatment. Person-years of observation started at the end of initial treatment for Hodgkin’s disease and continued until death, second cancer, or last day of follow-up. For purposes of assessing incidence according to treatment exposure only, person-years of observation started 1 year after initiation of treatment. The first year of exposure was not counted when breaking down results by treatment, because it was considered unlikely that any events during the first year could be because of treatment (3 events were seen). In addition to using three eventual treatment categories, RT, RT-R-CT, and CMT, another person-years analysis counted exposure time in the RT-R-CT group before initiation of CT as RT exposure and exposure time after initiation of CT as combined RT and CT exposure.

Age and gender-specific incidence rates from surveillance epidemiology end results (SEER) were multiplied by corresponding person-years of observation to obtain the expected number of events.36 Estimation of relative risk was based on the assumption that the observed number of second cancers followed a Poisson distribution. Confidence intervals for relative risks (ratio of observed to expected number of cases) were calculated using exact Poisson probabilities.37 Observed to expected (O/E) results were calculated for all patients, and separately by type of treatment, age at treatment and sex. In addition, O/E results were calculated by 5-year intervals (<5, 5-<10, 10-<15, and ≥15 years of follow-up). Absolute (excess) risk was calculated by subtracting observed minus expected numbers of
SECOND MALIGNANCIES AFTER HD

cases and dividing by the person-years at risk. The result was multiplied by 10,000 and expressed as number of excess cases per 10,000 person-years.

Actuarial overall survival curves were calculated using the Kaplan-Meier method. Prognostic factors were tested for significance by univariate log-rank testing and by proportional hazards models. All P values are two-sided. All deaths regardless of cause were counted in the survival statistics.

RESULTS

Seventy-two of the 794 patients in this study have developed a second malignancy; 70 patients developed cancers after Hodgkin’s disease, 2 developed the other malignancy either before or at the time of diagnosis of Hodgkin’s disease (both breast cancers). Eight patients have developed acute leukemia, 10 have had NHL and 53 patients developed solid tumors at a median time of 5 years, 7.25 years, and 12.2 years, respectively, after Hodgkin’s disease. One patient developed multiple myeloma 16.5 years after initial treatment for Hodgkin’s disease. Four patients developed a third malignancy (ductal carcinoma in situ [DCIS] of the breast, carcinoma in situ [CIS] of the cervix, CIS of the vulva, and carcinoma of the lung). The time to development of a second tumor after Hodgkin’s disease is shown in Fig 1.

The RR of developing a second malignancy was 5.6 (Table 2). The AR of developing a second malignancy was 69.6 per 10,000 person-years (7.0% excess risk per person per decade of follow-up [pppd]). The highest RR occurred for the development of leukemia (RR = 66.2); however because of the low expected (background) risk, the AR was only 9.3 per 10,000 person-years. The RR and AR for NHL after Hodgkin’s disease were 18.4 and 11.1, respectively. The RR of solid tumors after Hodgkin’s disease was lower (4.7); however, the AR was greater (49 per 10,000 person-years) than for acute leukemia or NHL because of the higher background risk. Among the solid tumors, breast, gastrointestinal, lung, and soft tissue tumors had the highest absolute excess risks (Table 2).

Risk factors for the development of a second malignancy after Hodgkin’s disease are shown in Table 3. The most significant risk factor was the combined use of RT and chemotherapy. The RR following RT alone was 4.1; for RT + CT (initially or at relapse) the RR was 9.75 (P < .05, nonoverlapping confidence limits). The AR for RT was 51.1 per 10,000 person-years (5.1% pppd); for CT + RT it was 123.9 per 10,000 person-years (12.4% pppd). These differences were due not only to a higher RR of leukemia in patients receiving RT + CT than in patients treated with RT alone (RR of 178.5 v RR of 25.5, respectively), but also a higher RR of solid tumors in patients receiving RT + CT (RR of 7.8 v RR of 3.5, respectively). In a separate analysis of the RT, RT-R-CT, and CMT groups, the RR were 4.27, 5.8, and 12.9, respectively (P < .05, nonoverlapping confidence limits, between RT and CMT).

