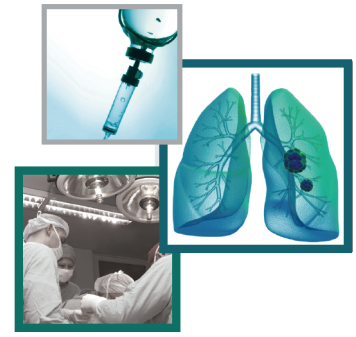
Review

For reprint orders, please contact: reprints@futuremedicine.com

Lung Cancer Management



Survival and quality-of-life outcomes in early-stage NSCLC patients: a literature review of real-world evidence

Nick Jovanoski*[,1], Kathleen Bowes[2], Audrey Brown[2], Rossella Belleli[1], Danilo Di Maio[1], Shkun Chadda[2] & Seye Abogunrin[1]

[1]F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, Building 002/OG18, CH-4070, Basel, Switzerland

[2]Genesis Research, West One, Forth Banks, Newcastle, NE1 3PA, UK

*Author for correspondence: nick.jovanoski@roche.com

Aim: Assess the long-term survival and quality-of-life outcomes in early-stage NSCLC (eNSCLC) patients. **Methods:** Review of long-term survival and quality-of-life after curative treatment in eNSCLC patients in observational studies. **Results:** Disease-free proportion decreased in stage III vs stage I patients. Recurrence-free proportion decreased with age and disease stage. Advanced stage and vascular invasion increased risk of late recurrence. Conditional 5-year relative survival rates did not exceed 87%, indicating higher mortality in eNSCLC survivors. Lower conditional survival rates and relative survival rates were associated with older age and advanced disease. Survivors of eNSCLC had poorer physical quality-of-life. **Conclusion:** Despite curative-intent therapy, survivors of eNSCLC still face significant risks of recurrence, excess mortality, and diminished quality-of-life.

Plain language summary: Early-stage NSCLC (eNSCLC) encompassing stage I and II, and resectable stage III disease is initially managed with curative-intent surgery and adjuvant chemotherapy to reduce the risk of recurrence. However, understanding the true curative potential and long-term outcomes is crucial for optimal clinical management. A literature review was conducted to identify observational studies describing long-term survival and quality-of-life outcomes following curative intent therapy in patients with eNSCLC. The proportion of patients who remained disease-free over time (without recurrence or death) statistically significantly decreased in patients with stage III disease compared with stage I disease. Similarly, the proportion of patients who remained recurrence-free over time decreased with increasing age and disease stage. A considerable risk of late recurrence (recurrence five or more years following resection) remained, increasing with advanced stage and tumor characteristics such as vascular invasion. Conditional 5-year relative survival rates did not exceed 87% in any study, indicating higher rates of all-cause mortality in long-term survivors of eNSCLC compared with members of the general population of the same age. Lower conditional 5-year relative survival rates, and 5 and 10-year relative survival rates were associated with older age and higher pathologic stage. Compared with the general population, survivors of eNSCLC reported significantly poorer physical quality-of-life, suggesting that symptoms persist after treatment. Overall, real-world evidence suggests that after standard curative-intent therapy, survivors of eNSCLC may not be considered fully cured, indicating a need for more effective adjuvant treatment in addition to the current standard of care.

Tweetable abstract: Survivors of eNSCLC have a risk of late recurrence, excess mortality and poorer physical quality-of-life, and they may not be fully cured by existing curative-intent therapy necessitating the need for more effective adjuvant treatment options.

First draft submitted: 2 March 2023; Accepted for publication: 22 June 2023; Published online: 11 July 2023

Keywords: cancer survivors' • carcinoma • disease-free survival • NSCLC • progression-free survival • quality-of-life

Lung cancer is the second most common form of cancer worldwide [1,2]. It is the leading cause of cancer-related deaths in the USA and Europe, and the WHO predicts that globally lung cancer death rates will continue to

Future Medicine

Table 1. Patient, intervention, comparator, outcome, and study design elements detailing study inclusion criteria.

PICOS elements	PICOS criteria
Population	Adult patients with early/resectable NSCLC (stage I–III) in the disease-free survival health state
Interventions/comparators	• Atezolizumab • Pemetrexed • Nab-paclitaxel • Gemcitabine • Vinorelbine • Nivolumab • Durvalumab • Cemiplimab • Avelumab • Tegafur ± uracil • Osimertinib •Pembrolizumab • Erlotinib • Cisplatin-based chemotherapy • Carboplatin-based chemotherapy • Gefitinib • Afatinib • Docetaxel • Radiotherapy • Best supportive care • Etoposide • Surgery
Outcomes	• The proportion of eNSCLC patients who remain free from disease over time • Relative survival of eNSCLC survivors • Quality of life of eNSCLC survivors
Study design	Prospective and retrospective observational studies

eNSCLC: Early-stage NSCLC; PICOS: Patient, intervention, comparator, outcome, and study design; QoL: Quality of life.

rise, particularly in Asia [3,4]. Lung cancer can be divided into two types; non-small cell, and small cell [5]. The most common histological type of lung cancer is NSCLC, which accounts for 85–90% of all cases [6]. This cancer originates in larger cells of the lung, such as epithelial cells [5]. Staging of NSCLC is performed using the tumor–node–metastasis (TNM) classification of malignant tumors, which describes the tumor size, spread to nearby nodes, and state of metastasis [7,8]. Under the TNM staging system, early-stages (stages I–III) of NSCLC (eNSCLC) are defined as having no metastasis, although the cancer may have spread to surrounding lymph nodes [9]. Around 23% of NSCLC diagnoses in USA are in the early stages of cancer [10].

