Second Tumors Revisited

Hank George, FALU
Vice-President/Technical Services
Home Office Reference Laboratory (HORL)

This paper is titled "Second Tumors Revisited" because it updates an earlier paper, "Second Tumors in Treated Cancer Patients: Implications for Life Underwriting," which appeared in the July-September, 1983 issue of The Journal of Insurance Medicine (Volume 14, Number 3). In retrospect, it may have been more appropriate to title this paper "Second Tumors: Here We Go Again!" considering that this author's FALU Project Paper also examined treatment-induced second tumors in potentially-insurable cancer survivors. That thesis, "After the Cure: Underwriting the Late Effects of Cancer Treatment," has been reproduced for distribution by the Life Underwriting Education Committee and may be obtained from the Committee's Information Research Coordinator Thomas W. Roberts, FALU, at the Life Insurance Company of Virginia.

Most of the major improvements in cancer survival rates in recent years are the result of one of two developments: earlier detection (melanoma) or effective radiotherapy and chemotherapy (Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic leukemia of childhood, etc.) Underwriters and medical directors are seeing increasing numbers of successfully-treated, disease-free and ostensibly-cured cancer patients as insurance applicants. Understandably, most of the emphasis in the appraisal of these risks is directed at securing the essential details of diagnosis and treatment. Then, if the tumor in question is not prescribed in the manual and if a sufficient disease-free interval has elapsed since treatment, coverage is offered on some basis. For life insurance risks, that coverage is apt to require a temporary flat extra premium, typically expiring in one to five years, whereupon the insured is "standard."

With the dramatic improvements in the disease-free survival rates for certain malignancies have come reports of second tumors in significant percentages of long-term survivors. The number of reports is growing and the etiologic link between these second tumors and certain forms of anti-cancer therapy is beyond dispute. The question which remains to be answered is whether the risk of developing a second tumor (or some other potentially-lethal late complication of therapy) is of sufficient magnitude to justify modifying our conventional approach to cancer risks. This paper will review the recent literature on therapy-related second tumors and suggest possible strategies for handling these cases.

In a summary report on a wide range of articles on chemotherapy-induced malignancies in the first issue (March, 1985) of Oncology Data Base Focus, the authors' consensus conclusion reads:

Because of the risk of developing a secondary malignancy — usually fatal — long term follow-up is needed for patients who have received aggressive chemotherapy or long term maintenance doses of alkylating agents.

The same note of caution is echoed by Hancock and his co-workers at Stanford. In their 1988 paper examining deaths among Hodgkin's disease survivors, they observe that "second neoplasms remain the most frequent cause of intercurrent death..."

Second tumors have been reported in survivors of many types of cancer. From an underwriting viewpoint, the most important one is probably Hodgkin's disease. Because of its radiosensitivity and its vulnerability to cytotoxic chemotherapy, the once-dismal outlook in Hodgkin's disease has changed dramatically in the last quarter century. Long-term, disease-free survival rates as high as 90-95% are commonly reported in Stage I disease. Moreover, even applicants with a history of extensive (Stage IV) Hodgkin's disease will tempt underwriters on the basis of 50% + long-term, disease-free survival rates in many patient series.

The critical role of multidrug chemotherapy protocols containing alkylating agents in the treatment of Hodgkin's disease, coupled with the large percentages of long-term survivors, explains Hodgkin's disease is the most commonly-encountered primary tumor in reports of therapy-related second tumors in the literature. Other frequently-insurable malignancies associated with treatment-induced second neoplasms include non-Hodgkin's lymphoma, breast carcinoma, testicular carcinoma, ovarian carcinoma, small cell lung carcinoma, metastatic gastrointestinal cancer and CNS glioma who enjoy long survival. Finally, there are reports of malignancies in patients with non-neoplastic disorders treated with alkylating agents.

The question of whether these second tumors are truly sporadic, an intrinsic part of the natural history of the first malignancy or overtly induced by therapy appears largely resolved. Studies have shown little or no increased risk of second tumors in patients with Hodgkin's disease (etc.) who have been spared alkylating agent therapy. In the words of one author who reviewed second tumors in Hodgkin's survivors, "the near absence of leukemias... without chemotherapy must imply that leukemia incidence in the absence of chemotherapy is either not increased at all or
increased very little over 'spontaneous' rates.’” Consistent cytogenetic findings in patients with acute nonlymphocytic leukemia and myelodysplastic syndrome following anticancer chemotherapy also strongly support the premise that these second neoplasms are indeed a delayed complication of therapy.º ²

Before dissecting the characteristics of therapy-induced second tumors, it is helpful to get an overview by synopsing papers detailing the findings in reviews of large patient series at major treatment centers. This overview will be confined to reports published since this author's earlier (1983) review paper.