Other risk factors included age at treatment for Hodgkin’s disease and gender. The RR of developing a second malignancy decreased with age at diagnosis from 33.8 (<17 years old), to 8.3 (17 to 39 years old), to 1.95 (>40 years old). However, the AR was constant regardless of age at treatment, because of the increased expected incidence of tumors in

Table 2. Relative Risk of Second Malignancy After Hodgkin’s Disease

<table>
<thead>
<tr>
<th>Observed/Expected</th>
<th>RR (95% CI)</th>
<th>AR/10,000 P-Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>All types</td>
<td>72/12.9</td>
<td>5.6 (4.4-7.0)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>8/0.12</td>
<td>66.2 (28.1-130.7)</td>
</tr>
<tr>
<td>NHL</td>
<td>10/0.54</td>
<td>18.4 (6.6-33.8)</td>
</tr>
<tr>
<td>Milt myeloma</td>
<td>1/0.11</td>
<td>9.0 (0.22-50.3)</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>53/11.3</td>
<td>4.7 (3.6-6.1)</td>
</tr>
<tr>
<td>Breast</td>
<td>13/1.99</td>
<td>6.5 (3.5-11.2)</td>
</tr>
<tr>
<td>GI</td>
<td>10/2.03</td>
<td>4.9 (2.3-9.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>8/1.77</td>
<td>4.5 (1.9-8.9)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>6/0.13</td>
<td>44.5 (16.3-97.3)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>4/0.7</td>
<td>5.7 (1.4-14.4)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3/0.74</td>
<td>4.1 (0.8-11.9)</td>
</tr>
<tr>
<td>GU/GYN</td>
<td>3/2.9</td>
<td>1.0 (0.2-3.1)</td>
</tr>
<tr>
<td>Other</td>
<td>6/1.1</td>
<td>5.0 (2.1-12.3)</td>
</tr>
</tbody>
</table>

Abbreviations: NHL, non-Hodgkin’s lymphoma; RR, relative risk; AR/10,000 P-Y, absolute excess risk per 10,000 person-years; CI, confidence intervals.

Table 3. Risk Factors for a Second Malignancy After Hodgkin’s Disease

<table>
<thead>
<tr>
<th>Cohort (P-Y)</th>
<th>Observed/Expected</th>
<th>RR (95% CI)</th>
<th>AR/10,000 P-Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (5,850)</td>
<td>72/12.9</td>
<td>5.6 (4.4-7.0)</td>
<td>69.6</td>
</tr>
<tr>
<td>Men (4,880)</td>
<td>35/7.1</td>
<td>5.0 (3.4-6.9)</td>
<td>57.2</td>
</tr>
<tr>
<td>Women (3,620)</td>
<td>37/5.8</td>
<td>6.4 (4.5-8.8)</td>
<td>86.2</td>
</tr>
<tr>
<td>Age &lt;17 (1,822)</td>
<td>14/0.41</td>
<td>33.8 (18.6-56.8)*</td>
<td>74.6</td>
</tr>
<tr>
<td>Age 17-39 (5,697)</td>
<td>44/5.3</td>
<td>83.0 (60.1-111)</td>
<td>67.9</td>
</tr>
<tr>
<td>Age &gt;40 (981)</td>
<td>14/1.72</td>
<td>2.0 (1.1-3.3)</td>
<td>68.6</td>
</tr>
<tr>
<td>RT (5,222)</td>
<td>36/8.8</td>
<td>4.1 (2.9-5.7)*</td>
<td>51.2</td>
</tr>
<tr>
<td>RT + CT (2391)</td>
<td>33/3.4</td>
<td>9.8 (6.7-13.7)</td>
<td>123.9</td>
</tr>
</tbody>
</table>

* Nonoverlapping confidence limits.
This twofold increased risk is primarily because of the late age of the first time greater than 15 years. Almost all the increase in AR with time greater than 10 years after Hodgkin's disease was seen for the development of solid tumors. The RR did not significantly increase with time in 5-year intervals of follow-up and by subtype. For all second malignancies, the RR increased from 35.9 per 10,000 person-years (6.8% pppd) compared to 34.9 per 10,000 person-years (3.5% pppd) for men (Table 4). This twofold increased risk is primarily because of the late development of breast cancer, which has a large impact on the AR.