Risk factors for NSCLC include increasing age, a history of smoking, previous cancer history, family history, other lung diseases (such as chronic obstructive pulmonary disease or pulmonary fibrosis), exposure to infectious agents and occupational exposure [8]. Treatment of NSCLC is stage-specific; stage I, II and selected stage III cancers are considered resectable. These 'selected' stage III cancers are T4N0 disease, and N2 disease where other nodal stations (besides the surgical target) are determined to be benign by biopsy. The standard treatment for NSCLC at these stages is surgery with curative intent, which may be accompanied by adjuvant or neoadjuvant chemotherapy [11]. However, patients who have undergone curative-intent treatment are at risk of cancer recurrence, development of second primary disease, or treatment-related comorbidities [11].

Understanding the long-term survivorship of eNSCLC patients following curative-intent treatment is essential to inform and improve adjuvant treatment strategies for these patients. The objective of this review was to collate real-world long-term outcomes for eNSCLC survivors, particularly the lesser reported (conditional) relative survival, and quality-of-life (QoL). To determine the probability of recurrence in long-term eNSCLC survivors, the more traditional outcomes of DFS and RFS have also been identified.

Methods

A targeted review was conducted to identify observational data describing DFS, RFS, conditional relative survival, relative survival, and QoL of adult patients with eNSCLC who are disease-free following surgery. Interventions and comparator treatments were limited to a range of treatments based on the current standard of care. These and the full list of PICOS (patient, intervention, comparator, outcome, and study design) criteria, are listed in Table 1.

Outcomes

In the studies discussed in this review, DFS was defined as the time from surgery to recurrence or death, unless stated otherwise [12]. The same definition was also used to describe RFS in some studies [13–16]. One study defined DFS from the time of first treatment [17]. Other studies defined RFS as the time from surgery to the time of recurrence or last follow-up showing no recurrence [18–20]; this definition was referred to as freedom from recurrence [21,22] or DFS [23–25] in several studies. Conditional relative survival (CRS) was defined as the probability of surviving a given number of years relative to a comparator population, having already survived a specified length of time [19,26,27]. Relative survival (RS) was defined as the ratio of the observed survival for patients with cancer to the expected survival of a comparable group from the general population [26].

Search strategy

Searches were conducted in March and April 2021, with results limited to studies published from 2006 onward. Studies older than 15 years were considered to have less clinical relevance due to the changing treatment landscape. Restrictions were also applied to limit publications to those in the English language, and the following countries: France, Italy, Spain, Germany, the UK, Netherlands, US, Japan, and South Korea. This review was conducted as part of a broader body of work and these countries were considered relevant to the geographic scope.

To identify survival outcomes, iterative search strategies were developed and conducted using Evid AI, an artificial intelligence (AI) driven literature assessment tool (AI) that aids searching and screening of scientific literature [28,29]. There are more than 100 million data points extracted from primary studies and reviews, sourced from PubMed and various conferences in Evid AI. The AI assesses up to 25 million articles per hour and structures the data to improve the relevance of the search results. Suppplementary electronic database searches were conducted in PubMed to identify HRQoL data. Searches of conference proceedings from ISPOR, ESMO, ASCO, and WCLC (restricted to the three most recent meetings) were also conducted, and backward citation chasing was perdormed for all identified studies to identify any additional relevant publications.

Study selection & data extraction

Abstracts were assessed for inclusion, according to the pre-specified PICOS criteria by a single reviewer, and the full texts of records considered relevant after the first pass were retrieved for further review by a single reviewer. As this is not a formal systematic review requiring a PRISMA diagram, we recorded only details of included studies; excluded studies and reasons for exclusion were not documented. Studies were included if they reported on the following outcomes: disease-free survival, recurrence-free survival, instances of second primary lung cancer (SPLC), relative survival, conditional relative survival, and QoL. Prioritization criteria were applied to identify the most relevant studies for inclusion (Supplementary Table 1).

Relevant information from included studies was extracted in Microsoft Excel by one reviewer and included details of the study design, baseline characteristics, and the outcomes of interest.

Results

A total of 2255 unique records were identified from searches. Following screening, 51 real-world studies of patients with eNSCLC who underwent curative-intent surgery were included in the review. Seven studies were prospective, observational in nature [22,23,30–34], while the remaining were retrospective analyses. Results from included studies should always be compared in light of differences between the populations, including patient demographics, disease characteristics, and treatment factors such as the margin of resection.

Patients who remain disease-free over time

This review was targeted at real-world evidence in long-term survivors, and was limited to studies meeting the specified PICOS criteria, capturing only a select few studies. To identify the probability of recurrence in long-term eNSCLC survivors, data on DFS, RFS, and other recurrence-related outcomes were identified. DFS and RFS are commonly reported outcomes in oncology; the results detailed herein are not a comprehensive summary of all publications reporting these outcomes in eNSCLC.

Disease-free survival from eNSCLC

DFS rates were typically reported at 5 years [12–17], with some publications also providing rates at timepoints from 1 to 4 years [14,17]. The percentage of patients remaining disease-free over time following surgery appeared to drop

Table 2. Real-world disease-free survival outcomes of patients with early-stage NSCLC by treatment.

