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An examination of two dichotomies: Women with lung cancer and living with lung cancer as a chronic disease

TIZIANA VAVALÀ,[1]* MAUREEN RIGNEY,[2]* MARIA LUCIA REALE,[3] SILVIA NOVELLO[3]‡ AND JENNIFER C. KING[2]‡,

[1]*Department of Oncology, Saluzzo, Italy;* [2]*GO_2 Foundation for Lung Cancer, Washington, DC, USA;* [3]*Department of Oncology, University of Turin, San Luigi Gonzaga Hospital, Orbassano, Italy*

ABSTRACT

Lung cancer remains the leading cause of cancer death globally, yet with many recent advances in the diagnosis and treatment of lung cancer, the face of the disease is shifting. Historically, lung cancer is often thought of as a predominantly male disease with more than twice as many men as women being diagnosed worldwide—mostly due to the influence of smoking as the leading risk factor. However, lung cancer is also the second leading cause of cancer death in women and there is a growing population of young women who have never smoked and are being diagnosed. The past decade has seen groundbreaking innovations in both the early detection and treatment of lung cancer. In this new era, survival rates are beginning to increase and many of those diagnosed are finding themselves in a new situation—living long term with a deadly cancer. Here, we review pertinent aspects of women and lung cancer as well as the concept of living with lung cancer as a chronic disease to give a new perspective on the changing face of lung cancer treatment and care.

Key words: chronic disease, gender differences, lung cancer, survivorship.

INTRODUCTION

Due to changes in worldwide smoking patterns from prevention efforts, the advent of lung cancer screening, and significant advancements in lung cancer treatment options, the population of people living with lung cancer today is shifting. Within this population, there are overlapping subgroups characterized by two key dichotomies: women living with a predominantly male disease and people living long term with a deadly cancer.

Correspondence: Maria Lucia Reale, Department of Oncology, AOU San Luigi Regione Gonzole, 10, 10043 Orbassano, Torino, Italy. Email: realemarialucia@gmail.com; Jennifer C. King, GO_2 Foundation for Lung Cancer, 1700 K Street, NW, Suite 660, Washington DC 20006, USA. Email: jking@go2foundation.org

*T.V. and M.R. contributed equally to this study.

‡S.N. and J.C.K. are equal senior contributors.

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Lung cancer is the third most frequently diagnosed cancer and the second leading cause of cancer-related death among women. As in men, the main risk factor for women is cigarette smoking. However, the higher percentage of this disease in younger and non-smoking women, as compared with younger and non-smoking men, suggests the presence of other biological factors which render female lung cancers a distinctive entity, with implications for epidemiology, prevention and treatment. Hormonal status is a potential explanation: oestrogens are involved in lung cancer development and evolution through cell proliferation induced by oestrogen receptor (ER) interaction and cross-talk between ER and growth factor receptors. Furthermore, immunotherapeutic approaches in current clinical practice suggest that gender differences in the immune system influence dissimilar evolution of solid tumours.

Improved diagnosis and treatment now mean that patients with lung cancer are living longer than ever before. Around the globe, more and more people are balancing the great hope and vast uncertainty of living with advanced lung cancer as a chronic disease. A chronic disease lasts 1 or more years, requires ongoing medical attention and/or limits activities of daily living. If uncontrolled, any chronic disease can be life threatening. Little is known about how to live long term with a disease that has traditionally been lethal. This group faces a unique dichotomy of embracing survivorship while still living with a deadly disease. New management strategies and interventions are needed to ensure both proper medical care and appropriate psychosocial support for this growing population.

This review summarizes the literature and evidence for these two overlapping groups of people with lung cancer as well as the many questions that remain to ensure the best treatment and survivorship care.

THE DICHOTOMY OF LUNG CANCER IN WOMEN

Introduction

Literature suggests that lung cancer development and evolution is different between men and women.

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Considering a dissimilar biology and clinical presentation, lung cancer in women should be judged as a distinctive entity.[1,2] About 20% of women (vs 7% of men) with a lung cancer diagnosis have never smoked; as a consequence, hormonal influences are under investigation.[3,4] In the last few years, immunotherapeutic approaches highlighted gender differences in the immune system as possibly influencing a different evolution of solid tumours and lung cancer.[5,6]

However, despite these scientific progresses, no 'gender-driven' approaches are presently available. Personalized sex-based investigations need to be fully developed to significantly improve knowledge about lung cancer in women.

Epidemiology

Lung cancer is the most commonly diagnosed cancer (11.6% of total cases) and the leading cause of cancer death worldwide (18.4% of total cancer deaths).[7] It is the most common cancer among men, with the highest rates in Eastern Asia and Eastern Europe, but considerably lower rates in Africa (Fig. 1).[7]

Among women, it is the third most frequently diagnosed cancer after breast and colorectal cancer. It represents 8.4% of all female cancers, with more than 720 000 new lung cancer cases in 2018. Rates are highest in North America, Northern and Western Europe and Australia/New Zealand. Incidence varies among regions according to different smoking habits, type of exposures, quantity and duration of tobacco consumption (Fig. 1).[7]

Lung cancer is the leading cause of cancer death in men in most countries and the second leading cause of cancer death among women, representing 13.8% of all cancer cases, with more than 570 000 deaths in 2018.[8]

Smoking trends and lung cancer risk

Overall, 71% of all lung cancer deaths and about half of female lung cancer deaths are linked to tobacco consumption.[9] Similar to men, women with a smoking history have a 25-fold increased risk of death from lung cancer compared to never-smokers. For those who quit smoking, the risk gradually decreases over the next 10–15 years.[10–12]

The controversial theory that females can be more vulnerable to the negative consequences of tobacco use has been analysed in prospective studies, which did not confirm a higher risk of lung cancer among females than males with similar levels of tobacco use.[13,14]

