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LETTER TO THE EDITOR

Second Primary Cancers After Thymoma

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Dear Sir,

Associations between thymomas, the most common tumor of the anterior mediastinum, and conditions such as myasthenia gravis, pure red cell aplasia and hypogammaglobulinemia are well documented.[1] Little analytic data exist, however, with regard to the risk of second primary cancers among these patients,[2] and no study to date quantifies risk among long-term survivors. Although the clinical significance of second cancers may supersede the immunologic associations,[3] most reports (reviewed by Pan *et al.*[4]) consist of case series from single institutions, are based on small numbers and include only estimates of crude prevalence. Engels *et al.*[2] recently made an important contribution to the literature by describing the risk of second cancers ($n = 66$) among 733 patients with thymoma reported to population-based cancer registries that comprise the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (1973–1998). We extend these observations with several additional years of follow-up in the SEER Program, and estimate the cumulative risk and absolute excess risk of second cancers; we also provide new information on second cancer risk according to time since thymoma diagnosis and the administration of adjuvant radiotherapy and include estimates of radiation dose to selected organs following typical treatments for thymoma.

We included all patients diagnosed with thymoma as a first primary cancer who survived 2 or more months and were reported to population-based cancer registries that participate in the SEER Program (1973–2000). Data routinely gathered by these registries include patient demographic information, tumor histology, and initial course of cancer therapy according to one of several broad designation. Patients were grouped into categories of surgery alone, any radiotherapy or other type(s) of treatment. Complete surgical resection is the cornerstone of treatment for thymomas, although radiotherapy (tumor dose range: 30–60 Gy) has been used to treat all stages of disease, given the tumor's radiosensitivity.[5] The SEER Program database was searched for all invasive second cancers and standard methods, described previously[6] were used to quantify relative and absolute risks. Patient follow-up ended December 31, 2000. Estimates of the cumulative probability of second cancer were derived using life-table methods that adjusted for competing causes of death.[7] Radiation doses to specific organs were estimated using methods described by Stovall *et al.*[8] Treatment simulation was based on standard anteroposterior fields,[9] with a total administered tumor dose of 50 gray (Gy).

We evaluated 815 patients with thymoma. The mean age at diagnosis was 54.7 years (range = 6–91 years). Second cancers occurred in 81 patients (Observed-to-expected [O/E] ratio = 1.54; 95% confidence interval [CI] = 1.22–1.91); absolute excess risk [AER] = 62 excess cancers per 10,000 patients per year), with similar risks in men (O/E = 1.50, O = 47) and women (O/E = 1.59, O = 34). The pattern of site-specific risks did not differ meaningfully from those observed in a previous report[2] based on a subset of the population. Twenty-three patients died due to their second cancer (median survival = 13.0 months; range = 1–134 months).

Risk for all second cancers was elevated in the intervals of 2 months–1 year, 1–4 years, 5–9 years or 10 or more years after thymoma (p-trend = 0.63) (Table I). Five cancers occurred among 15-year survivors (O/E = 1.25; 95% CI = 0.40–2.92). Significantly increased risks (O/E = 1.70) were restricted to patients whose initial course of therapy included radiotherapy, although patients who received surgery alone had a 37% excess. Among 568 patients given any radiation, second cancer risk (O/E = 1.75; O = 42) was similar for those who also underwent surgical resection ($n = 397$) compared to the risk (O/E = 1.54; O = 14) among 171 patients not treated with surgery. After radiotherapy for thymoma, the risk of solid tumors in the intervals 2 months–<1 year, 1–4 years, 5–9 years or 10 or more years was 1.14, 1.31, 1.74 and 1.50, respectively (p-trend = 0.52). Cancers among 10-year survivors treated initially with radiotherapy included lung (O = 3), esophagus (O = 1), colon (O = 2), uterine corpus (O = 1), and prostate (O = 1), and non-Hodgkin's lymphoma (O = 1); the risk for solid tumors at sites (lung and esophagus) likely to be in the radiotherapy field was 4.0 ($p < 0.05$), compared to 1.89 ($p > 0.05$) for the others. The cumulative risk of all second cancers was 9.8% (95% CI = 7.8–11.8%) and 12.8% (95% CI = 9.8–15.9%), respectively, 10 and 15 years after diagnosis of thymoma.

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TABLE I – SECOND PRIMARY CANCERS FOLLOWING THYMOMA BY INITIAL THERAPY AND TIME SINCE DIAGNOSIS[1]

	Time since diagnosis of thymoma											
	2 months–<1 year		1–4 years		5–9 years		10+ years		All intervals		95% CI	AER[3]
	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E		
Persons entering interval (*n*)	815		678		360		159		815			
Person-years within interval (*n*)	620		1,977		1,225		760		4,582			
Treatment group (No. with thymoma)[2]												
All patients ($n = 815$)	8	1.34	29	1.39	28	1.87[4]	16	1.46	81	1.54[4]	1.22–1.91	62[4]
Surgery only ($n = 167$)	2	1.42	7	1.39	7	1.67	5	1.04	21	1.36	0.84–2.08	49
Any radiotherapy ($n = 568$)	6	1.53	21	1.55	20	2.09[4]	9	1.51	56	1.70[4]	1.28–2.20	74[4]

[1]Patients were diagnosed with thymoma (ICD-10 8580/3)[10] as a first primary cancer from January 1, 1973 through December 31, 2000, reported to the Surveillance, Epidemiology, and End Results Program, and survived 2 or more months. Follow-up ended 12/31/2000. AER, absolute excess risk; CI, confidence interval; O, observed number of second cancers; O/E, observed-to-expected ratio of second cancers.– [2]Treatment group represents only the first course of therapy reported to the SEER Program. Data on subsequent therapy are not available. For patients managed with surgery only, 79% had localized or regional disease, and 21% had either distant disease or were unstaged. Comparable percentages among patients who received any radiotherapy were 70% and 30%, respectively. Among 80 patients whose treatment did not include surgery or radiotherapy, but included either chemotherapy or other/unspecified therapies, the risk of second cancers was 0.93 (95% CI 0.25–2.38; O = 4).–[3]Excess number of second cancers per 10,000 patients per year.–[4]$p < 0.05$.