Study (year)	Country	Treatment	Disease stage (n)	Median follow-up (months)	2-year DFS, % (95% CI)	5-year DFS, % (95% CI)	Ref.
Maniwa (2016)	Japan	Surgery	cN0–1 (779)	45.5	–	73.3	[12]
		Surgery	cN2 (29)	45.5	–	50.6	
		Surgery	cN2–pN2 (24)	45.5	–	52.5	
Brandt (2019)	US	Surgery (complete resection) + neoadjuvant chemotherapy	IB–IIA (92)	74.4	–	49.0 (39.0–61.0)	[17]
		Surgery (complete resection) + adjuvant chemotherapy	IB–IIA (92)	69.6	–	48.0 (38.0–61.0)	
Endo (2012)	Japan	Surgery (complete resection)	I (213)	65.8	–	75.0†	[13]
		Surgery (complete resection)	II (37)	65.8	–	48.6†	
		Surgery (complete resection)	III (65)	65.8	–	25.1†	
Tsutani (2014)	Japan	Surgery (complete resection) + adjuvant chemotherapy	IA (191)	48.7	–	78.1†	[14]
		Surgery (complete resection)	IA (609)	48.7	–	71.5†	
Lee (2018)	South Korea	Surgery (complete resection) + chemoradiotherapy	IIIA (570)	33.6	–	29.2 (25.1–34.0)†	[35]
Janjigian (2011)	US	Surgery (complete resection) + adjuvant erlotinib/gefitinib	I–III (56)	24.0	89.0 (77–95)†	–	[16]
		Surgery (complete resection)	I–III (111)	24.0	72.0 (61–80)†	–	

DFS is defined as time between surgery and recurrence/relapse or death. Recurrence-free survival is defined as time from initial operation to recurrence or death.
†Recurrence-free survival.
–: No information was available; DFS: Disease-free survival.

significantly with disease stage; in a study of 315 patients who underwent complete resection at Tokyo University Hospital, the 5-year DFS rates were 75%, 48.6%, and 25.1% ($p < 0.001$) in patients with stage I, II, and III disease, respectively [13].

Adjuvant chemotherapy following surgery may not necessarily improve disease-free survival in patients with eNSCLC. In a study of 800 patients with stage I NSCLC across several sites in Japan receiving adjuvant chemotherapy after curative surgery, the proportion of patients remaining disease-free over time was not statistically significantly different from those who did not receive adjuvant chemotherapy (78.1% vs 71.5%, respectively; $p = 0.69$) [16]. Another study investigating the effects of adjuvant erlotinib or gefitinib on DFS found that the 2-year DFS of stage I-III patients in the US was not statistically significantly higher than that of patients who did not receive adjuvant chemotherapy (89% vs 72%, respectively; $p = 0.06$) [14].

A comparison of neoadjuvant chemotherapy and adjuvant chemotherapy among surgically treated TNM stage cT2–4N0–1 (clinical stages I-IIIA) patients in the US showed similar 5-year DFS in both treatment arms (49% for neoadjuvant therapy vs 48% for adjuvant therapy, $p = 0.70$) [17]. Table 2 provides additional details of studies reporting on disease-free survival outcomes of patients with early-stage NSCLC, by treatment.

Absolute probability of recurrence beyond 5 years

A prospective study of 328 patients with stage IA NSCLC in Japan reported 5- and 10-year locoregional recurrence-free probabilities of 84.8 and 78.2%, respectively, after sublobar resection [32]. In a study of 119 stage IB NSCLC patients treated in South Korea, adding platinum-based adjuvant chemotherapy to surgery improved survival without recurrence. Five-year DFS in patients who received platinum-based adjuvant chemotherapy was significantly higher compared with those who did not receive adjuvant chemotherapy (74.0 vs 51.3%; $p = 0.011$) [25].

Evidence suggests that the probability of recurrence is higher with increasing disease stage. A comparison of 10-year recurrence-free probabilities after segmentectomy in 179 Japanese patients with cT1 N0 M0 (clinical stage IA) NSCLC, stratified by T stage, indicated higher in more advanced disease (median follow-up of 108 months; 10-year recurrence-free probability rates were 100% in cTis, 97% in cT1mi or cT1a, 90% in cT1b, and 69% in cT1c ($p < 0.001$)) [35].

Table 3. Real-world recurrence-free survival outcomes of patients with early-stage NSCLC by treatment.

Study (year)	Country	Treatment	Stage (n)	Median follow-up	5-year RFS, % (95% CI)	p-value	10-year RFS, % (95% CI)	Ref.
Shin (2021)	South Korea	Surgery (complete resection)	All (8798)	–	65.5 (64.3–66.8)	–	58.8 (57.0–60.5)	[18]
			I (5617)	–	78.2 (76.7–79.6)	–	71.2 (69.0–73.4)	
			II (1943)	–	50.6 (47.8–53.2)	–	43.9 (40.4–47.7)	
			III (1238)	–	31.3 (28.0–34.5)	–	26.5 (23.0–30.1)	
Yun (2020)	South Korea	VATS	I–III (500)	51.5 months	61.4	–	–	[19]
		Open thoracotomy	I–III (649)	51.5 months	56.5	–	–	
Kneuertz (2020)	USA	Lobectomy	0–IIIB (540)	44.8 months	54.0 (49.0–59.0)	–	–	[20]
Landreneau (2014)	USA	Segmentectomy	IA–IB (312)	5.4 years	70.0 (63–78)†	0.470	–	[21]
		Lobectomy	IA–IB (312)	5.4 years	71.0 (64–78)†		–	
Schuchert (2012)	USA	Segmentectomy	IA–IB (305)	37 months (mean)	75.0†	0.840	–	[22]
		Lobectomy	IA–IB (594)	37 months (mean)	76.0†		–	
Marushima (2020)	Japan	Surgery + adjuvant chemotherapy (nab-paclitaxel + carboplatin)	IB, II and IIIA (29)	32.6 months	65.2	0.344	–	[23]
		Surgery	IB, II and IIIA (47)	60.9 months	34.8		–	
Park (2016)	South Korea	Surgery	I, aged ≥70 years (285)	47.6 months	53.3‡	<0.001	–	[24]
		Surgery	I, aged <70 years (1055)	47.6 months	80.2‡		–	
Park (2013)	South Korea	Surgery (complete resection) + chemotherapy (platinum-based)	IB (60)	49.0 months	74.0‡	–	–	[25]
		Surgery (complete resection)	IB (59)	49.0 months	51.3‡	–	–	

