

A PEER-REVIEWED ARTICLE

## Early lung cancer detection in HIV: The role of CT screening in high risk cases

*Marco Ruiz, MD, MPH*

The incidence of AIDS-defining cancers has decreased with the use of antiretroviral therapy, while the incidence of non-AIDS defining malignancies has increased,<sup>1,2,3,4,5</sup> as has the proportion of mortality associated with non-AIDS defining malignancies in HIV-infected patients.<sup>6</sup> In fact, cancer is responsible for 7%-15% of mortality in the HIV population.<sup>7</sup> Malignancies in the HIV-infected population have an earlier onset and worse prognosis compared to the general cancer population.<sup>6</sup>

Lung cancer is prevalent in the HIV-infected population; it is more frequently diagnosed when locally advanced or metastatic, diagnosed at a younger age, more aggressive with higher rates of relapse, and has decreased progression-free survival when compared to lung cancer in the general population.<sup>8,9</sup> The oncogenic roles of HIV, smoking, age, and increased susceptibility of carcinogens have all been correlated to a higher risk of developing lung cancer.<sup>9</sup> Human papilloma virus may also be associated with certain cases of bronchial squamous cell carcinoma.<sup>10</sup>

The efficacy of screening remains controversial and current guidelines do not recommend screening for lung cancer for the general population.<sup>11</sup> Previous trials using chest X-rays and sputum cytology have failed to show early detection and reduction in mortality in patients not affected by HIV.<sup>11</sup> However, new reports suggest these two tools combined may have a modest benefit in early detection of lung cancer.<sup>11,17</sup> CT scanning has proven to be cost-effective,<sup>11,12,13,14</sup> but advantages in terms of morbidity, mortality, or long-term outcomes in patients with lung cancer have not been demonstrated.<sup>15</sup> CT scanning may, however, be a potential tool for early detection and survival in high-risk HIV populations.

This article will explore the relevance and potential utility of CT scanning in early lung cancer detection in HIV-infected patients. Trials of CT scanning in high-risk non-HIV-populations will be reviewed. Recommendations for the use of CT scanning as a means of screening for early detection in HIV-infected patients will be explored.

### **Lung cancer in HIV-infected patients**

Lung cancer is one of the most common non-AIDS-defining malignancies among HIV-infected patients.<sup>15</sup> Recent studies suggest that lung cancer risk is three to four times higher in HIV-infected patients than in uninfected persons, after adjusting for other factors such as smoking intensity and duration.<sup>15</sup> One study calculated the incidence as 6.7/100,000 HIV-infected patients in the post-antiretroviral period.<sup>9</sup>

All major cancer subtypes are equally increased (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma), making the HIV-infected population a high risk group.<sup>15,36</sup> The most significant risk factor is smoking but other factors have been identified: potential oncogenic activity of the HIV virus, prolonged moderate or severe immunosuppression, and aging.<sup>9,15,16</sup> Other studies have suggested that men who have

sex with men and intravenous drug users should also be included as high-risk groups.<sup>8,9,29,30</sup>

*In vitro* studies have shown that tat (transactivator of transcription) gene product from HIV can increase the expression of the proto-oncogenes c-myc, c-fos and c-jun, and downregulate the tumor suppression gene p53 in lung adenocarcinoma cell lines.<sup>16</sup> The role of a possible increase in genomic instability in the increased risk of lung cancer among HIV-infected patients has been suggested by a study of sixteen polymorphic markers on eight chromosome arms frequently deleted in lung cancer.<sup>9</sup> This study pointed out that microsatellite instability was six times more frequent in the HIV-infected patients.<sup>9</sup> A recent study showed that overexpression of Pokemon, a transcription factor that is a central regulation gene of the important tumor suppressor alternative reading frame (ARF), is present in non-small cell lung cancer (NSCLC). Pokemon causes carcinogenesis by inhibiting ARF and its detection may be useful for the prognostic evaluation of patients with NSCLC. The role of Pokemon in HIV-infected patients has not been studied.<sup>9,33</sup>