Stanford (1988)
Tucker and co-workers reviewed 1507 cases of Hodgkin's disease treated from 1968 through 1985. Eighty-three (83) second tumors were identified, with the ten-year actuarial risk of developing a second tumor calculated to be 9.9%. The most common second malignancy was acute nonlymphocytic leukemia (t-ANLL), accounting for 27 of the 83 new cancers. With an expected incidence of 0.2 cases of ANLL in this population, the observed incidence was 115 times expected (O/E). The second most common new tumor was lung cancer, with 14 cases observed versus 1.8 expected.³

National Tumor Institute, Milan (1986)
Valagussa and colleagues studied 1329 case histories of Hodgkin's disease treated between 1965 and 1982. With a mean follow-up of 9.5 years, there were 68 second tumors including 19 cases of t-ANLL and six cases of non-Hodgkin's lymphoma (NHL). Among subsets of patients receiving chemotherapy, those salvaged with MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) following post-radiotherapy relapse had the highest t-ANLL risk (15.5% + 7.4% at 12 years). Valagussa and co-workers also reported a mean latency period (from start of chemotherapy to diagnosis of t-ANLL) of 55 months (range 23-127 months). Finally, they observed a statistically-significant difference in the actuarial risk of t-ANLL based on patient age at commencement of treatment. Patients age 40 and under had a 2.7% risk at 12 years, whereas patients over 40 had a 7.0% risk of therapy-provoked leukemia.⁴

Finsen Institute, Denmark (1987)
Pedersen-Bjergaard and his colleagues reported seven bladder carcinomas in a series of 471 patients treated with cyclophosphamide for non-Hodgkin's lymphoma. The cumulative risk was 3.5% ± 1.8% at 8 years and 10.7% ± 4.9% after 12 years, from onset of chemotherapy. The latency period ranged from 77 to 141 months.

Although hemorrhagic cystitis, a well-recognized complication of cyclophosphamide treatment, developed in 33 patients, this was not felt to be directly related to the risk of carcinoma.⁵

University of Pittsburgh (1987)
Baker and co-workers detailed a long-term retrospective study of 119 rheumatoid arthritis treated with cyclophosphamide, matched against 119 RA controls who did not receive the alkylating agent. After 11 years, there were 37 second tumors in 29 patients in the study group versus 16 new neoplasms in 16 controls. Predictably, the second cancers in the study group included six bladder carcinomas and five hematologic malignancies.³

Characteristics of Second Tumors
A number of factors associated with the risk of developing therapy-related second tumors can be identified and described. In the following paragraphs, these factors will be reviewed individually.

Types of Chemotherapy
A wide range of chemotherapeutic agents with demonstrated tumorcidal activity fill the armamentarium of the clinical oncologist. Most of these belong to one of several classes of compounds, distinguished by their specific anti-tumor effects. These classes include antimetabolites, alkylating agents, anti-neoplastic antibiotics, nitrosoureas, vinca alkaloids and a growing number of additional drugs. Of these classes, two have been convincingly implicated in the induction of second tumors: alkylating agents and nitrosoureas.
In the word of Amery De Gramont and his co-workers at St. Anthony's Hospital in Paris:15

therapy-related acute nonlymphocytic leukemia (t-ANLL) is a major hazard in patients treated with cytotoxic regimens, and especially those using alkylating agents for first malignancies.

Jens Pedersen-Bjergaard, reporting on the experience with second tumors at Denmark's Finsen Institute, concurs, observing that "our results accord with the many reports that t-ANLL is a serious, rather frequent complication of chemotherapy with alkylating agents."28

Specific alkylating agents implicated in t-ANLL leukemogenesis include cyclophosphamide,25 melphalan,14 17 chlorambucil24 15 17 and busulfan.37 The multi-drug MOPP regimen, used extensively in the management of Hodgkin's disease, contains an alkylating agent, nitrogen mustard, and a similar compound, procarbazine, and has been repeatedly identified with t-ANLL.11 20 38 43 46 In addition, cyclophosphamide is a well-documented bladder cancer carcinogen.3 36

The nitrosoureas, like the alkylating agents, are cytotoxic. Two nitrosourea compounds, CeeNU 33 38 and methyl-CeeNU 4 have been associated with t-ANLL induction.