RFS is defined as time between date of surgery and date of recurrence or last follow-up showing no recurrence. Freedom from recurrence is define as the time from surgery to first diagnosis of recurrence. Disease-free survival is defined as the time from surgery to first imaging interpretation of recurrence.
†Freedom from recurrence.
‡Disease-free survival. No p-values were reported for 10-year outcomes.
–: No information was available; RFS: Recurrence-free survival; VATS: Video-assisted thoracoscopic surgery.

A study of 1,340 patients with stage I NSCLC at a South Korean medical center found that elderly patients had significantly worse RFS compared with younger patients (53.3 vs 80.2%, respectively; $p < 0.001$) [24]. No statistically significantly higher risks of recurrence were observed for any particular histologic type, gender, smoking status, or comorbidity. A summary of RFS outcomes by treatment modality and stage is provided in Table 3.

Conditional probability of recurrence beyond 5 years

Recurrence-free probabilities of patients who had already survived for 5 years following complete resection were reported in two studies using data from the Japanese Cancer Centre database [36,37]. The 1-year disease-free survival rate of patients with stage I-III NSCLC, conditional on having already survived 5 years, was 96.7%, dropping to 91.7% after 3 years, and 86.7% after 5 years. The second study reported that, for patients who were disease-free 5 years after treatment, the probability of remaining disease-free after an additional 5 years was 93.3%, although this patient population was limited to those with stage IA disease only [19]. Both studies concluded that patients with selected tumor characteristics such as vascular invasion have a statistically significant risk of late recurrence [36,37]. The presence of cancer in the lymph nodes was also a significant predictor of recurrence at 5 years following surgery ($p = 0.022$) [36]. A study of 8,798 patients with stage I-III NSCLC who underwent surgery with curative intent, from the South Korean Lung Cancer Registry, reported that 5-year conditional RFS was lower in older patients at the time of surgery, and the gap remained even after 5 years [19].

10.2217/lmt-2023-0003

Table 4. Real-world conditional relative survival rates at 5 years stratified by age and disease stage.

Stage	Age (years)	Patient population at 5 years (n)	5-year CRS (95% CI)
I	45–59	1346	79 (77–81)
	60–74	2365	68 (67–70)
II	45–59	336	78 (74–82)
	60–74	421	64 (60–69)
III	45–59	361	68 (64–72)
	60–74	418	58 (54–62)

p-values not available.
CRS: Conditional relative survival.
Data taken from [26].

Second-primary lung cancer

Studies examining the development of second primary lung cancer (SPLC) with time from treatment for the initial cancer suggested a decreased rate of SPLC diagnosis with time [38]. The cumulative incidence of SPLC at one, 3 and 5 years following initial treatment was 1.9%, 11.7%, and 16.7%, respectively [38]. Another study found that 51.7% of patients with SPLC developed the condition within 5 years of initial treatment, falling to 34.5%, 5 to 10 years from initial treatment and 13.8% more than 10 years from initial treatment onwards (conditional on survival at the specified time periods) [39]. A third study reported that 12 patients in a cohort of 315 developed a new metachronous primary lung cancer over an eight-year observation period. The rate of SPLC diagnosis did not increase with time, although one instance was reported in the final year of observation, suggesting that stabilization was not reached in the eight-year period [13].

Retrospective analyses of SPLC development showed that the proportion of patients who developed a SPLC following surgical resection ranged from 2.8 to 5.2% (with follow-up times ranging from 33 to 65.8 months) [13,18,40–42]. Instances of SPLC were higher among patients who received stereotactic ablative radiotherapy (SABR), ranging from 6.0 to 9.2% (at follow-up of times of 32.9 and 52 months, respectively) [38,43]. The higher rates observed in patients with SPLC after SABR may be because SABR is often offered as a treatment for those who ineligible for surgery; patients in the aforementioned SABR studies were older than those in the studies of surgical resection, which may also explain higher instances of SPLC.

(Conditional) relative survival of eNSCLC survivors

Conditional relative survival

According to studies based in the US [27], South Korea [19], and the Netherlands [26], the 5-year conditional relative survival (CRS) of eNSCLC patients who had survived 5 years following diagnosis or surgery ranged from 58% (stage III patients) [26] to 85.6% (stage I–III patients) [19]. For patients who had survived 10 years following diagnosis or surgery, the 5-year CRS ranged from 72% (stage III patients) [26] to 86.8% (stage I–III patients) [19]. These were large database studies, consisting of between 8,798 and 96,480 subjects [19,26]. Rates were calculated relative to the general populations of the respective countries, with two studies stating that the comparator populations were of a similar age and gender ratio [26,27].

The 5-year CRS was lower in older patients and patients with higher disease stage (Table 4) [26]. This finding was consistent between studies [19,27]. Furthermore, patients with certain comorbidities (diabetes mellitus, cardiovascular disease and lung disease) had lower conditional 5-year relative survival than patients with no comorbidities [19]. Outcomes by ethnicity, based on a study of 96,480 NSCLC patients identified using the Surveillance, Epidemiology, and End Results (SEER) database, suggested that Native Americans and Alaskan natives with stage I disease had lower 5-year CRS rates compared with other groups, although this difference diminished with time [27]. A summary of 5-year CRS rates stratified by age and disease stage is provided in Table 4.

