



# LIFE AFTER LUNG CANCER: SURVIVORSHIP RESEARCH AND BEHAVIORAL INTERVENTION ARE NEEDED

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**ABSTRACT:** Primary lung cancer is very heterogeneous in its clinical presentation, histopathology, and treatment response. Lung cancer survival is mostly determined by disease stage and treatment modality, and the five-year survival rate has been in a plateau of 15% for three decades. Lung cancer survivors often exhibit poor functional capacity, poor patient-reported physical functioning, and compromised quality of life. Each cancer survivor has a complex array of potential risks, target problems and potential long-term outcomes. Surgery, radiation, chemotherapy can result in both local and systemic sequelae. The physical and psychosocial consequence of survival from lung cancer and its treatment have been also recognized as important outcome measures of lung cancer treatment in addition to length of survival. Cancer survivorship research is aimed to identify, examine, prevent, and control adverse outcomes related to cancer diagnoses and treatment.

## INTRODUCTION

Lung cancer has a higher incidence of tumors in the world. In America were estimated 214,402 patients in 2008; despite the historically poor prognosis for patients diagnosed with primary lung cancer, population-based Surveillance and Epidemiology and End Results data indicates a minimal but statistically significant increase in the percentage of survivors over the past years: 15.9% and 18.0% patients living at least 5 years respectively in 1992-95 and 2001-07 years of diagnosis. According to these data, of lung and bronchial cancer cases, 15% were diagnosed while the cancer was still confined to the primary site (localized stage); 22% were diagnosed after the cancer had spread to regional lymph nodes or directly beyond the primary site; 56% were diagnosed after the cancer had already metastasized (distant stage);

and for the remaining 8%, the stage was unknown. The corresponding 5-year relative survival rates were: 52.9% for localized, 24% for regional, 3.5% for distant, and 8.7% for unstaged<sup>1</sup>. Although overall survival remains low, the overall growth, aging of the population and advancements in early detection and treatment will significantly increase the number of long-term cancer survivors<sup>2,3</sup>. People who are alive five years after a diagnosis of primary lung cancer are referred to as long term lung cancer (LTLC) survivors. Information about LTCT, the great majority of whom have non-small-cell lung cancer (NSCLC), is almost non-existent. Because of the generally poor prognosis for lung cancer, the overwhelming focus of quality of life (QOL) research in patients with lung cancer has been on patients with active advanced stage disease<sup>4</sup>. QOL in patients with lung cancer at varying times after diagnosis highly correlates with base-



line prognostic factors which the disease stage, histology, Karnofsky scale, weight loss, and sex<sup>10</sup>. In a cross-sectional survey of long-term lung-cancer (LTLC) survivors, fatigue and anxiety were reported as major problems and their physical functioning scores were worse than other cancer survivors<sup>11</sup>. Changes in QOL over time have been evaluated among 164 LTLC survivors in a pilot study; 34% of these survivors experienced a significant decline in their overall QOL at the five-year follow-up<sup>12</sup>. According to the limited information in the literature, the QOL of long-term survivors of lung cancer showed substantial deficits relative to other patient populations, indicating a need for targeted interventions. Information about QOL of survivors of lung cancer can provide health care providers with a perspective of post treatment recovery, including the positive aspects of long-term rehabilitation, and anticipated problems and issues that can be shared with patients and families. Factors that might put some survivors at a higher risk for diminished QOL can be identified, and rehabilitation programs and long-term surveillance can be tailored appropriately.

## LONG-TERM HEALTH AMONG LUNG CANCER SURVIVORS

Surgery, maintenance treatment, time to first progression of the tumor of >3 months, a PS of 0-1 at first progression, the number of chemotherapy agents received, and LDH levels, are significant predictors of long-term survival<sup>5</sup>. The long-term adverse consequences of cancer treatment has received limited attention among patients with adult-onset cancers. In particular, the high mortality rate has made it difficult to adequately assess treatment-related late toxicity. Most studies have considered the issues and possible resolution of

clinical symptoms with full recovery after six months after surgery, but few have been conducted to evaluate the long-term issues that have arisen after years the approach therapeutic<sup>6-9</sup>. Were also sometimes included control groups of patients with other forms of cancer or noncancer patients undergoing similar surgical procedures, patients with tumors of different histology and stage. The majority of studies also address the issues of survivors of non small cell lung cancer who underwent surgical resection with minimal attention to those with small cell lung cancer or those who have undergone adjuvant treatment<sup>10-12</sup>. However, since it is estimated that because of population growth, aging and improved diagnostic and therapeutic procedures, the number of tumors that occur in people aged 65 and number of survivors could double within 30 years, it becomes essential assess all the consequences, too late, for the diagnosis and treatment of lung cancer to ensure adequate quality of life for these patients<sup>13</sup>. The common complications seen in long-term lung cancer survivors include dyspnea, functional status/fatigue, pain, emotional distress, cognitive difficulties, relationships, sexual dysfunction, and alterations in communication abilities. The prevalence and patterns of lingering symptoms are described next.

