Lung Cancer 131 (2019) 31–39

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Lung cancer survivors and employment: A systematic review

Flora Vayr[a], Frédéric Savall[b,c], Laurence Bigay-Game[d], Jean-Marc Soulat[a,b], Christos Chouaid[e], Fabrice Herin[a,b,*]

[a] Occupational Diseases Department, Toulouse-Purpan, University Hospital Toulouse, F-31000, France
[b] INSERM UMR 1027, Université de Toulouse III, Toulouse, F-31000, France
[c] Laboratory of Molecular Anthropology AMIS, UMR 5288 CNRS, France
[d] Pneumology Department, Toulouse-Purpan, University Hospital Toulouse, F-31000, France
[e] Pneumology Department, Centre Hospitalier Intercommunal Creteil, Ile de France, France

ARTICLE INFO

Keywords:
Lung cancer
Lung neoplasms
Employment
Survivorship
Immunotherapy
Return to work

ABSTRACT

Background: The aim of this systematic review is to identify, in a comprehensive manner, the impact of lung cancer on the employment status of survivors.

Methods: The *Preferred Reported Items for Systematic Reviews and Meta-analyses* (PRISMA) statement was used as a formal guideline. The systematic review includes scientific papers published between January 2000 and October 2018. The search strategy queried the database MEDLINE. Inclusion criteria comprised: (1) inclusion of patients diagnosed with lung cancer (LC) (2); assessment of employment status or employment outcomes or work adjustments or return to work (3); inclusion of scientific papers published in peer-reviewed journals (4); inclusion of articles written either in English or in French. Literature reviews were not included.

Results: A total of 642 scientific papers were retrieved. Twenty-three articles were included in the systematic review: 5 longitudinal studies and 18 cross-sectional studies. LC survivors are 2–3 times more likely to be unemployed as compared with control groups. Previous studies highlight a median duration of sickness absence increased for LC survivors compared to control groups. The strongest decline in earnings was observed among LC survivors as compared to other cancer types.

Conclusions: LC is associated with a significant impact on employment of patients. The promising results of recent therapeutic strategies could lead to a better social and professional prognosis. A reduction of indirect costs is to be expected.

1. Introduction

For years, lung cancer (LC) has been considered as a severe disease characterised by poor prognosis and short-term survival. Nowadays, promising results of new therapies are broadening the therapeutic perspectives for LC patients. Early detection and more effective treatments have provided a notable improvement of long-term survival rates [1,2]. Immunotherapy, with highly selective humanized monoclonal antibodies, have shown satisfying results in terms of efficiency and low toxicity [3,4]. Despite the severity of the disease, more individuals are now able to resume their normal activities after diagnosis and treatment. As their mental and physical functioning is improving, patients can consider a social and professional rehabilitation. Return to work (RTW) is defined as recovery of the ability to perform work tasks after sick leave. This process is challenging for patients, who may face sequelae of the disease, side effects of their past and current treatments and potentially a psychological trauma after cancer. However, the professional rehabilitation of cancer survivors represents a crucial threshold and should be medically supported [5]. RTW is associated with health-related quality of life of patients [6]. Resuming work helps to regain a sense of normalcy, self-satisfaction and confidence. Moreover, RTW represents a priority for economic reasons, both at the individual and societal scale. LC can be associated with an increased social vulnerability and impoverishment. On a larger scale, LC and its treatments raise challenges in terms of economic sustainability. A clear understanding of the impact of new therapies is crucial in order to determine their cost-efficiency. Thus, the promising efficiency of immunotherapies could allow RTW of LC survivors and reduce indirect costs of the disease and its treatments. This remains to be demonstrated but represents an enthusiastic pathway for the economic sustainability

* Corresponding author at: Occupational Diseases Department, University Hospital, Toulouse, Bâtiment Turiaf, Place du Dr Baylac, 31059, Toulouse Cedex 9, France.
E-mail address: herin.f@chu-toulouse.fr (F. Herin).

https://doi.org/10.1016/j.lungcan.2019.03.010
Received 20 December 2018; Received in revised form 7 March 2019; Accepted 9 March 2019

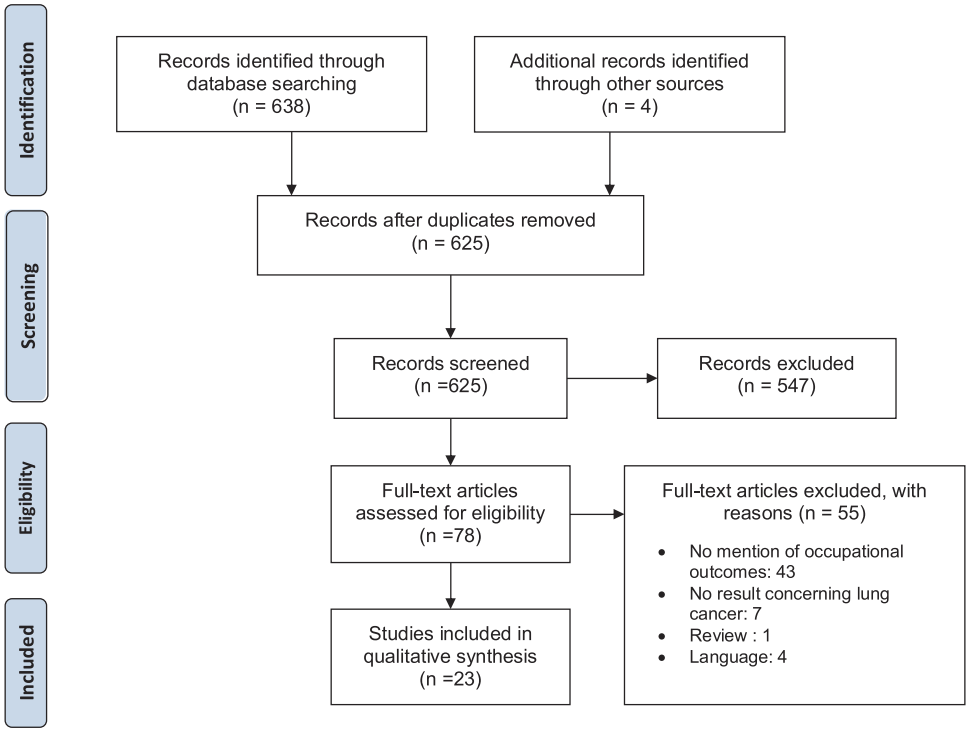

Fig. 1. Flow chart.

of immunotherapeutic molecules. As LC long-term survivorship represents a recent topic, few studies have addressed the question of employment status and return to work of LC survivors. The aim of this systematic review is to precise the risk of unemployment among LC patients, to examine the economic consequences of unemployment on LC patients and society and to identify a potential impact of the therapeutic evolution on the RTW prognosis of patients.