Although van Imhoff et al reported a case of apparent treatment-provoked ANLL in a patient receiving the PVB (cisplatin, bleomycin, vinblastine) for disseminated testicular carcinoma,44 such citations are rare. Prevailing evidence strongly suggests that antimetabolites, anti-neoplastic antibiotics, vinca alkaloids and other anti-tumor agents exert little, if any, leukemogenic effect. This was demonstrated by Valagussa and co-workers who found no cases of t-ANLL in patients receiving ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) contrasting with a 10.2% actuarial risk of t-ANLL with MOPP.45 Indeed, Valagussa and others have urged that treatment protocols devoid of alkylating agents and nitrosoureas be utilized wherever possible in lieu of MOPP and other regimens with proven leukemogenic components.

Relationship of Dose to Risk

Several authors have identified threshold doses of alkylating agents and nitrosoureas associated with subsequent tumor induction. In a paper comparing the leukemogenicity of melphalan to cyclophosphamide, Greene observes that 95% of t-ANLL cases in ovarian carcinoma patients receiving adjuvant melphalan arose after a 600 mg total dose. All leukemias following adjuvant cyclophosphamide developed after a 27,000 mg cumulative dose.17 Boise and his co-workers found a dose-response effect with adjuvant methyl-CCNU (Semustine). The average dose in patients who developed t-ANLL was 809 mg/m² versus 647 mg/m² in the whole patient population.6

Pedersen-Bjergaard reported a steep increase in t-ANLL ten years after alkylating agents based on drug dose. Low dose patients had a 6.4% leukemia incidence, compared to 11.3% in the intermediate dose and 37.5% in the high dose categories.38

Latency Period from Chemotherapy to Diagnosis of Second Tumors

Michels and her University of Minnesota co-workers reviewed 55 cases of therapy-induced hematologic neoplasia (39 t-MDS and 28 t-ANLL), finding an average latency period (measured from starting therapy to onset of the second disorder) of 55 months, with a range of 11 months to 192 months.44 Valagussa reported the identical mean latency (55 months) with a similar range (23-127 months) among Hodgkin's patients who developed t-ANLL at Milan's National Tumor Institute.35 In t-ANLL patients initially treated for small cell lung carcinoma, Johnson et al reported a 32-month mean latency, range 10-81 months.11

Greene's National Cancer Institute follow-up of ovarian carcinoma patients who received adjuvant alkylating agent therapy revealed 58% of t-ANLL cases developed within 12 months of chemotherapy cessation. By 24 months, 76% of leukemias were diagnosed and 88% were evident at 36 months. The longest interval from therapy discontinuance to t-ANLL onset was six years, with total latency, measured from the start of adjuvant therapy in this patient, being 11 years.17

Several authors report long latency periods. For example, DeGramont had three patients who developed t-ANLL at 110, 143 and 336 months, measured from first dose of chemotherapy.19 Kaldor and Day, commenting on data from the Connecticut Tumor Registry in a letter in the New England Journal of Medicine, observed that:

in a cancer registry-based follow-up of more than 28,000 survivors (including more than 21,000 person-years of follow-up 10 or more years after Hodgkin's disease), our group found that the risk of acute leukemia remained more than ten times higher than the background risk in the general population for at least 15 years, with 14 cases observed after 10 years.22

Blayney and co-workers reported a decreasing risk of t-ANLL after 11 years. They followed 192 patients for a median of 15.3 years and described a "window period" for t-ANLL 2-12 years after commencement of therapy.5 Tucker (Stanford) believes the risk of t-ANLL remains relatively constant for ten years from onset of therapy, with little risk thereafter.43

Age was also a significant factor when related to average latency in t-ANLL patients. DeGramont's patients who were under age 30 had an average latency of 77.7 months to t-ANLL onset, compared to 46.9 months in patients over age 50. Overall, seven cases of leukemia did not develop until ten years or longer from the start of chemotherapy.15
Patient Age and t-ANLL

Several authors document a steeply-increased risk of treatment-provoked myelodysplasia and acute leukemia in cancer patients who are diagnosed and treated by midlife or later. Finsen Institute data shows the 10-year t-ANLL risk following Hodgkin’s disease chemotherapy to be 5.6% inpatients under age 40, compared to 30.9% in those 40 or older.37 Valagussa reported the 12-year actuarial risk of t-ANLL at 2.7% for patients under age 40 and 7.0% at ages 40 or older.46