### Dyspnea

Dyspnea is a symptom frequently encountered in LTLCS.

Changes in pulmonary function may be affected by cancer and its treatments, by comorbid diseases and by lifestyle habits such as smoking. Surgical resection is the best treatment for patients with lung cancer, but it is also the main cause of the reduction of ventilatory capacity and of exercise tolerance, impairing the postoperative quality of life. Often this reduction of lung function is not

**TABLE 1. THE PREVALENCE OF LINGERING SYMPTOMS. WIN T, SHARPLES L, WELLS FC, ET AL. EFFECT OF LUNG CANCER SURGERY ON QUALITY OF LIFE. THORAX 2005; 60:234-238.**

Lingering symptoms	%
Dyspnea	30-50%
Chronic pain	30%
Fatigue	50-60%
Emotional distress	50%
Sexual dysfunction	20%
Late recurrence and new primary cancer	13-20

a transient effect but permanent and, for some, is cause of physical disability<sup>14</sup>. There are clear differences based upon the extent of resection. Several studies, in fact, support the benefit of the VATS procedure in improved functional recovery as compared to other approaches (lobectomy, pneumonectomy)<sup>15</sup>. Beyond the surgery, radiation therapy can cause changes in pulmonary function. Are well-known adverse effects by clinical radiation pneumonitis, defined as grade 2 or higher, is reported in 15 to 20% of lung cancer patients receiving external-beam radiotherapy<sup>16</sup>. Older age, low performance status, low pulmonary function, high radiotherapy dose, and chemotherapy exposure are possible additional risk factors. Although dyspnea is often a consequence of surgical and radiation treatment, the majority of studies reported ongoing problems of breathlessness in some survivors, often linked with reduction in exercise capacity<sup>17</sup>. Has been observed that a progressive resistance exercise training program improves muscular strength, endurance and consequently dyspnea. In particular, a study conducted on feasibility and efficacy of a progressive resistance exercise training intervention in post-treatment lung cancer survivors showed significant improvements in muscular strength and endurance. These changes in muscular strength are likely attributable to neuromuscular adaptations that occur in the early stages of resistance training. But the small sample size and the uncontrolled trial design requires further studies<sup>18</sup>.

### **Chronic pain**

Chronic pain is the most common complication after lung cancer surgery and, indeed, is one of the most commonly reported problems among LTLC survivors<sup>19</sup>. A usually mild but chronic pain after lung cancer surgery is known as the post-thoracotomy pain syndrome and is seen in up to 80% of patients following a thoracotomy, with severe and disabling pain occurring in 5%. Pain could last for 4 years in approximately 30% of the patients<sup>20</sup>. The exact etiology and risk factors for chronic post-thoracotomy pain are not well-understood. Chronic post thoracotomy pain sometimes has neuropathic features, less often is related to tumor recurrence<sup>21</sup>. Although the prevalence of chronic pain may be expected to differ by surgical procedure, especially with the emergence of the muscle and nerve-sparing VATS procedure, reports do not consistently support significant differences<sup>22</sup>. Treatments strategies of post-toracotomy pain vary, and reports for definitive treatment from clinical trials are not available<sup>23</sup>.

### **Fatigue**

Fatigue is common and found in nearly two-thirds of post-surgical NSCLC patients<sup>24</sup>. It's a form of unusual fatigue or loss of energy that takes advantage of the rest and can affect so important to the quality of life. These symptoms may occur at any time, at the beginning of the disease, during and after chemotherapy treatment and may recur years later by the end of treatment<sup>25</sup>. Fatigue is a disorder with effects at different levels: physical, emotional, cognitive, social behavior. In long terms lung cancer survivors fatigue is often related to dyspnea, anxious and depressive symptoms, and decrease functional status but multiple factors, including comorbid conditions, may be considered as contributors physical function<sup>26</sup>. In addition to functional decline, fatigue has been identified as a troublesome symptom. It is unclear if these are associated with aging or comorbidity because few studies has comparison groups. Further research studying the dynamic interplay of these symptoms is important to understand the best way to identify and effectively treat fatigue among lung cancer survivors. The relatively high prevalence of fatigue suggests the need for routine screening of all lung cancer survivors for clinically significant post-treatment fatigue<sup>27</sup>. If moderate or severe fatigue is present, patients should also be assessed for depressive and anxious symptoms<sup>28-30</sup>. Once identified, treatment of mood symptoms includes psychotherapy such as cognitive behavioral therapy and/or administration of medications such as antidepressants with dual anxiolytic effects<sup>31,32</sup>. For mild levels of anxiety and depressive symptoms, exercise and relaxation training can help alleviate symptoms<sup>33,34</sup>. Furthermore, it is important to assess for dyspnea and other pulmonary disease<sup>35</sup>. A comprehensive approach to the treatment of fatigue should encompass screening and management of depressive and anxious symptoms, dyspnea, and pulmonary disorders to promote optimal functioning throughout survivorship.