Relative survival

As with CRS, estimates of relative survival (RS) were lower in patients with increasing age and disease stage [19,26,44,45]. Analyses of The Netherlands and South Korean Lung Cancer Registries showed that 5-year and 10-year RS rates were higher in younger patients with eNSCLC compared with older patients within the same clinical stage [19,26,45]. Two-year, 5-year and 10-year RS rates worsened with increasing stage, according to data

Table 5. HRQoL outcomes of NSCLC survivors compared with cancer-free populations.

Study (year) Population size (n)	Scale	Time from surgery to measurement (years)	NSCLC survivors		Comparator population		p-value	Ref.
			Score, mean (SD)	Population size (n)	Score, mean (SD)			
Ostroff (2011)	SF-36 (PCS)	1–6	359	46.32 (10.85)	699	48.65 (9.62)	<0.0001	[33]
	SF-36 (MCS)	1–6	359	52.61 (9.25)	699	51.9 (9.39)	0.06	
Bryant (2012)	SF-12 (PCS)	≥1	111	35.8 (8.9)	NA	49.6 (9.9)	0.02	[34]
	SF-12 (MCS)	≥1	111	52.1 (10.7)	NA	49.4 (9.8)	0.03	

MCS: Mental component scores; PCS: Physical component scores; SD: Standard deviation; SF-36: Short Form 36 questionnaire; SF-12: Short Form 12 questionnaire.

from national cancer databases of The Netherlands, USA, UK and South Korea [19,26,44], although one of these studies reported comparable RS rates for stages II and III [19]. Similar trends were observed for median RS; among younger patients in the Netherlands, median RS was longer compared with older patients within the same clinical stages and diagnosis year, and patients with earlier stage NSCLC had longer median RS than patients with later stage NSCLC within the same age group and diagnosis year [45].

Evidence from the Netherlands Cancer Registry database suggested that RS has improved over time [45]. Between 1990 and 2014, median RS of stage III patients increased from 9 to 18 months among younger patients and from 6.4 to 10 months among older patients, and similar trends were observed in stages I and II. Disparities in RS between age groups for patients with stage I NSCLC diminished over time but did not change for patients with stage II disease. According to evidence from patients who underwent curative (R0) surgery for stage I-III NSCLC in South Korea, smoking and certain comorbidities (diabetes mellitus, cardiovascular disease, and lung disease) can negatively impact RS, although these determinants were only investigated in one study [19]. A full list of outcomes according to patient characteristics and comorbidities is provided in Supplementary Table 2.

There is also some evidence that RS outcomes for patients with early-stage NSCLC may differ according to geographic location. A population-based study utilizing the SEER Medicare database in the US and four UK-based databases that included the National Cancer Analysis System and Public Health England's National cancer Registration and Analysis Service, there were survival disparities between the US and England for older patients (aged >65 years) with eNSCLC [44]. Two-year RS was higher in the US compared with England for all stages, regardless of treatment, with the difference being most apparent for patients with stage IIIA NSCLC. Patients in England were also statistically less likely ($p < 0.001$) to be diagnosed at stage I disease compared with patients in the US, which may contribute to poorer overall RS outcomes in England [44].

Quality-of-life of eNSCLC survivors

Quality-of-life scores in survivors of eNSCLC relative to a comparator population were reported using the EORTC QLQ-C30, SF-36, and SF-12 questionnaires. One prospective US-based study compared SF-36 scores for stage IA or IB NSCLC patients at 1 to 6 years post-surgical resection with scores for similarly aged adults, all current or former smokers, who had screened negative for lung cancer in a lung cancer screening trial [33]. Another prospective study compared SF-12 scores for patients who had survived at least one-year following pneumonectomy with the general US population [30]. In the latter study, eNSCLC survivors reported significantly better mental component scores relative to the comparator population [30], although these results was not supported by the former study [33]. In both studies, eNSCLC survivors reported lower physical health scores relative to the comparator populations [30,33]. These results are summarized in Table 5.

Another prospective US-based study showed that female patients with eNSCLC between 6 months and 6 years post-surgery had similar SF-36 physical component scores (PCS) to adults aged 65–74 years (without lung disease), adults with lung disease, and long-term lung cancer survivors. Mental component scores (MCS) were also similar across comparator groups, although female lung cancer survivors had clinically better emotional QoL (MCS) than those with chronic lung disease [34].

A multi-center study based in Germany assessed HRQoL using the EORTC QLQ-C30 in patients with eNSCLC who had survived at least 1 year beyond diagnosis [46]. Among 461 stage I-IIIA patients, clinically relevant poorer QoL was observed for all functioning scales compared with values in the general population (standardized for age and sex). The largest detriments were observed for dyspnoea (40.85 points), role functioning (29.53 points), fatigue

Table 6. EQ-5D health utilities in early-stage NSCLC survivors.

Disease stage	Patient population (n)	Mean (SD)	Median (IQR)	p-value
I	105	0.77 (0.26)	0.81 (0.31)	0.266
II	39	0.74 (0.22)	0.76 (0.16)	
III (IIIA: 44.3%; IIIB 55.7%)	99	0.70 (0.29)	0.76 (0.26)	
Comparator population (UK general public aged 65–74 years)	NA	0.78 (NA)	NA	NA

EQ-5D: European Quality of Life 5 Dimension; IQR: Interquartile range; SD: Standard deviation.
Data taken from [47].