Lung cancer also occurs among never-smokers. This subgroup presents with specific clinical and demographic characteristics: adenocarcinoma as the most prevalent histology, higher socio-economic status, fewer comorbidities, Hispanic or Asian ethnicity and oncogenic addiction. It is significant that two-third cases of lung cancer in never-smokers occur in women, and that epidermal growth factor receptor (EGFR) mutation is more common in never-smokers than in previous or current smokers (51% vs 10%) and in women rather than in men (42% vs 14%; all $P < 0.001$).[15,16,17]

Environmental tobacco smoke and additional risk factors

Second-hand smoke also causes lung cancer. The highest mortality rate in this context occurs among women, particularly in societies with high rates of male smoking but low rates of female smoking.[18] In the United States, an estimated 3000 never-smoking women die each year from lung cancer because of second-hand smoke.[19] The prevalence of second-hand smoke exposure for females is approximately 60% higher than for men. Differences among countries are substantial and depend on smoking habits, workplace exposure (in regions where no robust smoke-free policies exist) and home exposure, where women are particularly affected by restricted indoor spaces, fumes from cooking or heating systems and inadequate ventilation systems.[18] Indoor fumes, such as from cooking oil, are important risk factors in several countries. The

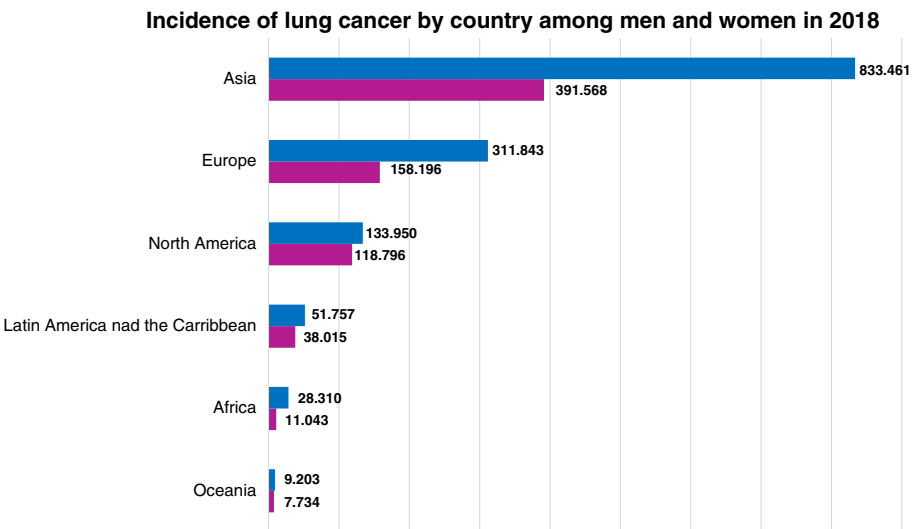

Figure 1 Incidence of lung cancer by country among men (■) and women (■) in 2018. The numbers on the bars indicate the new cases in each country. Data extrapolated and elaborated from GLOBOCAN 2018.[7]

similar incidence of lung cancer among Chinese and Western European women, despite considerable divergence in tobacco consumption between the two regions, may be related to high exposure to kitchen and carbon particles.[7,20]

Environmental or occupational substances such as asbestos, radon, chromium, arsenic, beryllium, vinyl chloride and polycyclic aromatic hydrocarbons are recognized as lung carcinogens.[21] These exposures have been analysed in patients with lung cancer that have known oncogenic driver mutations, a population that is predominantly female. Radon exposure is the leading risk factor for lung cancer among never-smokers. Different studies evaluated correlations between radon exposure and genetic alterations typically expressed by never-smokers, such as EGFR mutations or anaplastic lymphoma kinase (ALK) translocations; however, results were not conclusive.[22,23] A multicentre Spanish case–control study compared median values of residential radon between never-smoker patients (80% of whom were female) with EGFR mutations or ALK translocations with those without a recognized oncogene addiction, obtaining statistically insignificant differences.[22] Another prospective study analysed indoor radon concentrations in EGFR or BRAF mutated and ALK rearranged lung cancer patients (69% of whom were female) detecting a median concentration above World Health Organization (WHO) recommendations in more than 50% of patients, with no differences among the three molecular subgroups.[24]

Some studies have suggested that pre-existing lung diseases increase the risk of lung cancer in women.[25] A recent meta-analysis confirmed the potential connection between emphysema, chronic bronchitis, pneumonia, tuberculosis and lung cancer risk, even after adjustment for smoking status with no differences between men and women.[26] Additional research, specifically focused on the non-smoking and female population, is needed to better understand the potential relationship between these conditions and lung cancer.

A personal history of previous oncological diseases is considered another important risk factor for lung cancer. A recent study demonstrated that the rate of lung cancer increased among breast cancer patients who received radiation therapy compared to breast cancer patients who did not receive it. The risk is augmented in active-smoker patients.[27]

Viral infections can be involved in the development of lung cancer and gender differences may be involved. Ragin *et al*. documented an increased prevalence of human papillomavirus (HPV) in lung cancer cells than in non-cancerous cells.[28] Bae and Kim showed a significant effect of HPV infection in lung cancer in never-smoking women; in particular the summary odds ratio for lung cancer associated with HPV infection was 5.32 for women and 4.78 for the never-smokers. Further studies on the potential role of viral infections in lung cancer are needed.[29]

Gender-specific data about the effects of physical exercise or a controlled diet are still poor. For now, public health strategies recognize the value of healthy food and physical activity in cancer prevention.[30]