Table 5 shows the RR and AR of second malignancies by 5-year intervals of follow-up and by subtype. For all second malignancies, the RR did not significantly increase with time from treatment; however, the AR greatly increased because of an increase in the number of expected cases as patients age (and are followed longer). The AR increased from 35.9 for the first 5 years, to 56 for years 5 to 10, to 104 for years 10 to 15, to 217 per 10,000 person-years (21.7% pppd) for time greater than 15 years. Almost all the increase in AR with time greater than 10 years after Hodgkin's disease was because of second solid tumors.

More striking gender differences were seen for the development of solid tumors after Hodgkin's disease. Women had an AR of solid tumor development of 68.1 per 10,000 person-years (6.8% pppd) compared to 34.9 per 10,000 person-years (3.5% pppd) for men (Table 4). This twofold increased risk is primarily because of the late development of breast cancer, which has a large impact on the AR.

Table 5 shows the RR and AR of second malignancies by 5-year intervals of follow-up and by subtype. For all second malignancies, the RR did not significantly increase with time from treatment; however, the AR greatly increased because of an increase in the number of expected cases as patients age (and are followed longer). The AR increased from 35.9 for the first 5 years, to 56 for years 5 to 10, to 104 for years 10 to 15, to 217 per 10,000 person-years (21.7% pppd) for time greater than 15 years. Almost all the increase in AR with time greater than 10 years after Hodgkin's disease was because of second solid tumors.

The RR of developing leukemia was considerably higher in patients receiving RT + CT (RR = 178.5; AR = 25.0) than in patients treated with RT alone (RR = 25.4; AR = 3.6). Two patients did develop leukemia after RT alone; one patient had thalassemia trait and developed leukemia 5 years after TN1 and the other patient developed erythroleukemia 6 years after MPA. The RR of leukemia after Hodgkin's disease did not change with age at treatment; however, the AR increased from 5.2 for patients <17 years old, to 6.9 for 17 to 39 years of age, to 30.1 per 10,000 person-years for patients 40 years or older (3.0% pppd).

The relative risk of NHL after Hodgkin's disease did not differ significantly by gender, age at treatment, or treatment given for Hodgkin's disease. The AR was highest for patients 40 or older at treatment9 compared to an AR of 11.8 for patients 17 to 39, and 11.5 for patients <17 years of age. All 10 patients with NHL had intermediate or high grade lymphomas; the working formulation (diffuse large cell lymphoma in 5 patients, immunoblastic lymphoma in 3 patients, diffuse undifferentiated lymphoma, non-Burkitt's type in 1 patient, and diffuse small cleaved cell lymphoma in 1 patient).

Specific risk factors were also noted for patients who developed solid tumors after Hodgkin's disease. The RR of breast cancer was 6.5 for all women in this series with an AR of 13.0 per 10,000 person-years (1.3% pppd). The risk for developing breast cancer after Hodgkin's disease was greatest in women who were under the age of 25 at treatment (Table 6). The AR was 24.1 per 10,000 person-years (2.4% pppd) for women <15 years of age and 13.9 per 10,000 person-years (1.4% pppd) for those 15 to 24 years of age at diagnosis. The RR of breast cancer after Hodgkin's disease in patients 25 years or older at diagnosis was not statistically different from the expected incidence. However, these patients still appear to have a small absolute excess risk of breast cancer. Smoking appeared to be a risk factor for lung cancer after Hodgkin's disease. All but two patients who developed lung cancer were smokers. Four of the patients who developed gastrointestinal tumors had adenocarcinomas of the stomach; all were 17 or under at the time of treatment. Further analysis determined that the splenic pedicle portion of the paraaortic field would have covered the central gastric region in these patients.