2. Methods

2.1. Protocol

The "Preferred Reported Items for Systematic Reviews and Meta-analyses" (PRISMA) statement was used as a formal guideline [7]. Details are provided in Additional file 1 (S1_Appendix. PRISMA Checklist).

2.2. Eligibility criteria

Studies were included if they met the following criteria: (1) inclusion of patients diagnosed with LC (2); assessment of employment status or employment outcomes or work adjustments or RTW (3); inclusion of scientific papers published in peer-reviewed journals (4); inclusion of articles written either in English or in French. Literature reviews were not included.

2.3. Search strategy

A literature search was conducted using the electronic database MEDLINE. Studies published from January 2000 to October 2018 were retrieved. The following search terms were included: *lung neoplasms, return to work, employment, survivorship*. When available, Medical Subject Headings terms were used. In addition, the reference lists of selected articles were further reviewed to identify additional relevant papers. An overview of search terms is provided in Additional file 2 (S2_Appendix. Extensive overview of search terms).

2.4. Study selection

Titles and abstracts were reviewed to identify relevant articles by two independent reviewers. A second selection performed by two reviewers independently established the relevance of the full-text articles according to the predefined inclusion and non-inclusion criteria. When the initial reviewers disagreed on a study, a third reviewer was responsible for the final decision.

2.5. Data extraction

Data extracted comprised: identification of the article (authors, year of publication, journal) and the methodology used. The data gathered was used to address the following aspects: employment status of LC survivors, work adjustments performed to facilitate RTW of LC survivors, economic difficulties related to the impact of LC on employment.

2.6. Methodological quality assessment

The methodological quality of articles included was assessed with the Methodological Index for Non-randomized Studies (MINORS) [8]. Each study was scored on 12 components: clearly stated aim, inclusion of consecutive patients and response rate, prospective collection of data, endpoints appropriate to the aim of the study, unbiased assessment of study end points, follow-up period appropriate to the aim of the study, loss to follow-up, prospective calculation of the study size. In the case of comparative study, the four following items were added: an adequate control group, contemporary groups, baseline equivalence of groups, adequate statistical analysis. Scientific articles received 0–2 points for each of these 12 items. The global ideal score was 16 for non-comparative studies and 24 for comparative studies.

3. Results

3.1. Description of included studies

A total of 642 papers were retrieved from the electronic database,

Table 1
Methodological quality assessment based on MINORS.

Source	Aim [b]	Rate [c]	Data [d]	Measure [e]	Bias [f]	Time [g]	Loss [h]	Size [i]	Control [j]	Contemp [k]	Factor [l]	Analysis [m]	Total [n]
Yamauchi et al [18]	2	0	2	2	2	2	0	0	NA	NA	NA	NA	10/16
Endo et al [19]	2	2	2	2	2	2	0	0	2	2	0	2	18/24
Nekhlyudov et al [9]	2	2	2	2	2	2	1	0	2	2	1	2	20/24
Pearce et al [26]	2	0	2	2	2	2	0	0	2	0	0	2	14/24
Tevaarwerk et al [10]	2	2	2	2	2	2	2	0	2	2	0	2	20/24
Kim et al [22]	2	2	2	2	2	2	1	0	2	2	2	2	21/24
Torp et al [24]	2	2	2	2	2	2	2	0	2	2	2	2	22/24
Ross et al [27]	2	2	2	2	2	2	2	0	2	2	0	2	20/24
Lister J et al [31]	2	0	2	2	2	2	0	0	NA	NA	NA	NA	10/16
Sjövall et al [28]	2	2	2	2	2	2	0	0	2	2	2	2	20/24
Roelen C [16]	2	2	2	2	2	2	0	0	2	2	1	2	19/24
Roelen C [15]	2	2	2	2	2	2	0	0	2	2	1	2	19/24
Roelen et al [17]	2	2	2	2	2	2	0	0	2	2	0	2	18/24
Stanisic et al [30]	2	0	2	2	2	2	0	0	NA	NA	NA	NA	10/16
Earle et al [11]	2	2	2	2	2	2	1	0	2	2	0	2	19/24
Park et al [23]	2	2	2	2	2	2	0	0	2	2	0	2	18/24
Syse et al [25]	2	2	2	2	2	2	0	0	2	0	0	2	16/24
Molina et al [29]	2	2	2	2	2	2	2	0	NA	NA	NA	NA	14/16
Short et al [12]	2	2	2	2	2	2	1	0	2	2	2	2	21/24
Bednarek et al [13]	2	2	2	2	2	2	1	0	NA	NA	NA	NA	11/16
Taskila-Abrandt et al [20]	2	2	2	2	2	2	0	0	2	2	2	2	20/24
Taskila-Abrandt et al [21]	2	2	2	2	2	2	0	0	2	2	2	2	20/24
Bradley et al [14]	2	2	2	2	2	2	2	2	NA	NA	NA	NA	16/16

NA: not applicable.
0: not reported; 1: reported but inadequate; 2 reported and adequate.
[a]Assessed with the adapted Methodological Index for Non-Randomized Studies (MINORS).
[b] Clearly stated aim (0,1,2 points).
[c] Inclusion of consecutive patients and response rate (0,[[1,2]]].
[d] Prospective collection of data (0,[[1,2]]].
[e] Endpoints appropriate to the aim of the study (0,1,2).
[f] Unbiased assessment of study end points (0 or 2).
[g] Follow-up period appropriate to the aim of the study (0,1,2).
[h] Loss to follow-up less than 5% (0,1,2).
[i] Prospective calculation of the study size (0 or 2).
[j] An adequate control group (in the case of comparative study) (0,1,2).
[k] Contemporary groups (in the case of comparative study) (0 or 2).
[l] Baseline equivalence of groups (in the case of comparative study) (0,1,2).
[m] Adequate statistical analysis (in the case of comparative study) (0 or 2).
[n] Total: minimum equals 0; maximum equals 24 points.

including 17 duplicates. Titles and abstracts were analysed and 78 papers were considered relevant for the topic. After assessment of inclusion and non-inclusion criteria, 23 articles were included in the systematic review. Five were longitudinal studies and 18 were cross-sectional studies. The reasons for exclusion are reported in the flow chart (Fig. 1. Flow chart). Details concerning their quality assessment are given in Table 1 (Table 1). Methodological quality assessment based on MINORS). Six included articles were from the United States of America (USA) [9–14], 3 of each were from the Netherlands [15–17], 2 of each were from Japan [18,19], 2 of each were from Finland [20,21], 2 of each were from Korea [22,23], 2 of each were from Norway [24,25], and one of each was from Ireland [26], Denmark [27], Swiss [28], Spain [29]. Finally, two articles analysed data from different European countries [30,31]. Main results are reported in Table 2 (Table 2 Main results).