(24.25 points), social functioning (23.77 points), and physical functioning (20.97 points), indicating that patients experienced both functional impairment and persisting symptoms [46].

In another study, the EQ-5D questionnaire was distributed to 374 patients identified from the Netherlands Cancer Registry [47]. Utility values were calculated using data from the 245 patients who answered all questions in full. The mean survival time of treated patients was 2.6 years (range, 0.8 to 4.8). Results showed that survivors of NSCLC treated with radiotherapy, surgery, chemotherapy, or a combination of treatments were on average in good health, with utility scores only slightly lower than the average utility score of the general population of similar age (Table 6); the statistical significance of this difference was not reported [47].

Of the aforementioned studies, those analyzing the effects of patient demographics and treatment variables on HRQoL are summarized in Supplementary Tables 3 & 4. Two studies found that older patients had significantly better SF-36 mental component scores and EORTC QLQ-C30 emotional functioning, respectively, compared with younger patients [33,47]. The latter of these studies (which included stage IV patients) also found that older patients had significantly better fatigue but worse physical functioning [47]. This is in line with the expected relationship between QoL and age, with elderly patients being generally frailer and more affected by comorbidites than younger ones, and thus more likely to feature a lower physical functioning. Treatment combinations found to have a significant negative impact on HRQoL were chemoradiotherapy alone [48], and surgery combined with radiation and/ or systemic therapy (defined as chemotherapy, targeted therapy or immunotherapy) [47], however both of these analyses included advanced NSCLC.

Discussion

This targeted review aimed to provide a comprehensive understanding of the survival and QoL outcomes for long-term survivors of eNSCLC by analyzing evidence from observational studies. These findings suggest that even after successful surgery, patients with early-stage NSCLC who are disease-free following surgery are still at risk of cancer relapse after five or more years after surgery [36,37]. This risk increases with age [19], disease stage [13,35], nodal status [36], and certain tumor characteristics such as vascular invasion [36,37]. Interestingly, receiving chemotherapy before or after surgery in the real-world setting did not seem to affect how long patients remained disease-free [14,16,17]. This contrasts results from some phase II and phase III trials where adjuvant chemotherapy improved DFS in eNSCLC patients [48–50]. This discrepancy demonstrates that there is still uncertainty about how well chemotherapy after surgery works in real-life situations, and that there is a need for newer treatments to help patients stay disease-free longer [51]. The majority of studies were conducted in Japan, South Korea and USA and their results were largely similar.

The risk of developing a second primary cancer decreases over time [31,32,52] and is lower for patients who receive surgery as first-line treatment instead of SABR [32,52]. However, data from the SEER database suggests that lung cancer survivors are more likely to experience a subsequent cancer than survivors of most other common cancers [53].

The 5-year CRS rates did not exceed 87% in any identified study and ranged from 58% in patients with stage III disease [26] to 85.6% in patients with stage I-III disease [19]. These data indicate that long-term survivors of eNSCLC (those who have survived 5 or more years following surgery) still have a higher risk of dying than other people of the same age in the general population [19,26,27]. A study that looked at over a million patient records from the US SEER database found that patients with localized lung cancer had lower chances of surviving for 5 years than patients with ten other common types of cancer [54]. For example, the 5-year CRS rate for lung cancer was 76.9% while rates for localized disease in ten other cancer types including melanoma, breast, and prostate cancer were over 90%. The study also noted that the survival estimates for patients with lung cancer may have been confounded by smoking-related comorbidities in these patients [54].

Relative survival rates of NSCLC survivors were poorer for older patients, and for those with higher disease stage. This finding was consistent between studies [19,26,27,45]. Relative survival rates also appeared to be higher in the US compared with the UK [44]. Studies reporting CRS and RS data were large retrospective database studies that used data from cancer registries in the Netherlands, South Korea, and the US and UK to examining survival outcomes in broad NSCLC populations. However, the reliability of these studies may be affected by the general population data they used for comparison. All four studies calculated RS using data from the general population matched for age and sex, but did not take other health-related factors such as comorbidities into account in their analysis. Since many lung cancer survivors are likely to have additional smoking-related diseases, the relative survival values provided may not be an accurate reflection of lung-cancer related death. It is also important to note that the study by Shin *et al.* did not explain how they calculated RS [19].

Patients with NSCLC surviving at least 6 months after diagnosis reported impaired physical QoL compared with a comparator population across all studies [30,33,34,46]. This finding is in contrast with a study of 3,300 survivors of other common cancers (breast, colorectal, prostate, and non-Hodgkin lymphoma) conducted by the UK Department of Health, where the majority of patients reported no problems with good physical functioning 1, 3, 4 and 5 years following diagnosis [55]. The lower physical QoL of NSCLC survivors may be exacerbated by the fact that smoking-related comorbidities tend to be more prevalent in lung cancer patients than in other cancers [56]. The impact on emotional QoL was less clear as studies reported mixed results. The studies reporting QoL data were conducted in the USA, The Netherlands, and Germany, with small population sizes ranging from 111 to 461 patients. It is unclear if these patients can be considered 'long-term' survivors, as the timepoint for QoL data collection following surgery ranged from just 6 months to 6 years across studies. The findings from the studies identified in the review are in line with the expected relationship between QoL and age, with elderly patients being generally frailer and more affected by comorbidites than younger ones, and thus more likely to feature a lower QoL/physical functioning.