Glicksman et al calculated a life table estimate of the t-ANLL risk following Hodgkin’s disease therapy which varied dramatically by age:46

<table>
<thead>
<tr>
<th>Age at Diag.</th>
<th>t-ANLL Incidence After 46 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 40</td>
<td>2.9%</td>
</tr>
<tr>
<td>40-59</td>
<td>11.8%</td>
</tr>
<tr>
<td>60+</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

Coltman and Dixon (Southwest Oncology Group) assessed the seven-year post-treatment actuarial risk of t-ANLL following alkylating agent therapy for Hodgkin’s disease, broken down by age at Hodgkin’s diagnosis as follows:11

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>Risk of t-ANLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 20</td>
<td>2.4%</td>
</tr>
<tr>
<td>20-29</td>
<td>1.7%</td>
</tr>
<tr>
<td>30-39</td>
<td>4.8%</td>
</tr>
<tr>
<td>40 and over</td>
<td>20.7%</td>
</tr>
</tbody>
</table>

Hematological Parameters of t-ANLL and t-MDS

A variety of peripheral blood abnormalities have been consistently reported in newly-diagnosed treatment-induced myelodysplasia (preleukemia) and acute nonlymphocytic leukemia cases. While none are specific for therapy-related neoplasia, they may provide clues to medical directors and underwriters reviewing interim APS reports on previously-treated cancer patients.

DeGramont found thrombocytopenia (platelet count under 120,000/m$^3$), anemia (hemoglobin under 12 in males; 10 in females), leukopenia (WBC less than 3100/m$^3$) and macrocytosis (MCV greater than 100fl) to be the most consistent preleukemic phase abnormalities. Pancytopenia was present in 24% and both refractory and sideroblastic anemias were frequently seen.13

Michels reported similar findings. Mean hemoglobin in t-MDS was 8.9 gm/dl, with an average white count of 3000/m$^3$ and platelet count of 58,000/m$^3$. Other common findings included marked anisopoikilocytosis, macrocytosis, immature circulating neutrophils, atypical platelets and basophilia.14

MCV may be a useful marker for increased risk of secondary leukemia in Hodgkin’s disease. DeGramont compared 32 patients who developed t-ANLL following cytotoxic therapy to 64 matched controls, focusing on changes in the MCV index:

DeGramont found that preleukemic macrocytosis preceded the onset of overt t-MDS/t-ANLL and did not regress. He concluded that a MCV maximum increase from diagnosis to therapy completion which is 24fl or greater “appears to be the value which is most closely related to the risk of t-ANLL…”12

Outcome of t-ANLL

The prognosis in t-ANLL/t-MDS is dismal. With a few exceptions, all cancer survivors who contract therapy-induced leukemia succumb to their disease in 12 months or less.13 17 21

The preleukemic (myelodysplastic) phase has lasted as long as 55 months.13 Michels and her co-workers distinguish three stages in this process: panmyelosis with peripheral blood changes affecting white cells, red cells and platelets, followed by a frank myelodysplastic syndrome and, eventually, overt leukemia. Although some of their patients responded briefly to chemotherapy (ten complete remissions and nine partial remissions among 32 treated patients), all but one died in 1-31 months. The lone t-ANLL survivor was in complete remission for 38 + months at the time they published. In addition, three t-MDS patients had not yet developed acute leukemia.24

Kantarjian and colleagues (M.D. Anderson Hospital) report favorable cytogenetic features in a small subset of t-ANLL patients. Seven of eight patients with these characteristics achieved complete remission following anti-leukemic treatment. Because of the brief therapy response and relentless course of t-ANLL in all other series, the possibility that these cases involved etiologic factors other than chemotherapy was entertained by the authors.24

Actuarial Risk of t-ANLL

Most recent papers examining treatment-induced leukemia have included data on the actuarial risk of developing this second tumor following commencement of cytotoxic therapies. The following figures are representative:

<table>
<thead>
<tr>
<th>Actuarial Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Yrs.</td>
</tr>
<tr>
<td>Henry-Amar (1987)</td>
</tr>
<tr>
<td>Pedersen-Bjergaard (1987)</td>
</tr>
<tr>
<td>Blayney (1987)</td>
</tr>
<tr>
<td>Koletsky (1986)</td>
</tr>
<tr>
<td>Greene (1986)</td>
</tr>
</tbody>
</table>
Chak and her co-workers reported a 25% actuarial risk of t-ANLL at 3.1 years after starting intensive chemotherapy / radiotherapy for small cell lung carcinoma. In another paper where small cell lung cancer patients received large doses of alkylating agents and nitrosoureas, the risk of t-ANLL was calculated to be 14% after 43 months.