Most reports of cancer after thymoma have consisted of descriptive case series based on relatively small numbers of patients (median = 18, range = 4–48) (reviewed by Pan *et al.*[4]), with several series[3,4,11] also including antecedent or synchronous tumors. Although risk estimates for cancers associated with thymoma were provided in one hospital-based survey,[4] only 9 of 15 extra thymic cancers occurred after thymoma; compared to 206 patients who underwent thymectomy for nonthymomatous conditions, thymoma patients ($n = 192$) experienced significantly increased risk 4-fold risks of extra thymic cancers overall (15 cases compared to 4 cases). The report by Engels *et al.*[2] presented risk estimates restricted to second cancers after thymoma, utilizing population-based cancer registries. We extend these observations, demonstrating that excess second cancers persist throughout all follow-up intervals after diagnosis of thymoma, even among long-term survivors. Although increased risks of second cancers 10 or more years after diagnosis of thymoma seemed restricted to patients whose initial management included radiotherapy, an overall trend of increasing risk with time, as is typically observed with radiation-related cancers,[12] was not evident. Additional surveillance will be required to assess whether the long-term risk of second cancers differs in patients managed with surgery alone compared to those given radiotherapy. Two hospital-based studies that addressed the role of radiation in the occurrence of second cancers after thymoma[3,4] did not find evidence for a convincing effect. Based on small numbers, Pan *et al.*[4] observed that only 2 of 9 thymoma patients with second cancers had received antecedent radiotherapy, whereas Welsh *et al.* [3] indicated that the crude prevalence of second cancers in 46 patients who received adjuvant therapy (35%) did not differ significantly from patients ($n = 90$) given surgery alone (25%).

Despite these observations, the carcinogenicity of ionizing radiation is well-established,[12] and long-term follow-up of large numbers of thymoma patients will be required to quantify risks. Standard adjuvant radiotherapy (50 Gy) of thymoma can result in substantial doses of radiation to several sites, including active bone marrow (10 Gy), esophagus (30 Gy), lung (34 Gy) and stomach (1.9 Gy) (O/E = 1.76; O = 42). Previous studies[12] have shown the radio-oncogenicity of these organs at comparable doses, and nonsignificant excesses of second cancers at many of these sites (O/E = 2.9, 3.8, 1.4, 2.8, respectively) were reported in a subset of our series.[2] The pattern of risks over time suggest the interplay of several factors. The early excess may reflect intrinsic influences associated with immunological features of thymoma and possibly some small surveillance bias, whereas the late excess may reflect the effects of radiotherapy.

Reports[13,14] of patients who underwent thymectomy for nonthymomatous conditions have not demonstrated excess second cancers. It has been suggested[3,4] that thymoma may be intrinsically associated with the occurrence of extra thymic malignancies. To our knowledge, however, genetic syndromes of multiple primary cancers (*e.g.*, Li-Fraumeni Syndrome) that include thymoma have not been identified, and the most common sites of second cancer occurrence in other series of thymoma patients have shown no consistent pattern.[4] Significantly increased risks of second cancers after thymoma in the general population seem restricted to non-Hodgkin's lymphoma and soft tissue tumors, as reviewed by Engels *et al.*[2] Looking in the reverse direction in the SEER Program database (1973–2000), the risk of thymoma as a second primary cancer is elevated (O/E = 1.33; 95% CI = 1.0–1.73; O = 56), but site-specific patterns of risks are also not convincing for any particular initial primary cancer. It is of some interest that among newborns treated with radiation for enlarged thymus glands many years ago, no occurrence of thymoma has been reported, although thyroid cancer[15] and breast cancer[16] have been linked to the radiotherapy given.

Our results should be interpreted within the context of the strengths and weaknesses of data on multiple primary tumors reported to cancer registries. The SEER Program provides a large number of subjects and population-based data, which minimize the bias due to selection or referral patterns. The large sample size also permits examination of the latency patterns of risks. Because underreporting of second cancers may occur among long-term survivors migrating from areas included in the SEER Program, our estimates of increased risk may be conservative. Because registry data lack detailed, comprehensive information on cancer treatment, any resultant misclassification is likely to minimize differences in the risks that are observed between treatment groups.

Nevertheless, our data provide a reasonable estimate of the overall long-term risk of second cancers among patients with thymoma. Excess second tumors were evident in all time intervals after diagnosis and persisted among long-term survivors, suggesting the need for lifelong medical surveillance. Our cumulative risk estimates suggest that 15 years after thymoma diagnosis, extra thymic malignancies will have developed in about 1 in 8 patients. Further epidemiologic and laboratory investigations are needed to clarify the possible carcinogenic risks associated with therapies for thymoma and shared susceptibility mechanisms, including immunologic and genetic factors. Meanwhile, in proposing recommendations for the management and follow-up of patients with thymoma, it is important to recognize their long-term predisposition to second cancers.

Yours sincerely,

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