Our review is not without limitations. We did not use a traditional systematic literature review approach for this research because it was part of a broader review which aimed to address up to six questions. We however attempted to mitigate the impact of not adopting an SLR approach by using pre-specified inclusion criteria and standardized additional prioritization criteria. This ensured that the single reviewer did not cherry pick papers for inclusion. In addition, as far as we are aware, this paper is the first to attempt to comprehensively capture the outcomes documented here from multiple empirical studies.

Conclusion

This review provides valuable insight into the survival and QoL of long-term survivors of eNSCLC. The evidence consistently showed that patients who underwent curative-intent surgery had a considerable risk of recurrence five or more years following treatment. Relative and conditional relative survival data reported between studies were largely consistent, suggesting that long-term survivors of eNSCLC have excess mortality relative to a similarly aged general population. Disparities in CRS and RS were observed for older patients and those with more advanced disease. Compared with the general population, survivors of NSCLC reported significantly poorer physical QoL compared with other populations. However, these were not long-term studies. This result appears to contrast with findings in other cancers where no detriment in physical QoL was seen in long-term survivors of other cancers [57]. In conclusion, these data highlight the need for better adjuvant treatment strategies to improve long-term survival and QoL of patients who have undergone curative-intent therapy for eNSCLC.

Future perspective

Resectable NSCLC is often treated with surgery followed by adjuvant chemotherapy, which provides only a modest survival benefit of 5% at 5 years. Despite significant advances in the treatment of metastatic NSCLC with targeted therapies and immune-checkpoint inhibitors, the treatment of resectable NSCLC has remained stagnant for over 20 years, with chemotherapy being the mainstay of treatment. However, the recent introduction of adjuvant osimertinib in epidermal growth factor receptor (*EGFR*)-mutated NSCLC, adjuvant atezolizumab in PD-L1 positive NSCLC, and neoadjuvant nivolumab have shown clinically meaningful improvements in survival, heralding a new era for patients with early-stage NSCLC. Ongoing trials with novel drugs, such as tyrosine kinase inhibitors and immune-checkpoint inhibitors, are exploring their efficacy in the neoadjuvant or adjuvant settings, or as a combined perioperative approach (neoadjuvant and adjuvant). However, there are still questions regarding the optimal treatment sequence, drug combinations, and personalized therapies based on disease stage, biomarker

expression, and other patient-specific factors. Addressing these questions will be critical to reduce lung cancer-related death among patients with early-stage NSCLC.

Summary points

- Proportion of patients who remained disease-free over time (without recurrence or death) statistically significantly decrease in patients with stage III disease compared with stage I disease;.
- Proportion of patients who remained-recurrence free over time decreased with age and disease stage;.
- Considerable risk of recurrence 5+ years after surgical resection remained, increasing with disease stage;.
- Conditional 5-year relative survival rates did not exceed 87% in any study, indicating higher rates of all-cause mortality in long-term survivors of early-stage non-small-cell lung cancer compared with members of the general population of the same age, and decrease with age and disease stage;.
- Survivors of early-stage non-small-cell lung cancer reported significantly poorer physical quality-of-life;.
- Need for more effective early-stage treatment to improve long-term survival of patients.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/lmt-2023-0003

Author contributions

N Jovanoski, S Abogunrin, D Di Maio and S Chadda contributed to research design, synthesis and interpretation of findings, and critically reviewed draft manuscripts. K Bowes and A Brown contributed to acquisition, analysis and interpretation of review data and contributed to drafting and critical revision of the manuscript. R Belleli contributed to synthesis and interpretation of findings and critically reviewed draft manuscripts. All authors have read and approved the final manuscript.

Acknowledgments

The authors would like to thank E Kim (previously employed by Genesis Research, New Jersey, USA) and K McAllister (previously employed by Genesis Research, Newcastle upon Tyne, UK) for their research contributions to this review.

Financial & competing interests disclosure

This review was conducted by Genesis Research with funding provided by F Hofmann-La Roche Ltd.

N Jovanoski, S Abogunrin, R Belleli and D Di Maio are employees of F Hoffmann-La Roche Ltd. S Abogunrin holds F Hoffmann-La Roche stock. K Bowes, A Brown and S Chadda disclose that they are employees of Genesis Research, a company that received funding from F Hoffmann-La Roche Ltd for its role in conducting the study and developing the manuscript.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Funding writing assistance was provided to Genesis Research by F Hoffmann-La Roche Ltd.

Ethical conduct of research

This is research involved the use of secondary data available from publicly available literature sources and so did not require collection of information consent.

References

Papers of special note have been highlighted as: • of interest

1. American Cancer Society. Key Statistics for Lung Cancer (2022). www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html
2. Sung H, Ferlay J, Siegel RL *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 71(3), 209–249 (2021).
3. Duma N, Santana-Davila R, Molina JR. Non-small cell lung cancer: epidemiology, screening, diagnosis, and treatment. *Mayo Clin. Proc.* 94(8), 1623–1640 (2019).