Lung cancer prevention and early detection

Global reduction in tobacco consumption reflects progress in many countries to implement tobacco control measures. According to the WHO global report on trends in prevalence of tobacco use 2000–2025 third edition, 136 countries have already established at least one of the recommended measures of tobacco control and 116 countries are seeing their tobacco use rates decline.[31,32] Multiple activities and campaigns coordinated by public institutions, scientific societies and patient associations led to reductions in lung cancer incidence and mortality. The Centers for Disease Control and Prevention (CDC), for example, recommends statewide programmes informing about tobacco risks with mass-reach health communication interventions (through television, radio and social media), preventing initiation, promoting quitting with specific cessation services, eliminating exposure to second-hand smoke with specific smoke-free policies that increase tobacco product prices and decrease tobacco product market and availability. Furthermore, clinicians are called to identify and document patients' tobacco use and to treat smokers in a healthcare setting (with counselling and medications, if needed).[33]

The large, randomized NELSON trial demonstrated the value of low-dose computed tomography (CT) screening in significantly reducing lung cancer mortality in people at high risk of developing lung cancer. The cumulative rate ratio for death from lung cancer at 10 years was 0.76 in the screening group as compared with the control group in high-risk men (main analysis). Subanalyses of data among women (a small subsample) showed a rate ratio for death from lung cancer of 0.67 (Table 1).[34] These data suggest that lung cancer screening could be more effective in women, even if the number of women in the study was relatively low. Final data, from more extensive analyses, are still to come.[34,35]

Hormonal influences

Scientific literature suggests that lung cancer is affected by gender-specific factors. In particular, oestrogens play a significant role not only in normal lung tissue development, but also in lung inflammation and, possibly, lung cancer pathophysiology.[36]

ER belong to the nuclear steroid receptor superfamily, regulating expression of genes implicated in signal transduction, cell cycle control and survival. Two different genes encode for ER proteins (ERα and ERβ) expressed in different tissues and with variable distribution (i.e. normal breast tissue expresses both ERα and ERβ, whereas in lung, ERβ seems to be the dominant form).[37–40] Two studies hypothesized a prognostic value of ERα expression; however, no correlation with survival or poor prognosis was found, nor were there clear gender differences.[4,39,41] Interactions between ER and EGFR pathways were recently suggested: oestrogens induce transcription of oestrogen-responsive genes in the nucleus of lung cells and transactivate the EGFR and other growth factor signalling pathways.[42] While the ERα protein has been detected in lung tumours harbouring EGFR mutations on exon

Table 1 Lung cancer mortality with volume CT screening (data extrapolated from the NELSON trial)

Lung cancer mortality rate ratio in screening group compared to control arm (95% CI)	8-Year follow-up	9-Year follow-up	10-Year follow-up
Males XY	0.76 (0.60–0.97)	0.76 (0.61–0.96)	0.76 (0.61–0.94)
Females XX	0.41 (0.19–0.84)	0.52 (0.28–0.94)	0.67 (0.38–1.14)

Data in women have not yet been published in the final form.[34]
CT, computed tomography.

21, it seems that major biological effects are largely mediated by ERβ which is the key ER expressed in lung cancer. For now, a possible impact on gender-specific treatment is still unknown.[43–47]

With regard to progesterone, Ishibashi *et al.* described progesterone-synthesizing enzymes, such as StAR, P450scc and 3βHSD, in non-small cell lung cancer (NSCLC) tissues from 42 patients. This observation was confirmed in vitro, consequently progesterone receptor (PR) expression in NSCLC tissue could potentially be associated with local progesterone production and its subsequent activity.[48–50] However, clinical studies describing a correlation between low PR expression and prognosis in NSCLC patients are still controversial. In some pre-clinical studies, progesterone supplementation seems to inhibit PR-positive lung tumours evolution while in others, tumour progression was inhibited by its depletion.[49]

Further research is required to better understand the complex interaction between oestrogen and progesterone and possible hormonal effect on development and prognosis of lung cancer in women.

Gender perspectives towards immunotherapy approaches

Qu *et al.* demonstrated gender differences of the immune system in a study of primary cultures of human T cells. This was confirmed by Pinto *et al.*, who reported differential enrichment of immune-related genes in women.[51,52]

Immunological pathways and relevant components of tumour-induced immunosuppression such as cytotoxic T-lymphocyte protein 4 (CTLA-4) and programmed death-ligand 1 (PD-L1) are under evaluation for their potential impact on gender differences in lung cancer. Several meta-analyses have been recently completed on this topic.[53–56]

Botticelli *et al.* selected 36 phase II–III clinical trials. In the cohort of NSCLC patients, they documented no significant benefit with anti-programmed death-1 (PD-1) in overall survival (OS) nor in progression-free survival (PFS) in males versus females (hazard ratio (HR): 0.72, 95% CI: 0.64–0.83 vs HR: 0.81, 95% CI: 0.70–0.94, $P = 0.285$, HR: 0.66, 95% CI: 0.52–0.82 vs HR: 0.85, 95% CI: 0.66–1.09, $P = 0.158$, respectively).[52]

Wu *et al.* suggested in 2018 that males had a longer OS and PFS than females when treated with immune checkpoint inhibitors (ICI) versus controls, but that difference was not significant in NSCLC cohort trials. Of note, these analyses were biased by heterogeneity of trials, consideration of different cancer types and missing data about hormonal and PD-L1 status according to sex.[54]

Grassadonia *et al.* evaluated 12 635 patients with advanced cancer in 21 randomized controlled trials (RCT), finding that ICI were associated with more favourable outcomes in men, particularly considering anti-CTLA-4 agents.[55]

In a similar manner, Conforti *et al.* considered 11 351 patients with advanced cancers in their meta-analysis (67% men and 33% women). Of the overall cohort, 3482 (31%) were NSCLC patients, of whom 1478 were women. The pooled OS HR was 0.72 (95% CI: 0.65–0.79) in men and 0.86 (95% CI: 0.79–0.93) in women treated with ICI versus (respectively) men and women in the control groups.[5] Despite the large number of patients analysed, a smaller number of women was finally considered; in half of the included trials, women represented less than one-third of the overall population. The under-representation of women limits research on the interaction between gender and efficacy of ICI, also considering that previous observations were from meta-analyses and not from individual studies, which were underpowered to explore the effect of gender disparities on outcomes. Lastly, other biological variables might have influenced final results.[56]