3.2. Employment status

Working age LC survivors are characterized by high rates of unemployment. Syse et al (Norway, 2008) described the employment probability by cancer form and stage. LC survivors were less likely to be employed than the reference group (no cancer). This difference was found in both genders (Odds Ratio (OR) $_{men}$ = 0.37; 95% confidence interval (CI): 0.31–0.45 versus OR $_{women}$ = 0.58; 95% CI: 0.48–0.71) [25]. Likewise, LC survivors were less likely to be employed than cancer-free patients (Relative risk (RR) = 0.63; 95% CI: 0.56–0.71) in a cohort of 934 LC patients. LC patients were more likely to be retired in 1997 in comparison to referents matched for sex and age (RR = 1.53; 95% CI: 1.39–1.69). However, they did not have the highest risk of retirement in 1997 compared to other cancer types. This was explained by authors by the low life expectancy of patients, who often did not live long enough to retire (Finland, 2005) [20].

Moreover, LC patients seem to face earlier job loss according to two longitudinal studies. Earle et al (USA, 2010) reported that LC is associated with a higher risk of departing the workforce than the control group (colon cancer) (OR = 2.83; 95% CI: 1.54–5.19). The type of cancer was found to be associated with the time until job loss of patients. Thus, having a LC was associated with an earlier job loss than the reference group (stomach cancer) (HR = 1.31; 95% CI: 1.12–1.53) [11]. LC was a predictor of early job loss (Hazard ratio (HR) = 1.31 [1.12–1.53]) in a longitudinal study (Korea, 2008) [23].

The impact of LC on employment persists years after the diagnosis. Two to three years after diagnosis, 279 patients with LC were less likely to be employed as compared with a reference group in a Finland study (RR = 0.45; 95% CI: 0.34–0.59) (Finland, 2004) [21]. Kim et al (Korea, 2014) compared the employment status of 829 LC survivors at the time of diagnosis and at a median of 4.11 years after diagnosis with the general population. In total, 260 (31.4%) patients were unemployed at the time of diagnosis. After diagnosis and treatment, LC survivors were more likely to be unemployed (61.2%) than the general population (adjusted OR = 2.31; 95% CI: 1.66–3.22) and than survivors at the time of diagnosis (adjusted OR = 24.30; 95% CI: 11.40–51.79) [22].

Table 2
Main results.

Source	Date	Country	Study design	Population	Control group	Main results related to lung cancer
Employment status						
Torp et al [24]	2013	Norway	Longitudinal study	3,278 cancer survivors, 58 LC patients	N = 6368 No cancer	• Higher rate of unemployment 5 years after diagnosis on univariate analysis (OR female = 0.39; 95% CI: 0.19–0.81; p-value = 0.011; OR male = 0.39; 95% CI: 0.18–0.83; p-value = 0.014), and multivariate analysis for women (aOR = 0.32; 95% CI: 0.15–0.70; p-value = 0.004)
Earle et al [11]	2010	United States	Longitudinal study	2,422 cancer survivors, 812 LC patients,	N = 1610 Colon cancer	• Higher risk of departing the workforce (OR = 2.83; 95% CI: 1.54–5.19). • Earlier job loss (HR = 1.31; 95% CI: 1.12–1.53)
Short et al [12]	2005	United States	Longitudinal study	1,433 cancer survivors, 51 respiratory cancer patients	N = 94 Colon cancer	• Increased risk of quitting working (aOR = 1.21; 95% CI: 0.473–3.139) on univariate analysis • After adjustments, these results were not significant
Kim et al [22]	2014	Korea	Cross sectional	829 LC survivors,	N = 1,000 Volunteers from the general population	• Unemployment at diagnosis: 260 (31.4%) • After median of 4.11 years, higher rate of unemployment compared to the general population (adjusted OR = 2.31; 95% CI: 1.66–3.22) and to survivors at the time of diagnosis (adjusted OR = 24.30; 95% CI: 11.40–51.79)
Syse et al [25]	2008	Norway	Cross sectional	34,000 cancer survivors, 1068 LC patients,	N = 1,082,191 No cancer	• Higher risk of unemployment (OR men = 0.37; 95% CI: 0.31–0.45 versus OR women = 0.58; 95% CI: 0.48–0.71)
Taskila-Abrandt et al [20]	2005	Finland	Cross sectional	46,312 cancer survivors, 934 LC patients	N = 46,312 No cancer	• Higher risk of unemployment (RR = 0.63; 95% CI: 0.56–0.71)
Taskila-Abrandt et al [21]	2004	Finland	Cross sectional	12,542 cancer survivors, 279 LC patients	N = 12,542 No cancer	• Higher rate of unemployment 2-3 years after diagnosis (RR = 0.45; 95% CI: 0.34–0.59)
Tevaarwerk et al [10]	2016	United States	Cross sectional	680 cancer survivors, 134 LC patients	N = 282 Breast cancer	• Among the employment group, 16 LC patients were stably working and 58 were no longer working. This difference was not significant in a univariate analysis (OR = 1.0; 95% CI: 0.5–2.0)
Park et al [23]	2008	Korea	Longitudinal study	5,396 cancer survivors, 420 LC patients	N = 1312 Stomach cancer	• Significant predictor of early job loss (HR = 1.31 [1.12-1.53])
Bednarek et al [13]	2005	United States	Cross sectional	253 cancer survivors, 53 LC patients	NA	• 21 of 53 LC patients retired 1-7 years after diagnosis, 16 retired prior to diagnosis and 16 were employed 5-7 years after diagnosis
Bradley et al [14]	2002	United States	Cross sectional	253 cancer survivors, 58 LC patients	NA	• Among 36 male LC patients, 38.9% were currently employed 5-7 years post-diagnosis • Among 22 female LC survivors, 22.7% were currently employed at the time of study: 4 in full-time and 1 in part-time
Sick leave and return to work						
Endo et al [19]	2016	Japan	Longitudinal study	1,278 cancer survivors, 162 LC patients	N = 282 Gastric cancer	• Median time to RTW: 96.5 days • 122 patients returned to work: 31 had a full-time job and 91 performed a partial RTW • In a univariate analysis, longer time to full RTW (HR = 0.33; 95% CI: 0.24–0.45). This difference remained significant in the multivariate analysis (HR = 0.29; 95% CI: 0.21–0.39)
Park et al [23]	2008	Korea	Longitudinal study	5,396 cancer survivors, 420 LC patients	N = 1312 Stomach cancer	• Significant predictor of delayed re-employment (HR = 0.79 [0.55-1.16])
Sjövall et al [28]	2012	Swiss	Cross sectional	2,738 cancer survivors, 393 LC patients	N = 12,246 No cancer	• Highest increase in sick days both pre- and post-diagnosis (12 times the amount of sick days compared to their matched control patients) • A pick in sick leave 5 months post diagnosis • One year after diagnosis, 63% of LC patients were still on sick leave
Molina et al [29]	2008	Spain	Cross sectional	347 cancer survivors, 35 LC patients	NA	• Having LC was associated with continuing sick leave (p-value < 0.001). • LC was strongly associated with a low prognosis of RTW (85% of LC patients did not return to work)
Roelen et al [17]	2011	Netherlands	Cross sectional	5,074 cancer survivors, 448 LC patients	N = 271,834 Non malignant chronic disorders	• Median duration of sickness absence: 490 days (404-576). • 204 patients (45%) returned to full time job 2 years after diagnosis, 65 patients (15%) received a disability pension, 88 patients resigned (20%) and 91 died (20%). • Higher sick days percentages. 59% of them were absent form work for more than 12 months.