The relationship of chronic immunodepression to the excessive risk of lung cancer among HIV-infected patients is difficult to determine.<sup>9</sup> This hypothesis has been studied in transplant patients who share the same risk of lung cancer development independent of smoking.<sup>9,15</sup> Lung cancer, however, may develop at any point in the course of HIV disease.<sup>9,15,31,34,35</sup> The role of prolonged immuno-suppression before the start of antiretroviral therapy has been linked to the development of lung cancer in HIV-infected patients.<sup>9,34,35</sup> Some studies have indicated that the risk may be maximal in periods immediately before AIDS and subsequent to an AIDS diagnosis.<sup>9,15,34</sup> Recent studies have shown that in the post-antiretroviral period, the degree of immunodepression was less severe and the risk of lung cancer nonetheless higher in this period.<sup>9</sup> Therefore, the presence of immunosuppression may not fully explain the behavior of certain lung cancers in HIV-infected patients. Furthermore, the risk of lung cancer has been shown not to be closely related to CD4 cell count or HIV viral load.<sup>15</sup> The role of antiretroviral therapy with regards to lung cancer risk is controversial at this time.<sup>15</sup> Despite improved immune function on antiretroviral therapy, cancer immune surveillance is still inadequate in patients with HIV.<sup>15,30</sup> Two potential HIV-related immunologic mechanisms associated with lung cancer risk have been described: the presence of chronic pulmonary inflammation and repeated infections. These two mechanisms might explain the increased incidence of lung cancer in HIV-infected individuals.<sup>15</sup>

### **Clinical trials of CT scanning as early detection tool**

Numerous trials have been conducted using low-radiation-dose CT (LDCT) scanning. This technique is faster and less expensive than helical CT scanning and its capacity to detect small lung nodules is superior to chest X-ray.<sup>15,29,37</sup> Among the trials reviewed and their conclusions:

- The Danish Randomized Lung Cancer CT screening trial concluded screening may facilitate minimal invasive treatment with a low rate of false-positive results.<sup>18</sup>
- A Canadian study confirmed LDCT identified small, early-stage, resectable lung cancer in high-risk individuals.<sup>19</sup>
- A study from Spain concluded that the use of low-dose computed tomography in risk groups is valid for early diagnosis of lung cancer.<sup>20</sup>

- An Italian assessment of efficacy with low-dose CT concluded that LDCT results are substantially in line with other international studies.<sup>21</sup>
- A New York study concluded annual CT screening for lung cancer resulted in identification of a high proportion of patients with early-stage disease.<sup>22</sup>
- A study in Italy found, despite promising data from other studies, that evidence from randomized controlled trials is needed to support the use of low-dose computed tomography for early detection of lung cancer.<sup>23</sup>
- A Japanese study showed the potential for overdiagnosis in CT screening-detected cases.<sup>24</sup>
- The authors of a large collaborative study, the International Early Lung Cancer Action Program (I-ELCAP), concluded that annual spiral CT screening could detect lung cancer that was curable.<sup>25</sup> Though this study showed surprising results, some detractors felt it had many problems, including its lack of a control group, lack of an unbiased outcome measure, lack of consideration of what is already known about this topic from previous studies, and that it did not address the potential harms of screening.<sup>26</sup> Others mention that potential interobserver agreement among radiologists who read chest CT scans could be moderate to substantial and that this factor needs to be taken into account in the evaluation of results from these trials.<sup>27</sup>
- A Japanese study concluded low-dose CT screening substantially improves the 10-year survival for lung cancer with minimal use of invasive treatment procedures.<sup>28</sup>

The paucity of studies in HIV-infected patients is surprising. To the best of this author's knowledge, no trials of CT scanning in early lung cancer diagnosis in HIV-infected individuals have been published.