Van Rijsijk noted differences in ten-year t-ANLL actuarial risk in Hodgkin's disease based on the type of treatment given. Patients receiving both radiation and chemotherapy as initial Rx had a 3.0% leukemia incidence, whereas those who had initial radiotherapy followed by salvage chemotherapy had a 4.7% t-ANLL risk. The highest risk, 5.6%, was observed in patients who received chemotherapy only.

Papa et al report conflicting data. Chemotherapy alone was associated with the lowest risk (2.2%) compared to combination chemotherapy/radiotherapy for remission induction (6.2%) and radiation followed by salvage chemotherapy (4.8%).

When Hodgkin's disease patients received only radiotherapy, no excess risk of t-ANLL has been reported in most, but not all series. Although the leukemia-inducing capability of radiation is undisputed, several experts make a distinction between high-dose/cell-killing radiation given to these patients versus low-dose/cell-transforming therapeutic radiation exposure in other treatment settings where an increased risk of radiation-induced hematologic neoplasms has been reported (polycythemia vera, non-Hodgkin's lymphoma).

Treatment-Related Lung Carcinoma

Several reports in recent years have described an excess of primary lung carcinomas in previously-treated cancer patients who received chemotherapy and/or radiotherapy. Abernathy and her colleagues at Tulane described six lung malignancies in 288 lymphoma patients. All of these patients received chemotherapy, two had chest-area radiation and all six were smokers. A report from Maryland showed a three-fold increase over the expected lung cancer incidence in treated Hodgkin's disease and non-Hodgkin's lymphoma patients. Lubshitz (M.D. Anderson Hospital) acknowledged the same risk increase, with 23 lung cancers in 2708 lymphoma patients.

Tucker et al documented 14 lung carcinomas in 1507 Hodgkin's disease patients, an almost eight-fold increase over the expected incidence of bronchogenic carcinoma. All 14 were smokers and had been treated with radiation as well as chemotherapy. Valagussa reported ten lung cancers, all in previously-irradiated fields, with a median patient age of 48 (range 35-62). Only one was a non-smoker. Finally, List et al described four fatal lung neoplasms in 260 Hodgkin's disease patients at Vanderbilt. The risk ratio was 5.6 times expected.

A review of 35 lung carcinoma cases diagnosed in Hodgkin's disease survivors revealed a mean latency period, between diagnoses, of seven years, with a range of 18 months to 24 years. Nearly all patients had received supradiaphragmatic irradiation. Two patients developed a lung neoplasm after chemotherapy only. Tobacco use was noted in 53% and the predominant lung cancer histology was small cell carcinoma (42%), followed by adenocarcinoma (31%) and large cell carcinoma (14%). In contrast, the most common lung tumor type in cigarette smokers not at risk for therapy-induced neoplasia is squamous cell (epidermoid) carcinoma.

Non-Hodgkin's Lymphoma (t-NHL)

Several reports cited in this author's earlier paper (Krikorian-1979, Armitage-1983) identified an excess of non-Hodgkin's lymphoma (NHL) in patients treated with cytotoxic therapy for Hodgkin's disease. That risk appeared to be lower (0.9 - 2.1%) than the risk of t-ANLL. However, given the very low incidence of NHL overall, these cases did not appear explainable by coincidence alone. In more recent papers, Tucker, Valagussa and Koletsky (Yale) have all reported an increased risk of t-NHL. Tucker found an 18-fold increase over expected NHL incidence at ten years. At Yale, the actuarial risk of t-NHL was 3.5% at ten years. Valagussa observed the risk to be lower, calculating a 0.4% 12-year t-NHL risk in Hodgkin's disease patients receiving radiation plus MOPP chemotherapy. Interestingly, the t-NHL incidence was nearly five times higher (1.9%) in patients treated solely with radiation.

UNDERWRITING CONSIDERATIONS

In a highly instructive paper given at the 1986 Canadian Life Insurance Medical Officers' Association (CLIMOA) meeting in Winnipeg, Nathan L. Kobrinsky, M.D., Associate Professor of Pediatric Hematology-Oncology at the University of Manitoba School of Medicine, cautioned attendees against too-generous underwriting of applicants with a history of Hodgkin's disease treated with MOPP and other leukemogenic chemotherapy protocols. The risk of developing second malignant neoplasms is very high in patients who have received alkylating agents as part of their therapy.