(*continued on next page*)

Table 2 (*continued*)

Source	Date	Country	Study design	Population	Control group	Main results related to lung cancer
Ross et al [27]	2012	Denmark	Cross sectional	1,490 cancer survivors, 73 LC patients	N = 1,417 Other cancers	• Less likely to have returned to work after diagnosis (aOR = 0.10; 95% CI: 0.02–0.53). • Less likely to be currently employed (aOR = 0.09; 95% CI: 0.03–0.27)
Roelen C [16]	2011	Netherlands	Cross sectional	In 2002: 1209 cancer survivors, 132 LC patients In 2005: 1522 cancer survivors, 145 LC patients In 2008: 1556 cancer survivors, 166 LC patients	In 2002: N = 841 In 2005: N = 995 In 2008: N = 977 Cardiovascular disorders	• Time to partial RTW after LC in 2008 was longer than in 2002 (HR = 0.56; 95% CI: 0.37–0.85). • Time to full RTW was longer after LC diagnosed in 2008 as compared to 2002 (HR = 0.46; 95% CI: 0.29–0.72). • In 2002, among 44 female and 88 male patients, 65% of LC survivors returned to part-time job after diagnosis and 61% returned to full-time job. These proportions were significantly decreased in 2005 (52% partial RTW, 47% full RTW) and in 2008 (41% partial RTW, 33% full RTW) (p-value < 0.01)
Roelen C [15]	2011	Netherlands	Cross sectional	5,234 cancer survivors, 456 LC patients,	N = 318 Skin cancer	• Longer time to partial RTW (median days: 377, HR = 1.88; 95% CI: 1.51–2.25). • Longer time to full RTW (median days: 484, HR = 1.61; 95% CI: 1.31–1.92)
Work adjustments						
Nekhlyudov et al [9]	2016	United States	Cross sectional	615 cancer survivors, 117 LC patients	N = 498 Other cancers	• More likely to report making some change in employment or career (80%) (p < 0.001) • More likely to experiment any changes with work-related function and/or productivity (approximately 50%) (p < 0.001)
Short et al [12]	2005	United States	Longitudinal study	1,433 cancer survivors, 51 respiratory cancer patients	N = 94 Colon cancer	• Higher rate of work-related disability (aOR male = 0.603; 95% CI: 0.146–2.488 versus aOR female = 1.468; 95% CI: 0.468–4.607) on univariate analysis • After adjustments, these results were not significant
Economic consequences for LC survivors						
Syse et al [25]	2008	Norway	Cross sectional	34,000 cancer survivors, 1068 LC patients,	1,082,191 No cancer	• Men with LC earned -49,3% than the reference group (p-value < 0.05). • Women earned -33,5% than the reference group (p-value < 0.05)
Nekhlyudov et al [9]	2016	United States	Cross sectional	615 cancer survivors, 117 LC patients	N = 498 Other cancers	• More likely to stay at job due to concern about losing insurance (35%) of patients (p = 0.009)
Bradley et al [14]	2002	United States	Cross sectional	253 cancer survivors, LC patients	NA	• 36 male patients: • 38.9% currently employed 5-7 years post-diagnosis • 44.9 hours worked per week • Annual wage: $51,600 • 22 female patients: • 22.7% were currently employed 5-7 years post-diagnosis • 43 hours worked per week • Annual wage: $36,000
Social impact of the work loss						
Yamauchi et al [18]	2017	Japan	Cross sectional	NA Patient Survey, Basic survey on Wage structure, Labour force survey	NA	• Cost of work loss on treatment days in 2011: 314.10 million USD • Work loss: 495.32 million USD in the case that the product of "employment rate coefficient x productivity coefficient" is 0.5 • Work loss: 990.63 million USD in the case that the product of "employment rate coefficient x productivity coefficient" is 0 (LC survivors not able to work)
Pearce et al [26]	2016	Ireland	Cross sectional	233,000 projected deaths from all invasive cancers in Ireland between 2011 and 2030 48,922 projected deaths from LC	N = 184,078 Other cancers	• Value of lost paid production: 2.4 billion euros • Value of lost household production: 12,493 million euros • Value of lost paid production per death: 49,116 euros • Value of lost household production: 255,369 euros per death • LC was the costliest cancer
Impact of drug therapy						

(*continued on next page*)

Table 2 (*continued*)

Source	Date	Country	Study design	Population	Control group	Main results related to lung cancer
Stanisic et al [30]	2010	Europe	Cross sectional	France N = 1,481 Germany N = 1,492 Italy N = 820 Spain N = 745	NA	● Patients treated with bevacizumab-based combination therapy ● France: mean costs savings related to productivity losses were €21,667 at year 1 and €39,001 at year 1.5 per salaried progression-free patient returning to work ● Germany: mean costs savings represented respectively €21,171 and €38,107 per patient ● Italy, mean costs results in €17,578 at year 1 and €31,640 ● Spain, mean costs savings were estimated at €12,401 at year 1 and €22,322 per patient still working
Lister J et al [31]	2012	Europe	Cross sectional	NA Health economic model developed with a Markov model	NA	● The bevacizumab treatment group had increased gains in productivity and reductions of societal expenses (€5216, €6739, €3455 and €4046 per patient in France, Germany, Italy and Spain, respectively) as compared with the chemotherapy group (€1774, €2278, €1178 and €1377, respectively).

aOR: adjusted odds ration; CI: confidence interval; HR: hazard ratio; LC: lung cancer; NA: not applicable; OR: odds ratio; RR: relative risk; RTW: return to work.

Compared with control group, 30 women and 28 men with LC were less often employed 5 years after diagnosis ($OR_{female} = 0.39$; 95% CI: 0.19–0.81; *p*-value = 0.011; $OR_{male} = 0.39$; 95% CI: 0.18–0.83; *p*-value = 0.014). After adjustments with socio-demographic and work-related variables, the odd ratio remained significant for women (aOR = 0.32; 95% CI: 0.15–0.70; *p*-value = 0.004) (Norway, 2013) [24].