### **Emotional distress**

The persistence of feelings of depression and anxiety is common in people who have passed an oncological disease and may interfere with daily life<sup>36</sup>. Depression and emotional distress have been reported as higher among people with lung cancer than people with other cancers<sup>37</sup>. In some cases, the anxiety response can be excessive long-term and strong enough to limit the ability to lead their lives, sleep well, eat well. It is estimated that the incidence of depression in patients with lung can-



cer of all stages ranges from 15 to 35%. The anxiety ranges from 63% of lung cancer survivors, 58% of patients with cancer recurrence<sup>38</sup>. Depression is not routinely assessed in patients who receive palliative cancer treatment and the majority of published results of palliative treatment trials in lung cancer fail to address patients' psychologic distress, despite the fact that this has a major impact in determining QOL. It is observed a level of depressive symptoms, especially in patients with poor PS, which indicates that the psychologic status of lung cancer patients needs to be systematically addressed in their overall management<sup>39</sup>. Although depressed mood may be deemed understandable at the start of treatment for cancer, there is little reassurance that most of the reported depression was a transient reaction to the diagnosis. Although did not having often information on patients' emotional status before diagnosis, a study in which patients is observed from their first presentation with chest symptoms reported a doubling of depression, in those with a cancer diagnosis 3 months later. In this Scottish study, depression rates were in the normal population range at baseline but increased significantly and were maintained beyond the start of treatment, whereas anxiety levels dropped spontaneously<sup>40</sup>. Commonly held assumptions about older age and female sex being likely to increase the risk of depression were not supported, which is in accordance with other recent studies of the physically ill<sup>41</sup>. It is also important to stress that male patients are numerically more important in this regard, although they are less likely to reveal their emotional distress. The strong relationship between depression scores and impaired functional status was expected in light of the findings of other studies<sup>42</sup>, but the cause-and-effect nature of the association remains unclear from the literature. Until this is clarified by further research, it is in the interest of patients to consider both possibilities, as reversible causes of impaired activity may otherwise be overlooked. Thus clinical depression is known to cause agitation or anergia and fatigue, which will add to patients' functional limitations but may be improved with antidepressant treatment. This would help maintain optimal activity within the limits of patients' health status<sup>43</sup>. Research in patients with chronic symptoms and airflow limitation has demonstrated a relationship between depression and daily wheeze. Thus lung cancer patients with a history of chronic obstructive airway disease may already be emotionally vulnerable. In the advanced cancer setting, pain is frequently associated with the risk of depression at the expense of considering other physical symptoms. Data show that other common symptoms such as breathlessness, cough,

and tiredness are equally important, and clinicians should be more aware of this<sup>44</sup>. Frequently it is underestimate such symptoms, making the routine use of patient self-assessment mandatory. Often, did not have information on past psychiatric history or social support, which may also be important predictors of depression. Such information can be readily obtained in the context of a brief psychologic assessment. It is important that the well-being of the patient is assessed globally from the start of treatment and that assumptions are not made that the patient's mood is an understandable reaction that will improve as soon as treatment gets underway. The assessment process itself may be valuable to the patient, in feeling that relevant concerns are being explored and interest is being shown in the patient and not just in the disease<sup>45</sup>. It is often claimed that the poor prognosis of lung cancer is a disincentive to treat depression, because patients may not survive long enough to benefit from antidepressant therapy. Such an attitude is antagonistic to managing the whole patient instead of just the disease and is to be discouraged. The value to the patient of having mood disorder identified, discussed, and of receiving appropriate support and advice about intervention is considerable. Treatment of depression can improve the patient's sleep, appetite, concentration, interest, enjoyment, and even tolerance of treatment. The treatment of depression in cancer patients is now well described in the literature<sup>46</sup>. The clinicians can use information that is readily available to them to alert them to depression and thereby aid the provision of comprehensive palliative care.

