Review Article

Surveillance after surgical resection of stage I non-small cell lung cancer

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Abstract: Survivors of lung cancer treated with surgical resection remain at significant risk of developing a new primary metachronous non-small cell lung cancer (NSCLC), intrathoracic recurrence of the original primary cancer, and distant metastases. However, advances in computed tomography screening have improved the detection of these tumours during routine surveillance and have subsequently led to increased survival rates for this population. We present a summary of the most recent evidence regarding the optimal surveillance for survivors of Stage I NSCLC treated with curative resection.

Keywords: Non-small cell lung cancer (NSCLC); surveillance; curative resection

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Introduction

Surgical resection is the mainstay of treatment for stage I non-small cell lung cancer (NSCLC), with reported 5-year overall survival rates as high as 90% (1). Despite this successful treatment, NSCLC remains the leading cause of cancer death worldwide (2), partly because of its high recurrence rates and the elevated risk of developing subsequent new primary lung cancers. Recent data has demonstrated that surveillance after early lung cancer resection is not a futile exercise, since many patients can be diagnosed with new or recurrent cancer, and can be treated accordingly with high survival rates (3). In this article, we present an overview of guidelines and recent evidence surrounding the optimal surveillance regimen and follow-up care for survivors of stage I NSCLC.

Rationale for surveillance

Patients who have undergone successful resection of stage I NSCLC remain at risk of three cancer-related events: development of a new primary metachronous NSCLC, intrathoracic recurrence of the original primary cancer that was resected, and distant metastases.

New primary metachronous lung cancer (NPMLC)

It is estimated that 27% of patients who have been treated for stage I NSCLC will develop a NPMLC within 10 years of their index operation (4). The risk is highest within the first 24–36 months after surgery, with as much as 7% (5) of patients undergoing a second curative intervention for a NPMLC during that time. This risk does not decrease over time, and ranges between 2–6% (5,6) per person-year. Hence, younger patients and patients who have had very early stage cancers, who are expected to survive the longest, are at highest risk of developing a NPMLC. Fortunately, 75–80% of patients who present with a NPMLC are amenable to curative treatment using either surgery or radiation, with overall 5-year survival rates as high as 60% (7).

The National Lung Screening Trial has unequivocally demonstrated that screening with low dose computed tomography (LDCT) of the chest improves survival in populations at high risk for developing lung cancer (8).

Although the NLST excluded patients with a previous history of lung cancer, data from this trial can be extrapolated to apply to lung cancer survivors (9). Calls for a randomized controlled trial replicating the NLST for lung cancer survivors have largely been abandoned, and there is uniform consensus that the survivors of lung cancer require surveillance with LDCT (9).

Locoregional intrathoracic recurrence

Locoregional intrathoracic recurrence at the resection margins or in the lymph nodes should theoretically be a rare event after resection of truly node-negative pathological stage I NSCLC, but it isn't. Rates of locoregional recurrence range between 7% to 27%. (10-12). The risk is highest in patients who undergo sublobar resection, resection with residual microscopic disease (R1), or inadequate lymph node sampling (13). When adequate and complete nodal sampling is performed at the time of operation, close to 20% of clinical stage I patients are upstaged to pathological Stage II, because of occult nodal disease (14). With recent reports on sentinel lymph node sampling, it has been shown that as much as 22–44% (15,16) of occult nodal disease can hide in the sentinel nodes, and remain undetected by pathological assessment of the named nodal stations (17). Consequently, close to 39% of patients who were thought to have truly node-negative pathological stage I NSCLC in reality have nodal disease that is undetected and untreated, remaining at a high risk for locoregional recurrence (18).

Distant metastatic disease

Distant metastatic disease to the brain, liver, adrenal glands, and bone is also a rare occurrence after resection of stage I NSCLC, but is still reported (19-21). Unlike NPMLC and locoregional recurrence, distant metastatic disease is an incurable event, and is only treated when symptomatic. Therefore active extrathoracic surveillance to detect asymptomatic metastatic disease is not warranted (6).

Methods of surveillance

Chest X-ray

Chest X-ray (CXR) has largely been abandoned as a surveillance modality for survivors of lung cancer. CXR was the most common modality of surveillance in the past decade, despite reports of its very poor sensitivity in detecting NPMLC or locoregional recurrence (22). However, it was being used because there were no other alternatives for surveillance. A recent prospective, blinded trial showed that CXR was indeed a poor screening test, with a sensitivity for detecting NPMLC of 21% (7). As such, in the era of LDCT, there remains very little equipoise around the fact the CXR should not be used as the only modality for surveillance after resection of stage I NSCLC.