Predictive factors of the employment rate of LC survivors have been explored in a cross-sectional study. In a univariate analysis, factors associated with unemployment were older age, lower educational level, low household income and the number of comorbidities. Concerning the quality of life scales, poor social functioning (assessed by 2 items in a questionnaire: the interaction with the family and social activities), fatigue, dyspnea and insomnia were associated with unemployment. In a multivariate analysis, the factors significantly associated with unemployment after LC treatment were: age more than 50 years (aOR = 5.21; 95% CI: 2.10–12.93), monthly household income less than $3000 (aOR = 2.54; 95% CI: 1.67–3.85), 2 or more comorbidities (aOR = 1.78; 95% CI: 1.10–2.89), and poor social functioning (aOR = 8.02; 95% CI: 1.74–37.05). 322 (56.6%) patients had returned to work after diagnosis among the 569 patients who were employed at the time of diagnosis. Fatigue (78.6%) was the most frequent symptom reported by LC survivors who were working, along with lower wages (9.2%), reduced ability to perform work tasks (9.2%) and meaningless work (1.7%). Physical limitations (39%), fatigue (31.8%) and fear of worsening health (24.7%) were the most frequently reported items for LC survivors who were unemployed, retired or homemakers (Korea, 2014) [22].

3.3. Sick leave

Two longitudinal studies focus on the duration of sick leaves related to LC. LC was a significant predictor of delayed re-employment (HR = 0.79 [0.55–1.16]) in a cohort of 420 patients (Korea, 2008) [23]. Endo et al (Japan, 2016) explored return to work after sick leave due to cancer in a 365-day cohort including 162 LC patients. Lung cancer was characterized by a lower cumulative full RTW rate than other cancers. Within 365 days after initial days of sickness absence, the median time to partial/full RTW was 96.5 days. Twenty-two patients died, 7 resigned, 11 were disabled. One hundred twenty-two patients returned to work: 31 had a full-time job and 91 performed a partial RTW. In a univariate analysis, LC survivors had a longer time to full RTW than patients with the reference group (gastric cancer) (HR = 0.33; 95% CI: 0.24–0.45), *p*-value < 0.01). This difference remained significant in the multivariate analysis (HR = 0.29; 95% CI: 0.21–0.39; *p*-value < 0.01) [19].

Cross-sectional studies confirm these results. According to Molina (Spain, 2008), having LC was associated with continuing sick leave (*p*-value < 0.001). LC was strongly associated with a low prognosis of RTW in a cohort of 35 patients (85% of LC patients did not return to work) [29]. Among 448 LC patients (Netherlands, 2011), the median duration of sickness absence was 490 days (404–576). Two hundred and four patients (45%) returned to full time job 2 years after diagnosis, 65 patients (15%) received a disability pension, 88 patients resigned (20%) and 91 died (20%). Sick days percentages were higher as compared with the reference group for LC patients. Fifty-nine percent of them were absent form work for more than 12 months. LC employees had the worst RTW prognosis as compared to patients with non-malignant chronic disorders [17].

Among 73 LC patients, 19 were employed and had returned to work at a median of 2.8 years after diagnosis: 36% were currently employed and 15% had returned to work (Denmark, 2012) [27].

The duration of sick leave appears to be increased for LC patients both pre- and post-diagnosis. In a cohort of 2738 patients including 393 LC patients, Sjövall et al (Swiss, 2012) described that LC patients had the highest increase in sick days (sick leave and disability pension) both

pre- and post-diagnosis compared to cancer-free patients. LC patients had 12 times the amount of sick days compared to their matched control patients. Likewise, disability pension was more common among LC patients. A pick in sick leave was reported 5 months post diagnosis. One year after diagnosis, 63% of LC patients were still on sick leave. The authors highlight that for this cancer type, sick leave increased already during the pre-diagnostic phase. LC survivors had the highest number of sick days. Their decrease in sick leave after diagnosis was slower than in the control group [28].

The duration of sick leave is increased and return to work is delayed for LC patients. This pattern also applies for partial RTW. In a cohort of 456 LC patients, the time to partial RTW was longer for LC survivors as compared with the reference group (skin cancer) (median days: 377, HR = 1.88; 95% CI: 1.51–2.25). The time to full RTW was also longer as compared with the reference group (median days: 484, HR = 1.61; 95% CI: 1.31–1.92) (Netherlands, 2011) [15]. The time to partial RTW after LC in 2008 was longer than in 2002 (HR = 0.56; 95% CI: 0.37–0.85) (Netherlands, 2011) [16].

3.4. Work adjustments

In a cohort of 615 patients including 117 LC patients (USA, 2016), LC survivors were more likely to report changes in their employment or career decisions, including extended paid time off, unpaid time off, changing to a flexible schedule, changing from full time to part time, changing to a less demanding job ($p < 0.001$). Compared to other cancers, LC survivors experienced more interference between the disease and their physical or mental tasks at work. They reported an increased change of productivity ($p < 0.001$) [9]. Likewise, in another American cohort of cancer survivors (USA, 2005), respiratory cancer was associated with having work-related disability in both male and female patients ($aOR_{male} = 0.603$; 95% CI: 0.146–2.488 versus $aOR_{female} = 1.468$; 95% CI: 0.468–4.607) [12].

3.5. Economic consequences for LC survivors

LC survivors are confronted with a loss of wages after the diagnosis and treatment. The impact of cancer on employment and earnings at the individual level has been explored in a few countries. The strongest decline in earnings was observed for leukemia, brain, bone and lung patients in a cross-sectional study which included 34,000 cancer survivors. The modeled income for reference categories was $40,400 for men and $35,500 for women. Men with LC earned annually -49,3% than the reference group (cancer-free patients) (p-value < 0.05). Women earned -33,5% than the reference group (p-value < 0.05) (Norway, 2008) [25].

Studies reveal that economic difficulties have an impact on career choices and the decision to keep working despite the disease. Nekhlyudov et al (USA, 2016) reported cancer survivor's experiences with finances and employment. Among 615 cancer survivors who had been employed during or since their cancer, 26% reported that keeping their insurance was a factor for them to remain at their job. In the study, LC survivors were more likely than other cancer survivors to be concerned by these economic worries ($p = 0.009$) [9].

3.6. Social impact of the work loss

The economic impact of LC is explored in two cross sectional studies at a societal scale. The cost of work loss on treatment days was estimated for lung cancer (including tracheal and bronchial cancers) in 2011 at 314.10 million USD by Yamauchi et al (Japan, 2017). The authors also estimated results of the work loss on non-treatment days using the product of "employment rate coefficient" and "productivity coefficient". In the case that the product of "employment rate coefficient x productivity coefficient" is 0.5, the work loss for lung cancer (including tracheal and bronchial cancers) averages 495.32 million USD. When LC survivors are not able to work (coefficients are 0), the work loss was estimated at 990.63 million USD [18].

Likewise, the projected productivity losses for cancer-related mortality was assessed between 2011 and 2030 (Ireland, 2016). Lung cancer was the costliest of all cancers. The authors projected 48.922 deaths from LC. The value of lost paid production averaged 2.4 billion euros, which was almost twice as costly as the other cancers. The value of lost household production was 12,493 million euros. The value of lost paid production per death was 49,116 euros and the value of lost household production was 255,369 euros per death [26].