Survival following development of a second malignancy was poor in patients with leukemia (0 of 8 alive), gastrointestinal tumors (4 of 10 alive), lung cancer (2 of 8 alive), and sarcoma (1 of 6 alive). Survival from other malignancies such as NHL (6 of 10 alive), and breast cancer (11 of 13 alive) was more encouraging; however, we caution that longer follow-up time is needed to determine outcome in the
Table 7. Second Tumor Deaths in Patients Treated For HD

<table>
<thead>
<tr>
<th>Cause</th>
<th>RT Alone</th>
<th>RT-Relapse-CT</th>
<th>CMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>489</td>
<td>147</td>
<td>158</td>
</tr>
<tr>
<td>All second neoplasms (72)</td>
<td>18</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>ANLL (8)</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>NHL (10)</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Breast (13)</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal (10)</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lung (8)</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoma (6)</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Head and neck (4)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Melanoma (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Genitourinary/Gyn (3)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other (6)</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: ANLL, acute nonlymphoblastic leukemia.

breast cancer patients (see Table 7). Figure 2A shows the rate of survival from the development of a second malignancy for all patients, and Fig 2B shows survival from development of a second tumor by age at diagnosis. Survival was especially poor in patients developing a second malignancy who were ≥40 at the time of Hodgkin’s disease diagnosis. This is reflected in an AR of mortality from second malignancy of 84.8 for patients ≥age 40 at Hodgkin’s disease diagnosis (8.5% pppd) compared to an AR of 37 for patients age 17 to 39 and 26.3 for patients age ≤16.

DISCUSSION

It has been known for nearly 2 decades that patients have an increased risk of developing a second malignancy after initial treatment for Hodgkin’s disease. Second malignancies after Hodgkin’s disease have been grouped into 3 categories: leukemia, NHL, and solid tumors. Early studies reported a larger number of cases of leukemia, but with time, solid tumors now make up more than 50% of reported malignancies after Hodgkin’s disease. Solid tumors constitute 74% of all second malignancies in the current study. This is due, in part, to the decreasing use of the MOPP chemotherapy regimen and a corresponding reduction in acute leukemia incidence, and, in part, because of the longer follow-up of surviving patients. The median time to the development of solid tumors is greater than for NHL or acute leukemia. Nearly all of the excess leukemia risk occurs within the first 10 years after Hodgkin’s disease. Many of the solid tumors occur after this time and in our study the median time to development of a second solid tumor was not reached by 10 years. At present, there are only a few studies that report 10 to 15 year solid tumor data. Now it appears that at least 20-year follow-up is needed to assess the true incidence of solid tumors as the RR continues to be significantly increased 15 years and longer after Hodgkin’s disease.

Reports of second tumor risk often use methods that do not predict the “true” excess risk of malignancy after Hodgkin’s disease. Very high relative risk figures may appear alarming, but can be associated with a low or modest absolute excess risk if the expected risk is low. An example is the relatively high RR and low AR for development of acute leukemia in the current study. Actuarial risk curves of second malignancy incidence after Hodgkin’s disease often censor out deaths from other causes and do not show excess risk, so that with enough time the curves should approach 100% incidence. In contrast, reporting data as absolute excess risk provides an estimate of true risk. The numbers can be translated into percent risk per person per decade as in the current study, although we caution that this may be somewhat misleading, especially when the risk is not constant over the entire time interval.

In the current study, we report a RR of 5.6 and an AR of 69.5 per 10,000 person-years for second malignancies after Hodgkin’s disease. Similar results have been seen in other...
studies: Tucker et al report a RR of 5.2 and an AR of 72.9; Henry-Amar reports an AR of 60 for women and an AR of 73 for men; Van Leeuwen et al report a RR of 3.5 and an AR of 62.5. When RR and AR are calculated separately for each tumor subgroup, we report a lower AR (9.2) for leukemia compared to the other studies (ν 29, 11 to 16, and 18, respectively), a similar AR (11.1) for non-Hodgkin’s lymphoma (ν 9.2, 7 to 14, and 13.1, respectively), and a slightly higher AR (49) for solid tumors (ν 31.4, 35 to 38, and 32.4, respectively). Differences in the AR of solid tumors after Hodgkin’s disease are the most subject to change because of the long time interval to presentation of these tumors. Assuming that the RR of solid tumors continues to be increased after 15 years as strongly suggested in the current study (RR = 7.4; AR = 193.3), studies with a longer median follow-up will report a larger AR for solid tumors, but probably not for acute leukemia or NHL, than studies with a shorter median follow-up. Thus, variations in the minimum and median follow-up times of patients and the age of patients at the time of treatment could account for the differences between studies.