These considerations were strengthened by Wallis *et al.*, who evaluated a total of 23 studies in their meta-analysis. A total of 13 721 patients were included, of whom 67.9% were men and 32.1% women with advanced cancer. In particular, 11 selected trials concerned NSCLC patients while two involved small cell lung cancer (SCLC) patients, with a total number of 5424 male patients to 2682 females.[57] In contrast to Conforti *et al.*, in this meta-analysis there were no gender differences in OS from immunotherapy, with a benefit found for both men (HR: 0.75, 95% CI: 0.69–0.81, $P < 0.001$) and women (HR: 0.77, 95% CI: 0.67–0.88, $P = 0.002$).[57] These contradictory results may be explained by a different study selection in terms of type of ICI and regimens (Wallis *et al.*, in contrast to Conforti *et al.*, included, for instance, atezolizumab in their final evaluation), and an update with seven additional trials.[5,57]

The meta-analysis of Wang *et al.* with 9583 advanced lung cancer patients from 15 RCT (68.5% men and 31.5% women) documented a significant OS and PFS benefit from both PD-1/PD-L1 inhibitors alone and PD-1/PD-L1 plus chemotherapy in male patients. In contrast, in females, the benefit of ICI was less consistent: a PFS advantage was observed in the anti-PD-L1 treatment (HR: 0.56, 95% CI: 0.45–0.69) and combination therapy (HR: 0.53, 95% CI: 0.43–0.64), while OS benefit was only found for the anti-PD-1 treatment

(HR: 0.69, 95% CI: 0.52–0.93). This study presented particular limitations such as incomplete OS and PFS data from all included RCT or differences in the number of both men and women which may have finally influenced definitive results.[58]

Finally, Dafni *et al.* included 9236 metastatic NSCLC patients in their network meta-analysis, which compared the efficacy of treatment protocols with at least one ICI, with or without chemotherapy, as a first-line approach. In this study, gender was evaluated for a possible differential effect on PFS/OS benefit: the same treatment combinations confirmed an advantage in both categories, but it was interesting that pembrolizumab/chemotherapy appeared more favourable for women than men.[59]

At the present time, there are not conclusive data to recommend gender-specific treatment protocols. Supplementary prospective studies should be designed to specifically address sex differences. As stated by Colli *et al.*, well-conducted observational studies are needed to balance the meticulous but limited data from RCT. Combined results can represent one more step towards gender-optimized immunotherapeutic strategies.[56]

In summary, many different factors including environmental, hormonal and immunological influences may contribute to the sex-specific differences between lung cancer in men and women. This important area of study is just beginning to be elucidated and more research is needed to understand whether treatment decisions to account for sex should be further personalized in future.

THE DICHOTOMY OF LIVING LONG TERM WITH A DEADLY CANCER

The rapidly changing treatment landscape of lung cancer

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide (18.4% of all cancer deaths).[7] Historically, lung cancer has been considered a recalcitrant cancer, with an extremely low 5-year survival rate. In the United States, the 5-year survival rate is currently 19.4% for all lung cancers and only 5.2% when diagnosed as metastatic disease.[60] The low probability of survival has contributed to nihilism in the provider community and impacted treatment referrals and pathways for people with lung cancer.[61]

Fortunately, advances in treatment and detection have changed the lung cancer landscape dramatically in the past decade. In some countries, screening for lung cancer is available that can shift diagnosis to earlier stages and improve mortality rate for those at high risk.[34,62] In addition, NSCLC now has a host of treatment options, which can be personalized, based on biomarker testing results. Newer agents are resulting in significant improvements in OS for distinct subgroups of lung cancer patients. Immunotherapy has changed the space and improved odds of long-term survival. Notably, a recent study showed a nearly 30% 5-year survival rate on first-line single agent immunotherapy for patients with metastatic NSCLC that had high PD-L1 biomarker levels.[63] In addition, second- and third-generation targeted therapies are improving survival for biomarker-selected subsets of patients. For advanced ALK-rearranged lung cancer, the 5-year OS rate on frontline alectinib is 62.5%.[64,65] For EGFR-mutant lung cancers, osimertinib has now become the primary first-line option in many countries, based on the FLAURA trial where patients with advanced NSCLC on osimertinib had a median 38.6-month OS compared to 31.8 months for erlotinib or gefitinib.[66]

Collectively, these recent advances are resulting in incremental survival improvements, with the latest American Cancer Society statistics showing the largest drop in lung cancer deaths in a single year.[67] Specifically, as of 2017, the death rate has dropped from its peak for lung cancer by 51% among males (since 1990) and by 26% among females (since 2002). Improved survival from new, more effective therapies is resulting in people living with lung cancer while actively on treatment for extended periods of time. Consequently, more and more people are living with lung cancer as a chronic disease.

A brief history of chronic disease

Definitions of chronic disease vary. Broadly defined by the United States Centers for Disease Control, a chronic disease is a condition that lasts 1 or more years, requires ongoing medical attention and/or limits activities of daily living.[68]

In the 1800s, the term ‘chronic’ referred only to the extended period of disease and was not related to severity. In the early part of the 20th century, there was recognition that diseases could be disabling. As early as 1920, Casamajor recognized the changes and adjustments necessary to navigate living with a chronic disease.[69] Perrott and Holland[70] were the first to explicitly link chronic disease to disabling illness in 1937.

