Editorial

Can population data guide surveillance strategies for second primary lung cancers?

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Computed tomography (CT) screening for populations at high risk for lung cancer (LC) has demonstrated improvement in LC-specific mortality and overall survival through earlier identification of potentially lethal LC (1). Similarly, CT surveillance following the radical treatment of first primary lung cancer (FPLC) is crucial, as survivors remain at risk for both recurrence as well as second malignancies, particularly second primary lung cancer (SPLC). The reported rates of SPLC vary, with a review of 10 surgical studies of non-small cell lung cancer (NSCLC) patients estimating a SPLC risk of approximately 1–2% per patient-year (2). Other reports, including a single-center study involving 1,294 NSCLC early stage surgical patients estimated a SPLC rate as high as 2–6% per patient-year (3).

As SPLC can be difficult to differentiate from LC recurrence, criteria have been proposed to avoid misclassification. The most widely used definition requires a histologic difference between the new cancer and the first, or one of the following criteria: (I) a cancer-free interval of ≥2 years; (II) arising from carcinoma *in situ*; or (III) arising in a different lobe or lung without evidence of carcinoma in the common lymphatics or extrapulmonary metastases at the time of diagnosis (4). Variations of this definition typically extend the cancer-free interval; these and other discrepancies make studies of SPLC difficult to compare (5-7).

It is against this backdrop that Han *et al.* performed a population-based retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database to create a risk prediction model to estimate the 10-year risk of developing SPLC (7). Data were obtained from 20,032 patients who survived ≥5 years after FPLC diagnosis. Variables available in the SEER database included age at FPLC diagnosis, sex, race/ethnicity, stage, histology, tumor size, disease extent, and initial treatment modality. Of these, the authors found that histology, age, and disease extent were predictive factors, and in a risk stratification model, the tenth-decile and the first-decile groups had a cumulative risk of 12.5% *vs.* 2.9% respectively at 10 years ($P<10^{-10}$).

There are a few notable strengths and caveats to this study. Median follow-up was robust at 8 years after diagnosis of FPLC. As is the case with SEER data, the sample size was large and data from SEER is thought to be highly generalizable as it represents 28% of the eligible US population. In terms of limitations, the authors used a somewhat unique definition of SPLC compared to most other studies, defining SPLC as a second LC diagnosed at least five years after initial diagnosis of LC. This is relevant as unlike the incidence of recurrences, which peaks in the first few years post-treatment, the incidence of SPLC seems to increase over time and does not plateau. One single-center study of 2,151 patients who underwent surgical resection for stage I lung adenocarcinoma found that the cumulative incidence of SPLC at 5 and 10 years to be as high as 9.9% and 20.3%, respectively (8). In another single-center study involving 218 patients with LC who survived at least 3 years after their FPLC, authors found the mean time to recurrence and SPLC to be 36.1 months (range, 12–90 months) and 86.7 months (range, 19–180 months),

respectively (5).

SEER data is also limited by what information is available within the database. It does not contain information on important modifiable and non-modifiable risk factors for FPLC that may impact SPLC development, such as smoking history, other environmental exposures, chronic obstructive pulmonary disease, or family history. This limitation is important as the traditional risk factors for FPLC play the same role in the development of SPLC as per the field cancerization phenomenon first described by Slaughter in 1953 (9). However, the role of smoking in the development of SPLC seems to be more nuanced than its definite role in FPLC. One study found no difference in the incidence of SPLC between 308 never smokers and 1,843 ever smokers at 10 years (HR =1.3; 95% CI, 0.88–1.92; P=0.18) (8). In contrast, another study found that smokers were at an increased risk of SPLC (HR =1.08; 95% CI, 1.02–1.16; P=0.031) in a similar single-center study involving 1,484 patients (10). It is clear that more studies are needed to understand the risk factors of SPLC. The SEER database study also included patients diagnosed with FPLC during a time-period when regular CT surveillance was not routine, and it is difficult to generalize to current practices today.

The authors of the SEER database study suggest using a risk prediction model at 5 years after diagnosis of FPLC to decide if the benefits of surveillance outweigh the risks (7). However, this study does little to address surveillance within 5 years of diagnosis, a time when both recurrences as well as SPLC may occur. Current National Comprehensive Cancer Network guidelines for NSCLC surveillance recommend: (I) a chest CT every 6 months for 2–3 years and then yearly thereafter for stage I or II disease treated with surgery; or (II) a chest CT every 3–6 months for 3 years, every 6 months for 2 years, and then yearly thereafter for stage I or II disease treated with radiation, or stage III or IV oligometastatic disease treated with curative intent (11). In general, while cancer survivors tend to receive more frequent screening for new primary cancers than non-cancer controls, uptake is still less than ideal (12).

Recently, there has been debate as to whether CT scans are superior to a chest X-ray (CXR) in surveillance following curative treatment for NSCLC. Preliminary results from IFCT-0302, a randomized control trial of 1,775 patients who underwent resection of NSCLC, found no overall survival difference between patients who were followed with a clinical examination and CXR versus those who also underwent a thoracoabdominal CT scan every 6 months for the first 2 years, and yearly for 5 years (HR =0.92; 95% CI, 0.8–1.07; P=0.27) (13). In this study available only in abstract form, median follow-up was 8.7 years, with final results and publication pending. Other prospective studies and consensus guidelines are in favor of regular CT scans. One prospective study of 271 patients comparing 1,137 pairs of scans (CT and CXR at 3, 6, 12, 18, 24, 36, 48 and 60 months) following LC resection found that low-dose CT was more sensitive (94% *vs.* 21%; P<0.0001) in the diagnosis of new or recurrent LC (14).

This SEER data analysis raises the possibility of tailoring surveillance using a population-based prediction model, and has important consequences as the majority of patients who are treated for FPLC remain at significant risk of developing a SPLC. There are limitations to the study in terms of available data, and it does not address surveillance in the first 5 years following FPLC diagnosis. Current consensus guidelines recommend regular surveillance with CT scans. Research in SPLC will become more important as more FPLC are detected at early stages and as more patients undergo curative intent treatment, increasing survivorship.

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Footnote

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