In all long-term studies, the largest contribution to the absolute excess risk of second malignancies after Hodgkin’s disease is from solid tumors. Several studies have looked at the RR of solid tumors by 5-year intervals after Hodgkin’s disease. In two studies 15-year data are available. The RR of solid tumors reported by 5-year interval after Hodgkin’s disease by Van Leeuwen et al is 1.9, 2.6, 2.8, and 4.2 for 1 to 4 years, 5 to 9 years, 10 to 14 years, and ≥15 years, respectively. The relative risk of solid tumors in the data from Henry-Amar and associates is 1.18, 1.86, 2.33, and 1.73 for males, and 0.71, 1.99, 2.33, and 3.60 for females for 1 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 19 years after Hodgkin’s disease, respectively. The male/female differences in the Henry-Amar study reflect the long time to development of breast cancer compared to other types of solid tumors. In the current study, the relative risk for solid tumors is 3.68, 2.84, 5.85, and 7.4, respectively, by 5-year time interval. All these studies suggest that the RR is either level or slightly increased for the period more than 10 years after Hodgkin’s disease. More importantly, these level or slightly increased RR rates by 5-year interval have a large impact on the AR. In our study, the AR for each 5-year interval is 23.7, 22.7, 87.2, and 193.3, respectively. This is equivalent to an absolute excess solid tumor risk per person for each successive 5 years of follow-up after treatment of 1.2%, 1.1%, 4.4%, and 9.7%, respectively. The decrease in RR in males after 15 years in both the study by Henry-Amar and the International Data Base on Hodgkin’s disease gives some encouragement for the eventual return to baseline for solid tumor risk after Hodgkin’s disease, but 5 to 10 years of additional follow-up will be needed to further define this.

Risk factors for the development of a second malignancy after Hodgkin’s disease have been carefully defined in a number of studies. The risk of leukemia has been associated with the use of alkylating-agent chemotherapy and especially with the use of MOPP as compared to other regimens. One study reported the risk of leukemia to be increased when more than 6 cycles of MOPP were given compared to 6 cycles or less, and indicated that low platelet counts for long intervals after MOPP (suggesting marrow damage) were also associated with an increased leukemia risk. The increasing use of ABVD in upfront chemotherapy regimens for Hodgkin’s disease has reduced the risk of leukemia. None of the patients who received ABVD without MOPP in our study have developed a secondary leukemia although the numbers are small and follow-up time short. Although still controversial, some studies have implicated splenectomy as a modest risk factor in the development of leukemia; others have not supported this finding. Subtle alterations in the immune system after splenectomy, perhaps affecting host surveillance, have been suggested as a possible cause. Age older than 40 at diagnosis has also been cited as a risk factor for acute leukemia. Age older than 40 and MOPP chemotherapy were also risk factors for acute leukemia in the current study. Leukemia after RT alone is rare but a small increased risk has been reported at least in one study and was seen in our study. In most studies the use of RT in combination with CT does not increase the risk over CT alone. Similarly, the extent of the RT fields treated in combination with CT does not confer an extra risk. Survival following secondary leukemia has been poor, although several reports suggest a positive therapeutic role for high-dose chemotherapy and autologous marrow transplantation.

The risk of NHL after Hodgkin’s disease has been associated with older age at treatment, male sex, and combined modality treatment. In our study, when analyzing data by absolute excess risk, males had a 3.1-fold excess NHL risk compared to females, patients over 40 years of age had a greater than threefold increased risk over younger patients, and patients who received CMT had a 1.5-fold increased risk over patients treated with RT alone. Although some studies have reported poor outcomes following treatment for secondary NHL, our data suggest that at least half of these patients may be curable with aggressive multiantigen chemotherapy.