One hundred years after Casamajor, chronic disease management has only become more complex. By definition, chronic illnesses ‘may be episodic—have acute phases, be degenerative, or have remissions and create uncertainty for those affected and others around them’[71] (page 632). This uncertainty can make those diagnosed seem unpredictable and less desirable, both occupationally and socially.[72]

Cancer as chronic disease

In 1953, Morton and Morton presented the concept of chronic cancer through 17 cases,[73] but no definition of the term is offered. They found a ‘wide variation’ in the response to treatment and observed ‘prognosis in terms of survival time in an individual situation should be given cautiously since any case may be well above or below the general average’ (page 700). The ability to predict the length of survival of a given individual with cancer remains elusive today.

Importantly, in 1985, the National Coalition for Cancer Survivorship (NCCS) defined survivorship as beginning at the time of diagnosis and continuing for the balance of life. First put forth by an NCCS founder, Mullan,[74] three seasons of survivorship are outlined: acute, extended and permanent. People living with chronic cancer will recognize the acute season but

never achieve the seasons of extended and permanent survival.

The needs of people living with chronic cancer are often not addressed in the literature or in practice. Lists of chronic diseases do not always include cancer.[75] Even within relevant Institute of Medicine reports (2006's *From Cancer Patient to Cancer Survivor: Lost in Transition*; 2012's *Living Well with Chronic Disease*; and 2018's *Long-Term Survivorship after* Cancer *Treatment*), only brief reference is made to management of chronic cancer, with more focus on managing the long-term chronic, effects of cancer treatment.[76–78]

Berlinger and Gusmano[79] points out that, overall, cancer systems of care are not designed to meet the needs of people with chronic cancer. One example of the emotional toll this can take is the bell-ringing ceremonies held in many cancer centres to celebrate the end of treatment. It can be difficult, as a person living with chronic cancer, to be routinely reminded of the fact they will never reach this milestone. If a person with chronic cancer reaches the '5-year survival' benchmark, it is likely to have been accomplished through a complicated trajectory of physical and psychological ups and downs.

In 2012, Harley *et al.*[80] offered a thoughtful exploration of chronic cancer, recognizing limitations of the current, broad concept of survivorship and lack of a definition for chronic cancer and when it begins or ends. Harley *et al.*'s definition—that the cancer is incurable, advanced or metastatic but not at end-stage, and for which there are active treatments available to slow progression, prolong life or control symptoms—mostly resonates for chronic cancer.

Given the current state of cancer care, Harley *et al.*'s definition requires a few revisions (Table 2). Today, clinical benefits from immunotherapies often remain after treatment ends, so treatment no longer needs to be active for the person to remain in the chronic phase. Moreover, many people with cancer have survived for years with a mutation-driven cancer through following drug developments, changing from one targeted tyrosine kinase inhibitor to the next even when the drugs are only available in clinical trials. Harley *et al.*'s definition makes no mention of clinical trials so the proposed adaption (Table 2) includes as a treatment option, a rational clinical trial with expectation of potential clinical benefit for those who qualify.

Nearly 70 years after Morton and Morton's study, much of the chronic disease literature still does not include chronic cancer, focusing on conditions such as diabetes, asthma and hypertension. Chronic disease management models and strategies that do not include cancer do not always translate and may not address the unique needs of this population.

Table 2 Definition of chronic cancer (Adapted from Harley *et al.*,[80])

Defining characteristics of chronic cancer
Active, advanced or metastatic cancer
Is not considered curable
Treatment options including rational clinical trials are available to slow disease, control symptoms and/or prolong life OR the cancer is still responding to a prior treatment option (such as with immunotherapy)
Patient is not at end-stage

Conceptualizing lung cancer as a chronic disease

Despite advances in screening and treatment, lung cancer continues to be seen by some as an untreatable disease, a 'death sentence'.[81,82] Lung cancer is rarely, if ever, included in chronic disease literature; however, people have been living with chronic lung cancer for some time.

In 1942, Goldman explored 11 lung cancer cases in which the patient lived longer than 2 years.[83] The survival length of these patients was remarkable at the time but the article provides no insight into the experience of living with long-term lung cancer. Targeted therapies, in use since the early 2000s, can extend survival for months or years. A 2011 study[84] of 191 people who had taken gefitinib for a minimum of 5.4 years provides another historical example of people living with chronic lung cancer.

However, there is little guidance for those living with chronic lung cancer, who may have much in common with those living with other chronic diseases but also face specific challenges unique to a diagnosis of lung cancer. Survival may have been achieved by moving from one clinical trial to another, always testing the newest treatment approaches. Treatment resistance is a reality for those on targeted therapies so for them, 'normal' includes managing the anticipation of resistance and always looking for the next potential treatment or appropriate clinical trial. One lung cancer survivor, diagnosed with ALK+ lung cancer, recognized the toll this takes on the individual, calling her decade on clinical trials, 'a privilege and a burden'.[84]

Traditionally, lung cancer treatments result in high side-effect burden, which leads to diminished quality of life.[73] Lung cancer's link to smoking and the fact that it is more commonly diagnosed in lower socioeconomic populations[85] can change public perceptions about the disease. People diagnosed with lung cancer have greater unmet psychological and physical needs[86] and experience higher rates of distress compared with other types of cancer.[87]

Lung cancer stigma as a unique challenge

An especially difficult source of distress in lung cancer is stigma, 'a strong feeling in society that being in a particular situation or having a particular illness is something to be ashamed of'.[88] Lung cancer stigma is largely a consequence of the disease's close association with smoking, most notably outlined in the 1964 Surgeon General's report, *Smoking and Health*.[89] When smoking is viewed as a lifestyle choice rather than a powerful addiction, akin to heroin, cocaine and alcohol,[90] lung cancer diagnosed in a person with a smoking history may be viewed as 'self-inflicted'[91] and somehow deserved. The enduring results of lung cancer stigma at societal, interpersonal and personal levels have resulted in great disparities in research funding

and detrimental impacts on the treatment of people with lung cancer.