### **Guidelines**

Gomez *et al.* (2008)<sup>29</sup> compiled the available guidelines for CT scanning in early lung cancer detection. The American College of Chest Physicians in 2003 recommended against the use of single or serial low-dose CT scanning, pending the results of the National Lung Screening Trial (NLST). The United States Prevention Service Task Force in 2004 concluded that there was not sufficient evidence to recommend for or against screening of asymptomatic persons for lung cancer with either low-dose CT scanning, chest radiograph, or any other tests or combinations of them. In 2005, the American Cancer Society recommended against testing for early lung cancer detection in asymptomatic individuals.<sup>29</sup> No guidelines have been published for early lung cancer detection in HIV-infected patients or other high risk groups.

### **Who should be screened**

The construction of a high-risk group is difficult in the case of the HIV-infected population since the majority of these patients present late to primary care and have multiple co-morbidities. Immunosuppression, smoking history, age, and history of antiretroviral therapy may all be useful in defining a risk group that would benefit from screening. The majority of studies agree that lung cancer in the HIV-infected population is not fully explained by immunosuppression but the latter could still play a role in the development of lung cancer. In fact, recent studies are looking into length of suppression before treatment as one potential variable to consider in the development of lung cancer.<sup>15, 30, 34</sup> Patients considered to be in a high-risk group may include individuals

with an HIV history of more than five years with prolonged immunosuppression exposure, potentially defined by the appearance of an opportunistic infection. Recent reports challenging the definition of non-AIDS-defining cancer suggest that the length of time of this immunosuppressive state is critical to the development of certain non-AIDS-malignancies, including lung cancer.<sup>15, 30, 34</sup> Controversy remains over the relationship between immune surveillance system failure, chronic infections, chronic inflammation, and lung cancer risk in the HIV-infected population.

Prolonged and significant smoking history represents one of the main risk factors for lung cancer in non-HIV patients. The majority of studies included patients with smoking histories between 10–20 packs per year and smokers with recent quitting history. Even though smoking is not the only cause for lung cancer in HIV-patients, this criterion needs to be included in the high-risk group category.<sup>9,15,16-28</sup>

Age is well known to represent the most common cause for development of all types of cancers. In the trials studied, groups ranged from 45–60 years old. Although there is no consensus about the cut-off age for HIV-infected patients at higher risk for lung cancer, the majority of studies of lung cancer in HIV populations have found an increased prevalence in patients older than 45 years of age.<sup>8, 9,30,31,32</sup>

The effect of antiretroviral therapy in HIV-infected patients with lung cancer has been a matter of debate. Initial reports claimed that antiretrovirals had no effect on progression or even survival of patients with lung cancer and HIV. Recent studies indicate that antiretroviral therapy may have a positive effect on the progression of lung cancer. For purposes of building up a high-risk group, antiretrovirals might not matter; therefore patients who fall into the previous categories regardless of use of antiretrovirals should be included in the definition of high-risk group.<sup>9, 15, 16</sup>

## **Conclusions**

Lung cancer is one of the most common malignancies in HIV-infected individuals. Risk factors such as smoking, age, moderate prolonged immunosuppression, and increased susceptibility to carcinogens have been linked to development of lung cancer. The role of HIV virus itself and its interaction with other oncogenic viruses, such as HPV, in the pathogenesis and biology of lung cancer has not yet been deciphered. Other suspected high-risk groups, such as intravenous drug users and men who have sex with men (MSM), may benefit from screening.

Lung cancer is generally aggressive and detected late in non-HIV-infected populations. The same might apply to HIV patients. Some studies have even suggested that aggressiveness and relapse might be higher in HIV-infected persons. Undoubtedly, a better screening tool is needed. CT scanning may be the potential answer. It is interesting to note that, even though advocating bodies do not recommend single or serial CT scanning, HIV-infected patients may represent a very high-risk group with potential increased mortality compared to traditional high-risk lung cancer groups. This issue is still a matter of debate.

