The risk of second primary lung cancer: an unsolved dilemma

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Lung cancer is the leading cause of cancer-related deaths in the United States (1) and is a worldwide health problem. For patients who have been successfully treated for an initial primary lung cancer (IPLC), there remains a risk for the development of a second primary lung cancer (SPLC). The risk has been estimated at approximately 1–2% per patient per year (2). The results of the National Lung Cancer Screening Trial helped establish a role for lung cancer screening to detect the development of an initial lung cancer (3). The current guidelines are restricted by age and smoking status. The patients who were screened did not have a history of a prior lung cancer so the recommendations do not apply to patients with a history of treated lung cancer. There are suggestions per guidelines regarding monitoring for recurrence of the primary lung cancer but a surveillance strategy to detect the development of a SPLC has not been established (4). Considering that there is a reasonable risk for the development of a SPLC after treatment for an IPLC, it is important to establish parameters that identify which patients have the highest risk.

A paper entitled, "Risk stratification for second primary lung cancer" has recently been published by Han *et al.* in *J Clin Oncol* (5). Participants were identified from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. Over 20,000 patients were diagnosed with an IPLC between 1988 and 2003. The most commonly utilized definition of a SPLC fulfills any one of three criteria: (I) histology is different from the IPLC; (II) the new tumor is diagnosed 2 years after the initial diagnosis; (III) the new tumor is diagnosed in a different lobe or segment without positive intervening lymph nodes or metastases (6). The investigators utilized a stricter definition that required the SPLC to be a distinct pulmonary malignancy that was diagnosed ≥5 years after the primary tumor. They identified 1,018 patients with a SPLC. They reviewed the patient characteristics that were available in the data base and found that patient age at the time of IPLC diagnosis was the most important factor in predicting SPLC risk. Patients younger than 45 years or older than 75 years had a significantly reduced risk as compared to the reference range of 70–75 years. Patients with adenocarcinoma histology had a higher risk for the development of a SPLC only when compared to an "other" histology group which included carcinoids and bronchioloalveolar carcinoma which likely determined this reduced risk. Disease extent was also deemed to be important; however, patients who had more extensive disease at diagnosis of their IPLC probably did not survive long enough after the 5-year eligibility requirement for this study to get a SPLC thus reducing the risk. It would appear that on this initial analysis age at diagnosis of the IPLC remains to be the most important factor driving the development of the SPLC, however several potentially impactful risk factors, such as smoking, were not available in this data set.

The investigators used a risk prediction model to estimate an individual's risk of developing a SPLC (7), within 10 years after surviving 5 years from their initial primary. The risk varied substantially when stratified by age, histology and extent of disease. The age group of 60 to 64 years had the highest median risk at 10.97%. Stratification by deciles of estimated risk showed a

distinct separation between patients at lowest and those at highest risk in the 10th decile. Evaluating both ends of the spectrum, this analysis certainly helps one decide who absolutely should or should not be surveilled for the development of a SPLC but does not give us a definitive answer regarding some of the patients who land in the middle deciles. Finally, a hypothetical situation was created to identify the net benefit of the risk model in two scenarios, which is if all or no patients were screened. There appeared to be more clinical benefit for the utilization of the risk model than if all patients were or were not screened.

In a recently published manuscript from our group at the Karmanos Cancer Institute (8), we took a different approach looking specifically at risk of developing a SPLC rather than developing a risk model. The SEER database was also used to identify the participants. Patients with IPLC were identified from 1992–2007 with an additional 5-year follow-up period for the patients who developed a SPLC. A SPLC was defined using SEER criteria. The occurrence of multiple primary tumors was based on topography, histology, a single tumor occurring in each lung, tumors diagnosed more than 3 years apart and an invasive tumor diagnosed more than 60 days after an *in-situ* tumor (9,10). A 6-month latency exclusion period was added to distinguish a SPLC from late recurrence of the IPLC. The incidence of SPLCs was compared to the expected incidence in the general population by calculating standardized incidence ratios (SIRs).

An IPLC was diagnosed in 156,494 patients and a SPLC was discovered in 3% of the patients. Women had the highest SIR values with the youngest patients (20–49 years) having the highest SIR. For both men and women, SIR values increased with time since the IPLC diagnosis. Most of the patients who had a SPLC, initially presented with a localized IPLC. Most SPLCs were advanced stage at diagnosis. The median time to the development of a SPLC after the diagnosis of an IPLC was 59 months for men and 62 for women. The incidence rate of the development of a SPLC was 1.10% per patient per year and the risk did not plateau over time.

These are two studies both using population-based cancer surveillance data with the goal of trying to better define the patients who are at risk for SPLC after being diagnosed with an IPLC. The use of the SEER data base is a strength for both studies because it allows the collection of uniform information from large patient numbers with less bias than would be seen in a limited institution trial. The most significant contribution of the Han *et al.*'s study is the evaluation of risk stratification with the intention of developing a clinically useful prediction model. Prediction models are currently being utilized in other malignancies such as breast cancer to determine the need for particular treatments such as adjuvant therapy. In this case a reliable prediction model could help determine a surveillance strategy for SPLC. This model would need prospective validation. It is interesting to note that lung cancer survivors at a younger age (0–44 years) had a substantially lower risk of developing a SPLC while in the Thakur study the younger patients had the highest SIR values. The fact that the risk for the development of SPLCs is higher in younger individuals makes some sense because by living longer they have a better chance of eventually developing another malignancy. One major difference between these findings is that the Han *et al.*'s study only evaluated SPLC risk once a 5-year survival time point had been reached, while in our study, we evaluated risk of a SPLC diagnosed 6 months or more after IPLC. Surveillance guidelines need to be developed at these earlier time points, as well as for long term survivors.

All of these studies have similar significant weaknesses. The SEER database does not collect information on family history, presence of chronic obstructive pulmonary disease, smoking patterns and environmental exposure. It is important to note that the risk of lung cancer from smoking may not return to baseline even after 35 years of smoking cessation (11). These parameters can contribute to the development of lung cancer and knowledge of them could potentially strengthen a prediction model.

The information from these two trials could have a major implication regarding the monitoring of patients after treatment of their initial lung cancer. One of the trials suggests that the surveillance should continue indefinitely because the cumulative risk for development of SPLC increased over time and did not plateau. It is important to remember that lung cancers found at an earlier stage could also lead to more effective treatment resulting in a better survival. Molecular adjuncts such as next-generation sequencing could also be used to study the IPLCs and the subsequent SPLCs. Invaluable information could be obtained by evaluating these tumors at the cellular level. This would appear to be the ideal situation for a multi-institutional prospective study that would not only collect the important patient demographics that are missing but would also incorporate a screening strategy and correlative scientific studies. This would be a major undertaking that would take years to complete but could provide practice changing information.

Acknowledgements

Footnote

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