Research into the effects of lung cancer stigma has been ongoing since 2004.[91] Rates vary by study but Shen *et al.*[92] found 95% of people diagnosed with lung cancer reported having experienced stigma in one form or another. Current smokers, former smokers and never-smokers all may face stigmatization.[93] Individuals with a history of smoking who are diagnosed with lung cancer may experience shame and guilt.[94] Loved ones may say or do things that are stigmatizing[95] and differential treatment by members of the medical team may be delivered or perceived.[61,81] Those affected may experience an increase in depression and isolation[74,81] and tragically, lung cancer stigma can result in patients refusing, delaying or dropping out of treatment.[77–80]

Societal stigma affects everyone diagnosed. Individuals with lung cancer are subject to questions and comments from strangers and acquaintances based on public beliefs about the disease.[96] There are even adverse effects on drug development as lung cancer research has been underfunded compared to other cancers both at governmental levels and from non-profit research funding entities.[97] Until efforts to eliminate stigma are unified,[98] stigma will remain 'a part of the lung cancer experience'[81] (page 16).

A diagnosis of any chronic disease also carries the potential for stigma.[99] Unemployment from a chronic condition, particularly at a younger age, can lead to the perception that the person is no longer a valued member of society.[71] If un/under employment is lost or limited and results in reliance on public assistance programmes, an additional layer of stigma may also be felt.[100] Earnshaw *et al.* observed 'People living with chronic illnesses may be perceived as both unpredictable and having poor prospects, therefore representing poor social exchange partners…'[72] (page 3).

Thus, conceptualizing lung cancer as a chronic disease may compound an existing burden from 'intersectional stigma', defined by Turan *et al.* as the convergence of multiple stigmatized identities within a person or group[101] (page 1). This convergence has the potential to magnify the negative effects of lung cancer stigma on treatment-seeking behaviours, emotional well-being and societal relationships and must be addressed in any proposed management strategy for this population.

Subpopulations within the lung cancer community

As lung treatments change, so does the face of the disease. Much of the progress in treatment has been spurred by the discovery of distinct driver mutations. There are multiple actionable genetic changes for which, in the United States, there are classes of targeted therapies for seven genes (EGFR, ALK, ROS1, BRAF, NTRK, RET and MET). Many clinical trials are underway to target new alterations, including HER2 and KRAS G12C. There are also immunotherapy drug approvals based on PD-L1 protein levels. Only now are differences in the experiences and needs of these unique subpopulations being recognized.

Lung cancers that are driven by single targetable driver mutations are more prevalent in younger, never-smoking patients.[102] The *Genomics of Young Lung Cancer* study includes those diagnosed under the age of 40 and found that over 80% of participants have driver mutations in their cancer.[103] These subclasses of lung cancers often respond to targeted therapies for months or years. Each mutation is found in a small percentage of all lung cancers but those with known biomarkers are connecting online and organizing into global patient groups. Members of these groups often identify themselves as such: I am a ROS1der, an EGFR resister, an ALK positive, etc.

Lung cancer screening by low-dose CT scan has been shown to reduce mortality from the disease for those in high-risk categories.[34,62] A history of heavy smoking and advancing age are the two most important criteria that define high risk.[104] Because those with driver mutations are so often younger never-smokers, they are ineligible for lung cancer screening. As a result, like most cases worldwide, the lung cancer is often diagnosed incidentally or when symptoms of metastatic disease present.[105] Even when symptomatic, many never-smokers report being treated for other conditions before lung cancer is considered a possibility, sometimes delaying diagnosis for months.[106] The uncertainty around what caused the lung cancer and concerns around risk to other relatives that cannot be answered at this time only increase the burden of the disease for never smokers.[106]

Living with lung cancer as a chronic disease as a young person can result in long-term unemployment and financial consequences. Increased role strain exists for those caring for young children and/or ageing parents.[107] Fertility preservation has not been a regular concern for people diagnosed with lung cancer, but is incredibly important for those diagnosed at a young age. Long-term use of newer therapies is likely to lead to effects not yet understood. As a result, traditional care management approaches to lung cancer must be reconsidered.

Moving forward in understanding lung cancer as a chronic disease

The unique needs of those living with chronic lung cancer have been largely unexplored until now. There is a critical need to develop education and interventions to help support people in this unknown space. To do so, it is important to both learn lessons from research into other chronic diseases as well as to learn from the experts themselves—those who have been living long term with the disease. Similar to other chronic cancer patients, they are typically in continual treatment, sometimes for years suspended between unattainable cure and eventual death.

Adapting management strategies to lung cancer

Managing a chronic disease is a lesson in balancing illness-related burdens and demands while striving to

maintain as much normality and quality of life as possible. The physical toll of continual treatment and side effects can make it difficult to meet work and social obligations. Regular appointments and attending to other health-related matters can reduce time for other, more pleasurable events, such as family functions and vacations. It is necessary to plan ahead for potential emergencies and other eventualities.[108,109] Even when able to maintain employment and health insurance, co-pays, transportation and other treatment-related costs can create serious financial concerns. The unpredictability of costs may gravely affect the individual and family's physical and emotional well-being.[109]

The additive problems can result in serious consequences, including adherence issues; diminished health and well-being; increased reliance on external emotional and financial resources; employment uncertainty; and overall strain on relationships and support systems.[108] While not the focus of this review, the significant impact of chronic disease management on caregivers and other loved ones cannot be overstated.