LDCT

LDCT delivers an effective radiation dose of 1.5 mSV, compared to 0.16 mSV of a two view CXR and the 8 mSV (23) of a contrast-enhanced standard dose CT (SDCT). As such, it is has excellent sensitivity for detection of pulmonary parenchymal nodules (94%) (8), but it is less sensitive than SDCT for the detection of nodal and mediastinal abnormalities (24). LDCT has been demonstrated to be a very effective screening tool for lung cancer in large landmark trials such as the Early Lung Cancer Action Plan (ELCAP) (25) and the NLST (8). Although no randomized trials have been performed to study LDCT in the surveillance of lung cancer survivors, data can be easily extrapolated from ELCAP and NLST to apply to this population, because lung cancer survivors are at a much higher risk of developing a NPMLC (2–6% per person year) (5,6) than the NLST population ever was (0.645% per person-year) (7). Multiple institutions, including our own, have reverted to the use of LDCT for surveillance after lung cancer resection. Additional research to identify optimal intervals for LDCT follow-up and to evaluate the benefits of LDCT for particularly low-risk patients is needed (26). The ongoing Intense-CT trial (NCT02149576) at our site (27) will determine whether the use of a structured surveillance program can increase the rate of detection of new and recurrent cancers.

SDCT

SDCT scan is recommended by the National Comprehensive Cancer Network (28) and the American Association for Thoracic Surgery (29) as the modality of choice for surveillance after resection of lung cancer. The use of contrast enhancement and a relatively high dose of radiation allow for excellent visualization of the lung parenchyma and the mediastinal structures. In a recent study on surveillance after resection of Stage I NSCLC, Crabtree

Table 1 Summary of guidelines for follow-up of lung cancer following curative resection

Organization	Follow-up
National Comprehensive Cancer Network (28)	
Year 1–3	History, physical examination, and chest CT with contrast every 6 months
Year 3–5	History, physical examination, and LDCT every 12 months
After year 5	History, physical examination, and CT every 12 months
American College of Chest Physicians (30)	
Year 1–2	History and physical examination with CT every 6 months
Year 3–5	History and physical examination with CT every 12 months
After year 5	History and physical examination with CT every 12 months
European Society for Medical Oncology (31)	
Year 1–2	History and physical examination with contrast-enhanced, spiral-chest CT every 12 months
Year 3–5	History and physical examination and chest CT every 12 months
After year 5	History and physical examination and chest CT every 12 months
American Association of Thoracic Surgeons (29)	
Year 1–2	SDCT every 6 months
Year 3–5	SDCT every 12 months
After year 5	LDCT every 12 months for life
International Consensus (32)	
Year 1–2	History, physical examination, and CXR every 3 months. CT when indicated
Year 3–5	History, physical examination, and CXR every 6 months. CT when indicated
After year 5	History, physical examination, and CXR every 12 months. CT when indicated
American College of Radiologists (33)	
Year 1–2	History and physical examination every 2-4 months and CXR every 6 months. CT every 12 months
Year 3–5	History, physical examination, and CXR every 6 months. CT every 12 months
After year 5	History and physical examination. CT every 12 months

et al. demonstrated that SDCT leads to earlier and more frequent diagnosis of NPMLC when compared to CXR, but that this does not necessarily translate into a survival benefit (4). Other authors have successfully demonstrated that SDCT carries excellent accuracy (88%) and negative predictive value (99%) for the diagnosis and treatment of NPMLC in lung cancer survivors (21).

More recent guidelines (28-33) reflect the current evidence and recommend the use of CT, as opposed to CXR, for the follow up of patients receiving curative resection for NSCLC. A summary of current guidelines for surveillance after resection of stage I NSCLC are summarized in *Table 1*.

Role of survivorship

The role of survivorship programs must not be overlooked in the optimal management of stage I NSCLC, whose survivors are expected to live well beyond five years. Lung cancer survivors are at significant risk of experiencing fatigue, anxiety, dyspnea, chronic pain, depression, and overall decreased quality of life (34). These factors may be exacerbated by age, neoadjuvant therapy, and other comorbidities. In a pursuit of curative treatment

for patients with cancer, surgeons and other health care providers often overlook these conditions and fail to provide the appropriate survivorship care (35). Multidisciplinary survivorship programs that provide resources and support for smoking cessation programs, healthy lifestyle habits (i.e., nutrition and exercise), screening for other cancers, access to psychological and social support are key to a successful postoperative transition to daily life. Data shows that these supports can benefit patients well into the postoperative period, and recommends that clinicians counsel patients according to the Five A program—*Ask*, *Assess*, *Advise*, *Assist and Arrange* for adequate supports (36). A recent article by Pozo *et al.* (36) provides a list of organizations and resources that support survivorship care for lung cancer survivors.

Huang *et al.* of Memorial Sloan Kettering provide a model of survivorship care that centers around the engagement of a nurse practitioner-led thoracic cancer survivorship program (34). In this model, a trained nurse practitioner collaborates with the primary surgeon or oncologist to provide surveillance for lung cancer recurrence or development of metachronous tumors, screening for other cancers, health counselling for diet, exercise and smoking cessation, referrals to cancer support groups, psychological counselling and communication with the patient's primary health provider (34). An evaluation of the program demonstrated feasibility and cost-effectiveness. Most importantly, patient-reported satisfaction was high with 92% of eligible survivors choosing to remain in the thoracic survivorship program rather than receiving routine-follow up by their primary surgeon (34).

Summary

In summary, there is compelling evidence that surveillance with chest CT after resection of stage I NSCLC is a worthwhile exercise that can translate into early detection of NPMLC and recurrent lung cancer. With early detection and surgical treatment, survivors of stage I NSCLC are now expected to live longer than 5 years, serious consideration should be given to whole-patient survivorship care through structured survivorship programs.

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