## **Sexual dysfunction**

A high prevalence of sexual difficulties has been found in survivors of various cancer (breast, colon, ovary). Sexual dysfunction in cancer survivors is usually related to treatment rather than the disease itself. Cancer survivors most at risk for treatment related sexual dysfunction are those whose treatment damages the hormonal systems mediating sexual desire and pleasure. Psychological factors are also important. The risk of sexual dysfunction in cancer survivors is heightened by emotional distress, relationship conflict, and having a partner who is sexually dysfunctional. It is also important to remember that medications used to treat depression, anxiety, pain, nausea during and after cancer treatment frequently have side effects relating to sexual function<sup>47</sup>.

In a review published in 1985, Andersen reported that general sexual disruption or specific difficulties in reaching orgasm ranged from 21% to 39% in pa-

tients with a diagnosis of breast cancer<sup>48</sup>. Recently, we have conducted a study on psychological and sexual disorders in long term breast cancer survivors. The results shows that 34.7% of women with breast cancer had sexual problems, which is consistent with the rates reported in literature<sup>49</sup>.

Sexual dysfunction data for lung cancer survivors are practically nonexistent. Schag's study reported on a range of activities related to intimacy among married and single individuals. In a study of 69 women with lung cancer including 38% treated with curative intent, sexual disruptions were reported by more than 20% of the sample<sup>50</sup>. However, there are no reliable data in the literature nor the therapeutic indications.

### **Late recurrence and new primary cancer**

Recurrent disease may occur in a sub-group of LTLC survivors up to over 10 years after diagnosis, and the survivors are extremely vulnerable to developing new aerodigestive tract tumors, especially subsequent primary lung cancer (SPLC) and other smoking-related cancers. The Lung Cancer Study Group reported that the incidence of SPLC increased 2-fold after five years compared to the preceding five years after surgery. The cumulative risk of developing SPLC or other smoking-related cancers reaches 13%-20% at 6-8 years. Chest radiotherapy and continued smoking were found to significantly increase the risk of SPLC in these patients<sup>51</sup>.

Late effects of radiation and/or chemotherapy among LTLC survivors have not been defined. A few prospective studies have noted significantly lower HRQOL scores for survivors who experienced recurrence compared to scores of those who remained disease free. Increasing survivorship is linked with early cancer detection and the use of a low-dose non-contrast spiral computerized tomography, in high risk patients, as an early detection tool, could increase the number of survivors. A systematic review investigated survival benefits from follow-up of patients with lung cancer at all stages and it was observed a not-significant trend for intensive follow-up to improve survival, for the curative intent treatment subgroup, while asymptomatic recurrence was associated with increased survival, which was statistically significant.

### **Comorbidity**

In general, cancer survivors with other comorbid conditions (comorbidity) possess a 5-to-10 times higher likelihood of poor health and disability when compared to individuals without a history of

cancer or other chronic diseases<sup>52</sup>. In older cancer survivors, the presence of comorbidity was significantly correlated with impaired functional status regardless of the period of time from their cancer diagnosis. The prevalence and severity of comorbidity has been reported to be especially high in lung cancer patients when compared to survivors of other cancer sites.

However, the relative impact of comorbidity on 1-year survival was among the lowest and was disproportionate to the survival rates<sup>53</sup>.

Although most studies report a detrimental effect, the reported relative impact of comorbidity on lung cancer survival is not consistent among studies and may be influenced by the different methods of data collection or by the use of different assessment tools. Although the relative impact of comorbidity on survival in LTLC survivors is largely unknown, the frequency of comorbid conditions was significantly related to both the physical and mental health domains of QOL<sup>54</sup>.

### **NEW PERSPECTIVES BEHAVIORAL INTERVENTION**

The independent or combined effects of lung cancer treatment, aging, smoking and drinking, comorbid conditions, and psychosocial factors likely cause late effects including organ malfunction, chronic fatigue, pain, or premature death among LTLC survivors.