3.7. Impact of drug therapy

Few authors explored the impact of therapeutic choices on economic variables. Stanisic et al (Europe, 2010) examined the potential economic benefits related to RTW of LC patients when being treated with bevacizumab and platinum-based chemotherapy. The economic impact of the therapeutic program was analysed considering productivity losses due to LC. Mean costs savings related to productivity losses were estimated at €21,667 at year 1 and €39,001 at year 1.5 per salaried progression-free patient returning to work in the French setting. In Germany, mean costs savings represented respectively €21,171 and €38,107 per patient. In Italy, mean costs resulted in €17,578 at year 1 and €31,640. For Spain, mean costs savings were estimated at €12,401 at year 1 and €22,322 per patient still working [30].

The potential savings associated with a reduced productivity loss in patients with advanced non-small cell lung cancer were estimated in the European setting (2012). The bevacizumab treatment group had increased gains in productivity and reductions of societal expenses (€5216; €6739; €3455 and €4046 per patient in France, Germany, Italy and Spain, respectively) as compared with the chemotherapy group (€1774; €2278; €1178 and €1377; respectively). These gains were related to the duration of progression-free survival, which allowed patients to return to work. Reduced losses in labor costs were the main source of societal savings [31].

4. Discussion

4.1. Summary of evidence

LC survivors are 2–3 times more likely to be unemployed as compared with control groups (patients with no cancer or cancer with less impact on employment) (1120–222,425). Our findings highlight a median duration of sickness absence increased for LC survivors compared to control groups. This increase in sick days (sick leave and disability pension) occurs both pre- and post-diagnosis [17,19,28,29]. The time to partial or full RTW is increased in LC [16,19,28,29] with a median duration varying between 96.5 days and 2.8 years according to studies. RTW of LC survivors is characterized by the need for work adjustments including changes of schedules and reducing workloads [9]. Economic consequences related to LC diagnosis and treatments can alter patient's quality of life. The strongest decline in earnings was observed among LC survivors as compared to other cancers [25]. Finally, the social impact of the patients' work loss was assessed by Yamauchi et al and Pearce et al [18,26]. Cost of work loss was measured by projecting productivity losses or using the product of "employment rate coefficient and productivity coefficient". These studies highlight indirect costs associated with LC and its therapies. Stanisic et al and Lister et al explored the potential economic benefits related to RTW of LC patients according to therapeutic strategies [30,31].

The median age of LC survivors at diagnosis averages 70 years old and LC is characterized by a 5-year survival of 13% [32–34]. Therefore, LC is often considered as a disease of the elderly and the employment situation of patients is not explored. However, 30.3% of patients are aged between 20 and 64 years old according to the American National Cancer Institute. This working age population is concerned by working

difficulties and economic insecurity, justifying further scientific exploration to address this question. Working age LC survivors are characterized by higher rates of unemployment as compared to other cancer patients. Demographic and socio-economic characteristics of working age LC patients could partially explain this difference. Previous findings suggest that young patients (working age population) belong to a specific population with an over-representation of females [35–45] and a more advanced stage of disease at diagnosis compared to older patients [36,37,40,41,43–47]. Likewise, low educational level has been identified as a predictive factor of respiratory cancers in different studies [37–39]. In a French cohort, 146 young LC patients (median age 38 years) had a lower educational level than the general population [45].

4.2. Limitations

In the oncology field, studies tend to focus on the short-term efficiency and low toxicity of drugs. RTW is considered a long-term challenge and is often excluded from medical objectives. Studies focused on the impact of LC on employment remains scarce. Moreover, most studies are designed with cohorts of patients diagnosed with different types of cancer. Specific data on LC is limited.

A comparison of quantitative variables would have been interesting but the data provided by the review was not considered to be sufficient. The narrow breadth of information available concerning the economic benefits related to RTW of LC patients according to therapeutic strategies prevents to draw conclusions in the present study. However, this promising perspective highlights the need to explore this topic with future clinical settings.

Our conclusions are limited by the heterogeneity of studies included: study designs (longitudinal and cross-sectional studies), timelapses, countries with different national health insurance systems, populations, endpoints. Future research is required to understand the consequences of LC on employment, particularly when considering the different therapeutic strategies offered to patients.

4.3. Perspectives

To our knowledge, it is the first study to gather, in a comprehensive manner, employment data on LC patients. Studies have explored the proportion of cancer survivors who RTW and the work-related difficulties they face. Being employed is correlated with a better quality of life regarding physical functioning [48]. Conversely, change of employment status (dismissal, layoff or retirement) impairs all functioning scales and worsens fatigue, appetite loss, constipation, and economic difficulties on the EORTC QLQ-C30. Losing a job has a significant negative impact on an individual's well-being [48]. In the clinical setting, supporting and encouraging RTW of patients should therefore be a priority. As it facilitates physical recovery, maintains mental well-being and reduces economic difficulties, RTW may contribute to patients' recovery.

On a societal perspective, RTW of LC patients represents a priority as the costs associated with work loss and reduction of productivity have a significant impact. For healthcare systems, cancer management implies direct and indirect costs. Direct costs are represented by chemotherapy and immunotherapy drugs, hospitalizations, transportation, imaging and laboratory tests. Indirect cost are related to the lost days of productivity due to the disease for both patients and family caregivers [22,49]. Published data on indirect cost of LC management are scarce. Different variables have been considered to perform estimates such as lost days of productivity, short term disability and early death [50]. LC represents one of the costliest cancer [26]. Thus, reducing its indirect costs by facilitating RTW of patients is a promising pathway to maintain the economic sustainability of LC therapies.

The introduction of recent molecularly targeted agents and immunotherapies in the treatment of cancer has considerably renewed the prognosis of LC survivors. Agents targeting PD-1 are associated with favorable results in terms of progression-free and overall survival compared with platinum-based chemotherapy in LC patients [3,4]. PD-L1 inhibitors are associated with the improvement of patients' quality of life [51]. With these new treatments, LC survivors are likely to RTW after recovery. Future research is needed in this field. Assessing the benefit of immunotherapies in LC should not only consider clinical and paraclinical variables. The long-term benefits in terms of quality of life and professional rehabilitation of patients should be included in the analyses. New drug therapies may increase the patients' chance of resuming their former activities (including working); therefore, potentially reduce the economic burden they place on healthcare systems.

5. Conclusions

The risk of unemployment among LC survivors remains high. With an often delayed RTW compared to other cancers, LC patients are likely to experience economic and social complications. However, the introduction of novel molecularly targeted agents and immunotherapy drugs in the treatment of LC survivors is changing the prognosis of patients in terms of overall survival and quality of live. These promising results may be associated with a better RTW prognosis of patients. Future research should focus on the social and professional rehabilitation of patients who benefit from these therapeutic programs. A reduction of indirect costs due to loss of productivity, caregivers' implication and loss of work is to be expected and should be documented. As being part of a patient's recovery, the social and occupational reintegration of LC patients should be systematically assessed and supported.

Compliance with ethical standards

Research involving human participants and/or animals.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee, national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with humans or animals performed by any of the authors.