Trials need to be conducted in HIV-infected individuals. The design should include patients who fall in the high-risk group. Inclusion criteria could consider extensive smoking history (defined as current active smoking with more than 10 pack/year history or recent quitting history), individuals over the age of 45, subjects who have been exposed to moderate or severe long periods of immunosuppression (defined as T-cell counts less

than 200 for more than five years), and individuals currently on antiretroviral treatment regardless of their T-cell count. The initial CT scanning could be followed over three years with morbidity and mortality outcomes analyzed.

New trials will hopefully show the real impact of CT screening in early lung cancer detection in HIV-infected patients. Thorough analysis of short- and long-term outcomes, morbidity and mortality rates, survival with early treatment and interventions, progression-free survival, and quality of life are issues to consider in further analysis of the impact of CT scanning in early detection of lung cancer.❖

*Dr. Ruiz is Assistant Professor, LSUHSC Section of Infectious Disease; staff physician, Interim LSU Hospital HIV Outpatient Program (HOP) Clinic; and faculty, Delta Region AETC.*

#### REFERENCES

1. Long J, Engels E, Moore R, Gebo K. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals. *AIDS*. 2008; February 19; 22(4): 489-496
2. Martinez LJ, Lynch GR, Grimes RM. Non-Kaposi's cancers in HIV-infected patients at an urban teaching hospital. *International Conference AIDS* 1998; 12: 1104
3. Hainsworth JD, Greco FA. Treatment of patients with cancer of an unknown primary site. *The New England Journal of Medicine*. Volume 329: 257-263
4. Pentheroudakis G, Briasoulis E, Plavidis N. Cancer of unknown primary site: Missing primary or missing biology? *The Oncologist*. 2007; 12; 418-425
5. Van de Woux AJ, Jansen RLH, Speel EJM, Hillen HFP. The unknown biology of the unknown primary tumour: a literature review. *Annals of Oncology* 14: 191-196, 2003
6. Barbaro G, Barbarini G. HIV infection and cancer in the era of highly active antiretroviral therapy. *Oncology Reports* 17: 1121-1126, 2007.
7. Uhlenkott MC, Buskin S, Kahle E, Barash E, Abouafia DM. Causes of death in the era of highly active antiretroviral therapy: A retrospective analysis of a hybrid hematology-oncology and HIV practice and the Seattle/King County Adult/Adolescent Spectrum of HIV-related Diseases Project. *The American Journal of the Medical Sciences*. September 2008 Volume 336 Number 3
8. White JD, Bowman CA, Woll PJ. Lung cancer as the presenting feature of AIDS. *Lung Cancer* 33 (2001), 81-87.
9. Lavole A, Wislez M, Antoine M, et al. Lung cancer, a new challenger in the HIV-infected population. *Lung Cancer* (2006), 51, 1-11.
10. Klein F, Waleed FM, Kotb A, et al. Incidence of human papilloma virus in lung cancer. *Lung Cancer* 65 (2009), 13-18
11. Henschke CI, Yankelevitz DF. CT screening for lung cancer: Update 2007. *The Oncologist* 2008; 13: 65-78
12. Bazoos A, Bower M, Powles T. Smoke and mirrors: HIV-related cancer. *Current Opinion in Oncology* 2008, 20:529-533.
13. Kirk JD, Merlo C, Driscoll PO, et al. HIV infection is associated with increased risk for lung cancer, independent of smoking. *Clinical Infectious Diseases* 2007;45 1 July; 103-110.
14. Phillips AA, Justman JE. Screening HIV-infected patients for non-AIDS-defining malignancies. *Current HIV/AIDS reports*. 2009. May; 6 (2):83-92
15. Engels E. Non-AIDS-defining malignancies in HIV-infected persons: etiologic puzzles, epidemiologic perils, prevention opportunities. *AIDS* 2009, 23: 875-885
16. Pantanowitz L, Schlecht H, Dezube B. The growing problem of non-AIDS-defining malignancies in HIV. *Current Opinion in Oncology* 2006, 18: 469-478.