Based on the reports detailed in this paper and additional uncited reports in the recent literature, one is inclined to extend that warning to all applicants with a prior history of cancer, as well as non-neoplastic conditions (e.g. rheumatoid arthritis, lupus erythematosus), treated with alkylating agents, procarbazine and/or the nitrosoureas. This would apply to single-agent adjuvant therapy in (potentially-insurable) stage I carcinoma as well as multidrug protocols like MOPP which include one or more leukemogenic drugs.

Finally, the risk of second tumor induction may be highest in those patients retreated with a second course of chemotherapy or given salvage chemotherapy following initial radiotherapy and subsequent relapse.
From an underwriting point of view, the first step in minimizing the risk of extra deaths from therapy-induced malignancy is to insist on a minimal asymptomatic interval following completion of chemotherapy, before insurance is offered on any basis. Then, it may be appropriate to augment traditional temporary flat extras (assessed to cover the risk of primary tumor relapse/recurrence) with table ratings sufficient to cover the added risk of second tumors (and, possibly, other therapy-related, life-threatening complications).

Intrinsic to careful cancer underwriting is the unrelenting pursuit of APS records, including full details of the diagnosis and treatment plus all interim history. The latter is particularly important where the spectre of t-ANLL is concerned. Mild/moderate cytopenias and other peripheral blood abnormalities, some of which might be forgiven in other contexts, have been shown to be associated with myelodysplasia and subsequent t-ANLL. These findings are most likely to be seen on CBCs detailed on interim care APS reports. The same is true for symptoms (easy bruisability) and physical findings (splenomegaly) which may herald the onset of therapy-related leukemia.

Probably the most productive medical test worth considering in higher risk cases is a current complete blood count. Because the CBC is both inexpensive and readily accessible, it could easily be ordered in potentially-insurable cases of Hodgkin's disease, breast cancer, ovarian cancer and other tumors (and non-tumor conditions) wherever the admitted history includes the CBC is both inexpensive and readily accessible, it could be ordered in potentially-insurable cases of Hodgkin's disease, breast cancer, ovarian cancer and other tumors (and non-tumor conditions) wherever the admitted history includes recent abnormal cytology, laboratory values (e.g. anemia) or an acute care admission. The following observation by DeGramont supports this approach:

> Bone marrow and cytogenetic studies to formally diagnose t-MDS or t-ANLL are needed whenever any peripheral blood abnormality in cancer patients treated with cytotoxic therapy appears.

To maximize the pay-off from electively-ordered CBCs for underwriting purposes, all peripheral blood cell lines should be studied. This would include a white cell differential, red cell indices, a smear for morphological abnormalities and a platelet count.

Because of the well-documented association between cyclophosphamide and bladder tumors, a current microscopic urinalysis is a good investment wherever this alkylating agent was prescribed. This may include cases of rheumatoid arthritis and other insurable non-neoplastic disorders. Any unexplained hematuria would be of concern in these cases.

A sound underwriting approach to the lung cancer risk associated with cytotoxic therapy is more difficult to define. It would appear that smokers who have had chest-area irradiation (with or without chemotherapy) for Hodgkin's disease and non-Hodgkin's lymphoma would be at greatest risk, possibly justifying additional underwriting (chest x-ray) or an increased debit beyond conventional smoker rates.

Although the relationship of anti-tumor radiotherapy to an increased risk of atherosclerotic-like intimal proliferations is not discussed in this paper, the finding of suspicious ECG changes in younger individuals who received, for example, mantle irradiation for Hodgkin's disease should be a red flag in underwriting. These ECG changes may be harbingers of lesions in the coronary arteries and/or radiation-accelerated fibrosis of the conduction system.

Finally, a note of caution in cases where dysplastic nevi, acknowledged precursors to malignant melanomas, are reported following Hodgkin's disease. A recent paper by Tucker and co-workers observed that melanomas diagnosed in Hodgkin's disease patients tend to be considerably more aggressive than melanomas in the general population. This may have implications of the evolution of melanoma in susceptible dysplastic nevi. Given the prevalence of the latter, this scenario should not be uncommon in the growing numbers of Hodgkin's disease patients who are being seen by medical directors and their underwriter colleagues.

### References