Informed consent

No individual participants were included in the study.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.03.010.

References

[1] H. Sugimura, P. Yang, Long-term survivorship in lung cancer: a review, Chest. 129 (April (4)) (2006) 1088–1097.
[2] Y.H. Yun, Y.A. Kim, Y.H. Min, Y.J. Chang, J. Lee, M.S. Kim, et al., Health-related quality of life in disease-free survivors of surgically treated lung cancer compared

with the general population, Ann. Surg. 255 (May (5)) (2012) 1000–1007.
[3] Q. Zhao, R. Xie, S. Lin, X. You, X. Weng, Anti-PD-1/PD-L1 antibody therapy for pretreated advanced or metastatic nonsmall cell lung carcinomas and the correlation between PD-L1 expression and treatment effectiveness: an update meta-analysis of randomized clinical trials, Biomed Res. Int. 2018 (2018) 3820956.
[4] C. Wang, X. Yu, W. Wang, A meta-analysis of efficacy and safety of antibodies targeting PD-1/PD-L1 in treatment of advanced nonsmall cell lung cancer, Bull. Sch. Med. Md 95 (December (52)) (2016) e5539.
[5] D.M. Rasmussen, B. Elverdam, The meaning of work and working life after cancer: an interview study, Psychoncology 17 (December (12)) (2008) 1232–1238.
[6] D.S. Stone, P.A. Ganz, C. Pavlish, W.A. Robbins, Young adult cancer survivors and work: a systematic review, J. Cancer Surviv. Res. Pract. 11 (December (6)) (2017) 765–781.
[7] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement, Open Med. 3 (July (3)) (2009) e123–30.
[8] K. Slim, E. Nini, D. Forestier, F. Kwiatkowski, Y. Panis, J. Chipponi, Methodological index for non-randomized studies (minors): development and validation of a new instrument, ANZ J. Surg. 73 (September (9)) (2003) 712–716.
[9] L. Nekhlyudov, R. Walker, R. Ziebell, B. Rabin, S. Nutt, J. Chubak, Cancer survivors' experiences with insurance, finances, and employment: results from a multisite study, J. Cancer Surviv. Res Pract. 10 (December (6)) (2016) 1104–1111.
[10] A.J. Tevaarwerk, J.-W. Lee, A. Terhaar, M.E. Sesto, M.L. Smith, C.S. Cleeland, et al., Working after a metastatic cancer diagnosis: factors affecting employment in the metastatic setting from ECOG-ACRIN's symptom outcomes and practice patterns study, Cancer 122 (February (3)) (2016) 438–446.
[11] C.C. Earle, Y. Chretien, C. Morris, J.Z. Ayanian, N.L. Keating, L.A. Polgreen, et al., Employment among survivors of lung cancer and colorectal cancer, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 28 (April (10)) (2010) 1700–1705.
[12] P.F. Short, J.J. Vasey, K. Tunceli, Employment pathways in a large cohort of adult cancer survivors, Cancer 103 (March (6)) (2005) 1292–1301.
[13] H.L. Bednarek, C.J. Bradley, Work and retirement after cancer diagnosis, Res. Nurs. Health 28 (April (2)) (2005) 126–135.
[14] C.J. Bradley, H.L. Bednarek, Employment patterns of long-term cancer survivors, Psychooncology 11 (June (3)) (2002) 188–198.
[15] Ca.M. Roelen, P.C. Koopmans, A.J.M. Schellart, A.J. van der Beek, Resuming work after cancer: a prospective study of occupational register data, J. Occup. Rehabil. 21 (September (3)) (2011) 431–440.
[16] Ca.M. Roelen, P.C. Koopmans, J.W. Groothoff, J.J.L. van der Klink, U. Bültmann, Return to work after cancer diagnosed in 2002, 2005 and 2008, J. Occup. Rehabil. 21 (September (3)) (2011) 335–341.
[17] C.A. Roelen, P.C. Koopmans, J.W. Groothoff, J.J. van der Klink, U. Bültmann, Sickness absence and full return to work after cancer: 2-year follow-up of register data for different cancer sites, Psychooncology 20 (September (9)) (2011) 1001–1006.
[18] H. Yamauchi, C. Nakagawa, T. Fukuda, Social impacts of the work loss in cancer survivors, Breast Cancer Tokyo Jpn. 24 (September (5)) (2017) 694–701.
[19] M. Endo, Y. Haruyama, M. Takahashi, C. Nishiura, N. Kojimahara, N. Yamaguchi, Returning to work after sick leave due to cancer: a 365-day cohort study of Japanese cancer survivors, J. Cancer Surviv. Res. Pract. 10 (April (2)) (2016) 320–329.
[20] T. Taskila-Abrandt, E. Pukkala, R. Martikainen, A. Karjalainen, P. Hietanen, Employment status of Finnish cancer patients in 1997, Psychooncology 14 (March (3)) (2005) 221–226.
[21] T. Taskila-Brandt, R. Martikainen, S.V. Virtanen, E. Pukkala, P. Hietanen, M.-L. Lindbohm, The impact of education and occupation on the employment status of cancer survivors, Eur. J. Cancer 40 (November (16)) (1990) 2488–2493.
[22] Y.A. Kim, Y.H. Yun, Y.J. Chang, J. Lee, M.S. Kim, H.-S. Lee, et al., Employment status and work-related difficulties in lung cancer survivors compared with the general population, Ann. Surg. 259 (March (3)) (2014) 569–575.
[23] J.-H. Park, E.-C. Park, J.-H. Park, S.-G. Kim, S.-Y. Lee, Job loss and re-employment of cancer patients in Korean employees: a nationwide retrospective cohort study, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 26 (March (8)) (2008) 1302–1309.
[24] S. Torp, R.A. Nielsen, S.D. Fosså, S.B. Gudbergsson, A.A. Dahl, Change in employment status of 5-year cancer survivors, Eur. J. Public Health 23 (February (1)) (2013) 116–122.
[25] A. Syse, S. Tretli, Ø. Kravdal, Cancer's impact on employment and earnings–a population-based study from Norway, J. Cancer Surviv. Res. Pract. 2 (September (3)) (2008) 149–158.
[26] A. Pearce, C. Bradley, P. Hanly, C. O'Neill, A.A. Thomas, M. Molcho, et al., Projecting productivity losses for cancer-related mortality 2011 - 2030, BMC Cancer 16 (1) (2016) 804 18.
[27] L. Ross, M.A. Petersen, A.T. Johnsen, L.H. Lundstroem, K. Carlsen, M. Groenvold, Factors associated with Danish cancer patients' return to work. A report from the population-based study 'the cancer patient's World', Cancer Epidemiol. 36 (April (2)) (2012) 222–229.