17. Doria-Rose VP, Marcus PM, Szabo E, et al. Randomized controlled trials of the efficacy of lung cancer screening by sputum cytology revisited. *Cancer* 2009. Published ahead of print.
18. Pedersen J, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial: Overall design and results of the prevalence round. *Journal of Thoracic Oncology*, Volume 4, Number 5, May 2009.
19. Roberts H, Patsios D, Paul N et al. Lung cancer screening with low-dose computed tomography: Canadian experience. *JCAR vol 58, No 4, October 2007*.
20. Callol L, Roig F, Cuevas, et al. Low-dose CT: A useful and accessible tool for the early diagnosis of lung cancer in selected patients. *Lung Cancer* (2007), 56; 217-221.
21. Lopes Pegna A, Picozzi G, Mascialchi M, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. *Lung Cancer* 64 (2009), 34-40.
22. New York Early Lung Cancer Action Project Investigators. CT screening for lung cancer: Diagnoses resulting from the New York Early Lung Cancer Action Project. *Radiology: Volume 243: Number1 April 2007*.
23. Novello S, Fava C, Borasio P, et al. Three-year findings of an early lung cancer detection feasibility study with low-dose spiral computed tomography in heavy smokers. *Annals of Oncology* 16: 1662-1666, 2005.
24. Toyoda Y, Nakayama T, Kusunoli Y et al. Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography. *British Journal of Cancer* (2008), 98, 1602-1607.
25. The International Early Lung Cancer Action Program Investigators. Survival of patient with stage I lung cancer detected on CT screening. *New England Journal of Medicine*. October 26, 2006. Vol 355 No 17. 1763-1771
26. Welch HG, Woloshin S, Schwartz LM, et al. Overstating the evidence for lung cancer screening. *Archives of Internal Medicine*. 2007; 167(21):2289-2295.
27. Gierarda DS, Pilgram TK, Ford M, et al. Lung cancer: Interobserver agreement on interpretation of pulmonary findings at low-dose CT screening. *Radiology*. Volume 246: Number 1, January 2008.
28. Sone S, Takayama T, Honda T, et al. Long-term follow up study of a population-based 1996-1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography. *Lung Cancer* (2007), 58, 329-341.
29. Gomez M, Silvestri G. Lung cancer screening. *The American Journal of Medical Sciences*. January 2008 Volume 335 No 1.
30. Lavole A, Chouaid C, Baudrin L, et al. Effect of highly active antiretroviral therapy on survival of HIV infected patients with non-small-cell lung cancer. *Lung Cancer* 2009 Published ahead of print.
31. Bazot M, Cadranet J, Khalil A, Benayoun S, et al. Computed tomographic diagnosis of bronchogenic carcinoma in HIV-infected patients. *Lung Cancer* 28 (2000); 203-209.
32. Massera F, Rocco G, Rossi G, et al. Pulmonary resection for lung cancer in HIV-positive patients with low (<200 lymphocytes/mm<sup>3</sup>) CD4+ count.

*Lung Cancer* 29 (2000); 147-149.

33. Zhi-hong Z, Wang SF, Yu L, *et al.* Overexpression of P63 in non-small cell lung cancer and foreshadowing tumor biological behavior as well as clinical results. *Lung Cancer* (2008), 62, 113-119.

34. Bruyand M, Thiebaut R, Lawson-Ayayi S, *et al.* Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) Aquitaine Cohort. *Clinical Infectious Diseases* 2009. Published ahead of print.

35. Bedimo R, McGinnis KA, Dunlap M, *et al.* Incidence of non-AIDS-defining malignancies in HIV-infected versus noninfected patients in the HAART era: Impact of immunosuppression. *Journal of Acquired Immunodeficiency Syndrome* 2009. Published ahead of print.

36. Kawachi R, Watanabe S, Asamura H. Clinicopathologic characteristics of screen-detected lung cancers. *Journal of Thoracic Oncology*. 2009;4:615-619.

37. Fujikawa A, Takiguchi Y, Mizuno S, *et al.* Lung cancer screening: Comparison of computed tomography and X-ray. *Lung Cancer* (2008), 61, 195-201.