Early studies identified an excess of lung cancers after treatment for Hodgkin’s disease. With longer follow-up of large numbers of patients, nearly all organ systems are now recognized as being at increased risk for development of solid cancers after Hodgkin’s disease. Three major risk factors, extent of initial treatment, female sex, and age at treatment, have all been associated with an increased risk of solid tumors after Hodgkin’s disease. Treatment with RT alone is a significant risk factor for solid tumors with a higher RR seen with extensive (MPA or TNI) than local (mantle or involved field) irradiation. In addition, as seen in the current study, some authors have reported a greater RR with the use of chemotherapy and RT as opposed to RT alone, whereas others have not identified these differences. Patients with larger bulk disease or more advanced stage were likely to receive more intensive treatment, usually combined modality therapy. This makes it difficult to know how much of the excess tumor risk is disease versus treatment related. The increased risk in solid tumors after Hodgkin’s disease in women compared to men is largely, but not completely, because of the risk of breast cancer in young patients treated with mantle irradiation. As identified by us and others, this risk is largely seen in women who were under the age of 25 at the time of treat-
Age 40 or older at treatment for Hodgkin's disease appears to be associated with an increased risk of solid second tumors in some studies. Some have reported that the RR increases with age at treatment, whereas others report an increased overall incidence with age. We have, in contrast, found that the RR and AR for solid tumors decreased with the age in our patient population. Curiously, we found that most of the malignancies in older patients were NHL or acute leukemia as opposed to solid tumors.

Few studies have reported survival outcomes of patients who developed second solid neoplasms after Hodgkin's disease. The poor survival rate of patients over 40 at treatment in the current study is in part because of the higher incidence of acute leukemia and NHL in these patients.

With the tremendous success in management of Hodgkin's disease over the last 20 years, we are now gaining a greater appreciation for the long-term risks of treatment. These risks include the increased incidence of other neoplasms. Three separate approaches are being used to reduce the incidence and impact of second tumors: reducing the extent of treatment, encouraging prevention, and reducing mortality through early detection. Data from the current study and others suggest that smaller radiation fields and/or less use of chemotherapy may result in a lower risk of second solid cancers. A number of trials have been completed or are underway to define the minimal treatment needed to cure Hodgkin's disease. Some of these advocate continuation of surgical staging and limited RT for early stage Hodgkin's disease. Others propose less cycles of chemotherapy or alternative cytotoxic agents that may be less toxic. The development of nonalkylating regimens for Hodgkin's disease has already resulted in less risk of leukemia. More precise radiographic staging has allowed identification of patients with large mediastinal adenopathy who need initial chemotherapy; this allows smaller radiation fields to be used. Improvements in technology may permit a lower radiation dose to tissues at risk (ie, reduction of the volume of breast tissue treated in the mantle field in young women). In addition, in our study patients treated with RT who then received chemotherapy for relapse had a lower risk of second malignant neoplasms than patients initially treated with CMT suggesting that single modality treatment (except for patients with large mediastinal disease) may provide a strategy to reduce the risk of second tumors. Although the goal of all these strategies is to reduce second tumor risk when possible, this must be done without significantly increasing the risk of relapse of Hodgkin's disease. An increased risk of relapse results in both more extensive treatment and an increased risk of death from Hodgkin's disease.

Advances in prevention and early detection of second cancers should come with increased understanding of the molecular biological mechanisms of increased tumor susceptibility. At present preventative techniques are limited. We strongly encourage patients to avoid smoking and to limit excessive sun exposure to decrease the risk of lung cancer and melanoma, respectively. Although additional data is needed, it may be possible to reduce mortality from second tumors through early detection. We are recommending screening mammography in young women starting 8 to 10 years after treatment for Hodgkin's disease, annual gynecological exams for all women after Hodgkin's disease, and routine chest radiography at least once a year after 5 years of follow-up. Most patients are cured of Hodgkin's disease if disease-free for more than 5 years after treatment. Follow-up after that interval should concentrate on prevention and early detection of cardiac disease and second tumors.

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Second malignancies after treatment for laparotomy staged IA-III B Hodgkin’s disease: long-term analysis of risk factors and outcome

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