[28] K. Sjövall, B. Attner, M. Englund, T. Lithman, D. Noreen, B. Gunnars, et al., Sickness absence among cancer patients in the pre-diagnostic and the post-diagnostic phases of five common forms of cancer, Support Care Cancer 20 (April (4)) (2012) 741–747.
[29] R. Molina, J. Feliu, A. Villalba, B. San José, A.M. Jiménez, E. Espinosa, et al., Employment in a cohort of cancer patients in Spain. A predictive model of working outcomes, Clin. Transl. Oncol. 10 (December (12)) (2008) 826–830.
[30] S. Stanisic, H.G. Bischoff, D.F. Heigener, A. Vergnenègre, J. de Castro Carpeño, C. Chouaid, et al., Societal cost savings through bevacizumab-based treatment in non-small cell lung cancer (NSCLC), Lung Cancer Amst. Neth. 69 (August Suppl. 1) (2010) S24–30.
[31] J. Lister, S. Stanisic, K. Kaier, C. Hagist, D. Gultyaev, S. Walzer, Societal savings in patients with advanced non-squamous non-small-cell lung cancer receiving bevacizumab-based versus non-bevacizumab-based treatments in France, Germany, Italy, and Spain, Clin. Outcomes Res. CEOR 4 (2012) 299–305.
[32] Lung and Bronchus Cancer - Cancer stat Facts [Internet], (2019) cited Mar 5. Available from: https://seer.cancer.gov/statfacts/html/lungb.html.
[33] Survival patterns in lung and pleural cancer in Europe, Results From the EUROCARE-5 Study. - PubMed - NCBI [Internet], 2007 [cited 2019 Mar 5]. Available from: (1999) https://www.ncbi.nlm.nih.gov/pubmed/?term=Francisci+S%2C+Minicozzi+P%2C+Pierannunzio+D%2C+Ardanaz+E%2C+Eberle+A%2C+Grimsrud+TK%2C+Knijn+A%2C+Pastorino+U%2C+Salmeron+D%2C+Trama+A%2C+Sant+M%3B+EUROCARE-5+Working+Group%3A+Survival+patterns+in+lung+and+pleural+cancer+in+Europe+1999%E2%80%932007%3A+results+from+the+EUROCARE-5+study.
[34] W.A. Fry, J.L. Phillips, H.R. Menck, Ten-year survey of lung cancer treatment and survival in hospitals in the United States: a national cancer data base report, Cancer 86 (November (9)) (1999) 1867–1876.
[35] C.-L. Hsu, K.-Y. Chen, J.-Y. Shih, C.-C. Ho, C.-H. Yang, C.-J. Yu, et al., Advanced non-small cell lung cancer in patients aged 45 years or younger: outcomes and prognostic factors, BMC Cancer 13 (June (12)) (2012) 241.
[36] L. Kim, K.H. Kim, Y.H. Yoon, J.S. Ryu, S.J. Choi, I.S. Park, et al., Clinicopathologic and molecular characteristics of lung adenocarcinoma arising in young patients, J. Korean Med. Sci. 27 (September (9)) (2012) 1027–1036.
[37] Lung Cancer in Patients Younger Than 40 Years of Age. - PubMed - NCBI [Internet], (2019) [cited Mar 5]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Maruyama+R%2C+Yoshino+I%2C+Yohena+T%2C+Uehara+T%2C+Kanematsu+T%2C+Kitajima+M%2C+Teruya+T%2C+Ichinose+Y%3A+Lung+cancer+in+patients+younger+than+40+years+of+age.
[38] E. Radzikowska, K. Roszkowski, P. Głaz, Lung cancer in patients under 50 years old, Lung Cancer Amst. Neth. 33 (September (2–3)) (2001) 203–211.
[39] Lung Cancer in Patients Under Age 40. - PubMed - NCBI [Internet], (2019) [cited Mar 5]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Skarin+AT%2C+Herbst+RS%2C+Leong+TL%2C+Bailey+A%2C+Sugarbaker+D%3A+Lung+cancer+in+patients+under+age+40.
[40] Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: a surveillance, epidemiology, and end results (SEER) analysis. - PubMed - NCBI [Internet], (2019) [cited Mar 5]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19934774.
[41] Trends and Characteristics of Young Non-Small Cell Lung Cancer Patients in the United States [Internet], (2019) [cited Mar 5]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4443720/.
[42] M. Blanco, E. García-Fontán, J.E. Rivo, J.R. Repáaz, G.A. Obeso, M.A. Cañizares, Bronchogenic carcinoma in patients under 50 years old, Clin. Transl. Oncol. 11 (May (5)) (2009) 322–325.
[43] A. Dell'Amore, M. Monteverde, N. Martucci, F. Davoli, G. Caroli, E. Pipitone, et al., Surgery for non-small cell lung cancer in younger patients: what are the differences? Heart Lung Circ. 24 (January (1)) (2015) 62–68.
[44] S. Ramalingam, K. Pawlish, S. Gadgeel, R. Demers, G.P. Kalemkerian, Lung cancer in young patients: analysis of a surveillance, epidemiology, and end results database, J. Clin. Oncol. 16 (February (2)) (1998) 651–657.
[45] L. Bigay-Gamé, S. Bota, L. Greillier, I. Monnet, A. Madroszyk, R. Corre, et al., Characteristics of lung cancer in patients younger than 40 years: a prospective multicenter analysis in France, Oncology 95 (6) (2018) 337–343.
[46] Lung Cancer in Patients Under Age 40. - PubMed - NCBI [Internet], (2019) [cited Mar 5]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Skarin+AT%2C+Herbst+RS%2C+Leong+TL%2C+Bailey+A%2C+Sugarbaker+D%3A+Lung+cancer+in+patients+under+age+40.
[47] Clinical Features and Gene Mutations of Lung Cancer patients 30 Years of Age or Younger. - PubMed - NCBI [Internet], (2019) [cited Mar 5]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26332764.
[48] K. Kobayashi, S. Morita, M. Shimonagayoshi, M. Kobayashi, Y. Fujiki, Y. Uchida, et al., Effects of socioeconomic factors and cancer survivors' worries on their quality of life (QOL) in Japan, Psychooncology 17 (June (6)) (2008) 606–611.
[49] L. Chaker, A. Falla, S.J. van der Lee, T. Muka, D. Imo, L. Jaspers, et al., The global impact of non-communicable diseases on macro-economic productivity: a systematic review, Eur. J. Epidemiol. 30 (May (5)) (2015) 357–395.
[50] V. Zarogoulidou, E. Panagopoulou, D. Papakosta, D. Petridis, K. Porpodis, K. Zarogoulidis, et al., Estimating the direct and indirect costs of lung cancer: a prospective analysis in a Greek University Pulmonary Department, J. Thorac. Dis. 7 (February (Suppl. 1)) (2015) S12–19.
[51] O. Abdel-Rahman, H. Oweira, A. Giryes, Health-related quality of life in cancer patients treated with PD-(L)1 inhibitors: a systematic review, Expert Rev. Anticancer Ther. (September (26)) (2018) 1–9.