Current chronic disease management strategies exist, but as Hammer *et al.*[110] found, even those for chronic cancer seem incomplete to meet the needs of those receiving extended cancer treatment. None address the unique and specific needs of the lung cancer population. One promising chronic disease framework that may be adapted to lung cancer is THRIVE,[111] which was developed and published in 2018 by an international group of researchers after a thorough analysis and thoughtful synthesis of qualitative and quantitative chronic illness literature. The authors eloquently describe the range of emotions people living with chronic disease experience, which are completely relevant to lung cancer, including grief, loss of control and powerlessness. Disease stigma and potential isolation are also recognized. Structured as determinants of coping with chronic illness, the key findings are organized into the comprehensive, easy to understand THRIVE acronym: *T*herapeutic interventions; *H*abit and behavioural factors; *R*elational/social factors; *I*ndividual differences; *V*alues and beliefs; and *E*motional factors. THRIVE is not disease specific, is respectful of individual coping differences and infinitely personalizable.

It is easy to see coping with lung cancer as a chronic disease in all six THRIVE domains but of particular interest is that of *H*abit and behavioural factors. While for some diagnosed with lung cancer, smoking cessation is an important component of treatment, nearly 80%[112] of those diagnosed today are former or never smokers. A near universal reaction to a cancer diagnosis is the feeling of loss of control. Unlike some chronic diseases, behavioural changes like improving dietary habits and increasing activity levels, while important, will likely not directly influence the course of lung cancer as it might in diabetes and heart disease. THRIVE's *H* is not limited to lifestyle changes but includes establishing routines that are not disease-dependent; developing hobbies; expanding social opportunities; and developing goals that are flexible within the unknowns of the disease trajectory.

An important unknown for people living with chronic lung cancer are the cumulative physical and emotional effects on health-related quality of life from new lung cancer therapies taken over many years. It is premature to speculate on these effects but efforts are underway to study them. The Lung Cancer Registry,[113] which includes participants from 51 countries, and other studies are actively collecting quality of life data and will help elucidate some of the unique and problematic effects on both people with chronic lung cancer as well as long-term, out-of-treatment, survivors.[114] Better understanding of these long-term effects will inform key areas of THRIVE when used in lung cancer, most notably emotional factors and *I*ndividual differences.

Learning from first-hand experience

To begin to understand the key issues of people experiencing extended lung cancer treatment, and to inform future research, we surveyed and held in-person focus groups with people with lung cancer attending an advocacy summit. Those diagnosed at least 2 years prior who had been in treatment continuously or more often than not since diagnosis were invited to participate. Twenty-two survey responses were received, with 19 respondents participating in the focus groups and one interviewed separately. All but two participants were women. The age range at the time of diagnosis was 26–66 years. The range of year of diagnosis was from 2005 to 2017 and three quarters had originally been diagnosed at stage IV. The information gathered from these efforts provides important background for future research in this area.

What's in a name?. Collectively, responses from our participants reflect the real struggle it can be to define oneself when living in this space. Despite the widely accepted use of the NCCS definition of 'survivor', the term does not resonate with everyone diagnosed.[115] For those living with chronic lung cancer, this may be even more so. Prior to the focus groups, we surveyed participants and asked how they refer to themselves within the context of the diagnosis. Only 23% indicated they use the word survivor alone. Another 27% qualified it, saying they are a 'lung cancer survivor'. In subsequent group discussions, we learned that for some, survivor implies treatment has ended or even that the cancer has been cured. Other ways people identified themselves included, 'living while dying' and 'surviving with lung cancer'.

What about the term 'chronic disease'? Taylor and Bury raised concerns that use of the term could '… undermine political and professional awareness of the complexity of illness experiences…'.[116] To understand the thoughts of our group participants, we presented them with the previously outlined definition of chronic disease[68] and asked if it resonated. Interestingly, while all participants fit the definition included in Table 2, the majority did not identify with the concept of chronic lung cancer. Some found it helpful but many were unsure or quite negative in their reactions (Table 3). When asked for alternate terminology, participants who did not like the chronic concept suggested 'living with lung cancer', 'incurable', 'terminal', 'sometimes treatable', 'life-threatening' or 'terminally ill for an extended period of time'.

The struggle to achieve balance. The oft-stated goal after a cancer diagnosis of finding the 'new normal'[117] may never be achieved for those in this space, for whom as Berlinger and Gusmano indicate 'change is constant'[79] (page 122). Jeon *et al.*[109] wrote eloquently about the struggle to find balance while living with a chronic disease. This theme of balance within such an unpredictable disease was echoed by focus group participants as they answered questions related to changes they had made post-diagnosis and tips they could provide to others.

Table 3 Patient perceptions on the concept of lung cancer as a chronic disease. Responses from focus group participants who had been living with advanced lung cancer for more than 2 years

Patient perceptions on lung cancer being described as a chronic disease	
Positively identifies with the concept	Not sure/does not identify
It gives hope. I tell people, 'this is the face of lung cancer'	It's more than chronic
Better than 'survivor' because that implies cure. I tell people, 'I will always have this disease'	It's chronic but only until the point the medication stops working
Chronic allows people not to think of the disease as a death sentence	I'm not comfortable with calling it chronic, but I want it to be
I convinced myself of having a 'chronic' disease because the mind is powerful. It's not curable, but treatable	I want to say 'chronic' but I know it's 'terminal'
It's not the end of my story	If you measure life in 2–3 month increments, scan-to-scan, it's not chronic
Normalizing and explains why I have to go to the doctor so much	I do not expect to live to a 'ripe old age' like with a chronic disease like diabetes
People get it	Chronic sounds like a positive, ambitious goal

The dichotomy of their answers highlights the struggle to find balance (Fig. 2). The importance of being an informed patient was stressed, asking questions and even educating the oncologist, if necessary. But, it was also advised to stay off the internet to avoid depressing statistics and 'worst case' information. There are struggles to prioritize tasks of everyday living. When the focus is on the cancer and related appointments, it can lead to neglect of other health issues. How can going to the dentist be important when living with a life-threatening illness?