Defining a conceptual model as a guide, analyses should focus on disease specific survival as well as survival from competing causes of death in order to thoroughly evaluate the illness burden in lung cancer survivors. As the aging of the population is inevitable, survivors of lung cancer, especially those who are elderly, should receive continuous attention regarding their health and QOL beyond the expected cure of their primary cancer. Little information is available on the assessment of the late effects of cancer treatment in lung cancer survivors. A change in standard patient management, including the wider application of multimodality treatment options may or may not influence the significance of the issue of the possible late side effects of treatment. The occurrence of secondary cancers is an important health matter among LTLC survivors. These events should be further evaluated for risk factors, including the genetic and molecular effects of smoking and lung cancer treatment and the susceptibility possessed by the host and primary tumor. The impact of multiple factors that influence medical complications and QOL in LTLC survivors needs to be better characterized individually and in combination. The significance of the



interaction between aging-related comorbidities and frailty, and the adverse effects of lung cancer therapy, smoking, and their relationship with the vulnerability for subsequent death or other causes of health deterioration are largely unknown<sup>55</sup>. An understanding of these factors will allow precise risk estimation for efficient disease prevention strategies. One of the most important, and also challenging, steps is to establish a representative patient population to allow multidimensional research, which will enable the assessment of a longitudinal change in QOL and allows for an estimation of significant predictors of QOL in their relationship to different time points in survivorship.

### **Tobacco use and cessation**

Assessment of current and former smoking of lung cancer survivors is relevant because of the potential impact on recurrence, second primaries and comorbid condition. Smoking cessation can slow the decline in pulmonary function, and if smokers quit before extensive pulmonary damage, they may never develop clinically significant chronic obstructive pulmonary disease. Approximately 90% of lung cancer cases are attributed to lifetime smoking<sup>56</sup>. Smoking continues to be the leading cause of preventable death in the United States, and tobacco control is a priority for the Health Promotion of cancer patients.

### **Alcohol use**

A few studies have reported on alcohol use or substance abuse among people with cancer include lung cancer survivors<sup>57,58</sup>. According to the guidelines nutrition there are no reliable data on the correlation between alcohol consumption and the risk of cancer recurrence. Alcohol does have health benefits in some people – for instance, consuming a drink a day can reduce your risk of heart disease. But it also increases the risk of certain cancers, including those of the mouth and throat. While it is not clear whether drinking alcohol can cause cancer recurrence, it can increase risk of a second primary cancer.

### **Nutrition and weight**

There are limited data about weight, nutrition and physical activity an be used to recommend life changes for lung cancer survivors. The America Cancer Society reviewed the scientific evidence regarding the benefit of nutrition and activity intervention to decrease recurrence and increase HRQOL. Appropriate dietary guidance is an important component of self-care. Research to date suggests that overweight and obesity increase the risk of cancer recurrence and mortality (cancer-related and overall). In addition, although there are mixed findings with regard to diet composition and specific food choices, evidence well supports the consumption of plant-based, low saturated fat diets to promote overall health and survival<sup>59</sup>. Lung cancer survivors should for a healthy weight during treatment and recovery increase fruit and vegetable. There are insufficient evidence for recommendation regarding total fat intake. Limited information is available on nutritional supplement.

### **CONCLUSIONS**

The available date suggests that lung cancer survivors are different in profile of comorbidity and vulnerability and that there is a need to identify subgroups of survivors who are at an elevated risk of premature death and diminished QOL, that it is important to promote behavioral intervention and life changes, as reduction in tobacco use, to reduce the potential impact on recurrence and secondary primaries, and that survivorship research is underrepresented (exploring the use of tailored tests, evaluate the long term consequences of treatment in longitudinal study) and remaining an important priority in lung cancer research. The results of the research to date in lung cancer has been focused mainly on short-term survival; there is a shortage of knowledge about the health and quality of life in LTLC survivors at present. Only occasionally in the past, systematic evaluation of survival predictors and QOL attributes were simultaneously conducted in the same study. Intervention research on behavioural changes should be promoted to generate accurate knowledge as well as to develop long-term management and interven-

**TABLE 2. NEW PERSPECTIVES BEHAVIORAL INTERVENTION**

<i>Risk factors</i>	Molecular and genetic
<i>Comorbidity</i>	Physical and mental health
<i>Lifestyle</i>	Smoking, alcohol, nutrition
<i>Late recurrence and new primary cancer</i>	Follow up over ten years

tion strategies. Follow up guidelines in long-term lung-cancer patients include routine cancer surveillance, immunizations, health monitoring, counseling for wellness and health promotion, and cancer screening. Cancer surveillance requires smoking status assessment at each visit, counseling and referral for cessation as needed. Information about smoking cessation (e.g., advice, counseling, and therapy) should be provided to aid the treatment of lung cancer and to improve the quality of life of the patients.

Counseling regarding health promotion and wellness provides maintain a healthy weight, adopt a physically active lifestyle, consume a healthy diet with emphasis on plant sources, limit consumption of alcohol if one consumes alcoholic beverages.

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