It was also difficult to find stability in social relationships. Some lost friends when they were diagnosed. Others did not but said the relationships changed, even deepened. Although facing a terminal diagnosis, some participants did not want the perceptions of others to change. 'Just treat me like a regular person'. Others remarked that because they so often do not look sick, people can forget they have cancer and may not recognize their struggles. The importance of finding 'like' others was also stressed. Especially important are the online mutation-specific groups described above. However, deaths in these groups are inevitable and when one experiences repeated losses that are so similar, the grief can be immense. Survivor guilt, documented by Perloff *et al.* in those living long term with lung cancer,[118] can result from these experiences.

Balance is even difficult in goal setting and life outlook. Participants reported the need to cut out drama and to know where to focus sometimes with limited energies. Others said it is vital to 'grab life by the horns' and to 'live like there is no tomorrow'. The responses highlight the duality of living with lung cancer as a chronic disease (Fig. 2). The strength, resilience and perseverance shared in the experiences of focus groups affirmed how much there is to learn and provide a

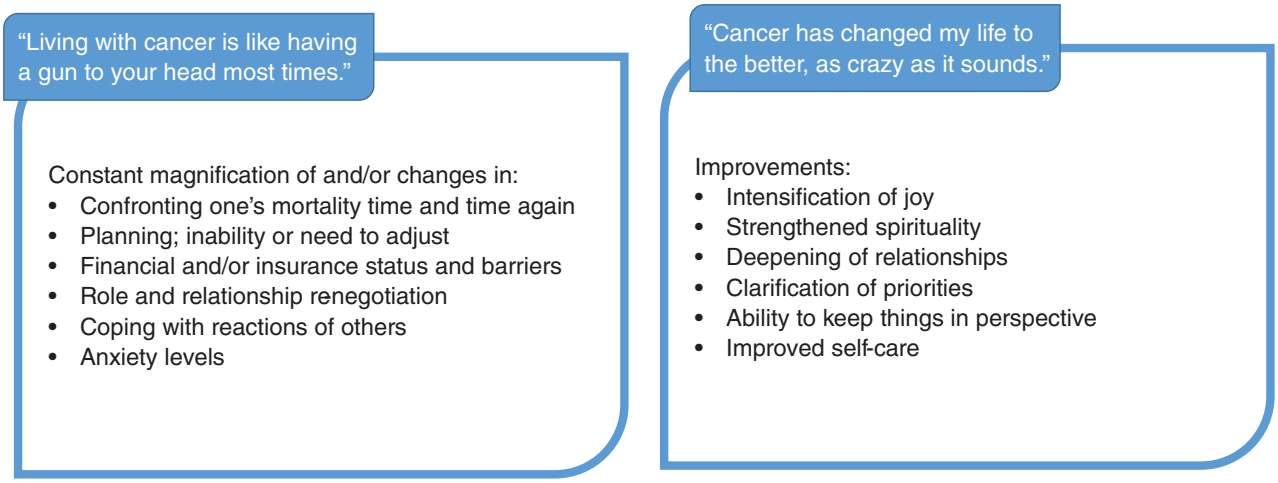

Figure 2 The duality of experiences of living with lung cancer as a chronic disease.

call-to-action for us to learn more and to provide personalized information and support to these individuals.

It is perhaps fitting that we now examine lung cancer as a chronic disease. In 1990, White[119] made the case that research into the causal effects of smoking on lung cancer rates fundamentally changed how chronic disease epidemiology was conducted. The need for improved epidemiological methods to determine if smoking was truly casual led to methodology that has advanced the study of chronic disease today. With today's rapid advances, the lung cancer community faces new challenges: To implement systemic changes and new approaches in order to care for the physical, social and emotional well-being of those living with lung cancer as a chronic disease.

CONCLUSIONS

Even as we know more about lung cancer than ever before, there remains many unknown factors.

It seems women have different susceptibilities to developing lung cancer, and respond to treatment differently. These specific aspects, and others, underline the need for further studies aimed at identifying sex-specific factors. Previous efforts have been not sufficient and more research is urgently needed, considering that lung cancer remains the least funded of the major cancers affecting women.

As people live with lung cancer for longer and longer periods of time, we look to both the cancer and the chronic disease communities to mobilize so that we can understand the specific patient-centric approaches and public health changes that are needed properly care for this fast growing population.

The Authors: T.V. (MD) is an Oncologist and Referent for Lung Cancer Patients Management for SC Oncology, ASL CN1 (Cuneo, Italy),with research interests in lung cancer, gender differences in lung cancer, lung cancer in young adults and translational research. M.L.R. (MD) is an Oncology Fellow, University of Turin, Italy, with research interests in lung cancer, supportive care and gender differences in lung cancer. S.N. (MD, PhD) is an Ordinary Professor at the Oncology Department of the University of Turin, Italy, with research interests in lung cancer, supportive care, screening, gender differences in lung cancer, translational research and new drugs. M.R. (MSW) is Director of Support Initiatives for GO_2 Foundation for Lung Cancer. Her main research interests are the health and well-being of those at risk and living with lung cancer, particularly related to stigma and psychosocial support. J.C.K. (PhD) is Chief Scientific Officer for GO_2 Foundation for Lung Cancer. Her main research interests are in translational oncology and psychosocial and survivorship issues in those living with lung cancer.

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Abbreviations: ALK, anaplastic lymphoma kinase; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte protein 4; EGFR, epidermal growth factor receptor; ER, oestrogen receptor; HPV, human papillomavirus; HR, hazard ratio; ICI, immune checkpoint inhibitor; NCCS, National Coalition for Cancer Survivorship; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, progesterone receptor; RCT, randomized controlled trial; WHO, World Health Organization

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Visual Abstract The dichotomy of lung cancer in women.

Visual Abstract Lung cancer as a chronic disease.