4. World Health Organization. International Agency for Research on Cancer Globocan Europe Fact Sheet 2020 (2020). https://gco.iarc.fr/today/data/factsheets/populations/908-europe-fact-sheets.pdf
5. American Society of Clinical Oncology. Lung cancer – non-small cell: introduction (2021). www.cancer.net/cancer-types/lung-cancer-non-small-cell/introduction
6. Soerjomataram I, Lortet-Tieulent J, Parkin DM *et al.* Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet* 380(9856), 1840–1850 (2012).
7. Goldstraw P, Chansky K, Crowley J *et al.* The IASLC Lung Cancer Staging Project: proposals for Revision of the TNM stage groupings in the forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol.* 11(1), 39–51 (2016).
8. National Cancer Institute. Recurrent cancer: when cancer comes back (2020). www.cancer.gov/types/recurrent-cancer#:~:text=Regional%20recurrence%20means%20that%20the,called%20metastasis%20or%20metastatic%20cancer
9. National Comprehensive Cancer Network. Lung cancer – early and locally advanced: non-small-cell lung cancer (2019). www.nccn.org/patients/guidelines/content/PDF/lung-early-stage-patient.pdf
10. American Lung Association. State of Lung Cancer 2020 Report (2020). www.lung.org/getmedia/381ca407-a4e9-4069-b24b-195811f29a00/solc-2020-report-final.pdf
11. Postmus PE, Kerr KM, Oudkerk M *et al.* Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 28(Suppl. 4), iv1–iv21 (2017).
12. Maniwa T, Takahashi S, Isaka M, Endo M, Ohde Y. Outcomes of initial surgery in patients with clinical N2 non-small cell lung cancer who met 4 specific criteria. *Surg. Today* 46(6), 699–704 (2016).
13. Endo C, Sakurada A, Notsuda H *et al.* Results of long-term follow-up of patients with completely resected non-small cell lung cancer. *Ann. Thorac. Surg.* 93(4), 1061–1068 (2012).
14. Janjigian YY, Park BJ, Zakowski MF *et al.* Impact on disease-free survival of adjuvant erlotinib or gefitinib in patients with resected lung adenocarcinomas that harbor EGFR mutations. *J Thorac Oncol.* 6(3), 569–575 (2011).
15. Lee JS, Lee KH, Cho EK *et al.* Nivolumab in advanced non-small-cell lung cancer patients who failed prior platinum-based chemotherapy. *Lung Cancer.* 122, 234–242 (2018).
16. Tsutani Y, Miyata Y, Kushitani K, Takeshima Y, Yoshimura M, Okada M. Propensity score-matched analysis of adjuvant chemotherapy for stage I non-small cell lung cancer. *J. Thorac. Cardiovasc. Surg.* 148(4), 1179–1185 (2014).
17. Brandt WS, Yan W, Zhou J *et al.* Outcomes after neoadjuvant or adjuvant chemotherapy for cT2–4N0–1 non-small cell lung cancer: a propensity-matched analysis. *J. Thorac. Cardiovasc. Surg.* 157(2), 743–753; e743 (2019).
18. Kneuertz PJ, D'Souza DM, Richardson M, Abdel-Rasoul M, Moffatt-Bruce SD, Merritt RE. Long-term oncologic outcomes after robotic lobectomy for early-stage non-small-cell lung cancer versus video-assisted thoracoscopic and open thoracotomy approach. *Clin Lung Cancer.* 21(3), 214–224; e212 (2020).
19. Shin DW, Cho JH, Yoo JE *et al.* Conditional survival of surgically treated patients with lung cancer: a comprehensive analyses of overall, recurrence-free, and relative survival. *Cancer Res Treat.* 53(4), 1057–1071 (2021).

- **Demonstrates that significant excess mortality persists in lung cancer patients and that age and disease stage appear to have a significant effect in the outcome.**

20. Yun JK, Park I, Kim HR *et al.* Long-term outcomes of video-assisted thoracoscopic lobectomy for clinical N1 non-small cell lung cancer: a propensity score-weighted comparison with open thoracotomy. *Lung Cancer.* 150, 201–208 (2020).
21. Landreneau RJ, Normolle DP, Christie NA *et al.* Recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I non-small-cell lung cancer: a propensity-matched analysis. *J. Clin. Oncol.* 32(23), 2449–2455 (2014).
22. Schuchert MJ, Awais O, Abbas G *et al.* Influence of age and IB status after resection of node-negative non-small cell lung cancer. *Ann. Thorac. Surg.* 93(3), 929–935; discussion 935–926 (2012).
23. Marushima H, Kimura H, Miyazawa T *et al.* Survival outcomes of adjuvant chemotherapy with modified weekly nab-paclitaxel and carboplatin for completely resected nonsmall cell lung cancer: FAST-nab. *Anticancer Drugs* 31(2), 177–182 (2020).
24. Park B, Lee G, Kim HK *et al.* A retrospective comparative analysis of elderly and younger patients undergoing pulmonary resection for stage I non-small cell lung cancer. *World J Surg Oncol.* 14(1), 13 (2016).
25. Park SY, Lee JG, Kim J *et al.* Efficacy of platinum-based adjuvant chemotherapy in T2aN0 stage IB non-small cell lung cancer. *J Cardiothorac Surg.* 8, 151 (2013).
26. Janssen-Heijnen ML, van Steenbergen LN, Steyerberg E, Visser O, De Ruysscher DK, Groen HJ. Long-term excess mortality for survivors of non-small cell lung cancer in the Netherlands. *J Thorac Oncol.* 7(3), 496–502 (2012).

- **Demonstrates that significant excess mortality persists in lung cancer patients years after treatment, which could be explained by smoking-related comorbidities.**

27. Wang SJ, Fuller CD, Thomas CR Jr. Ethnic disparities in conditional survival of patients with non-small cell lung cancer. *J Thorac Oncol.* 2(3), 180–190 (2007).

28. Lionikaite V, Curry A, Brown A. POSC300 validation of artificial intelligence for performing systematic literature review searching for clinical efficacy and safety data. *Value in Health.* 25(1), S207 (2022).
29. Michelson M, Dogra R, Goldberg N. Artificial intelligence derived literature searches can provide more relevant data, more quickly than traditional reference databases: a case study. *Curr. Med. Res. Opin.* 37, 7 (2021).
30. Bryant AS, Cerfolio RJ, Minnich DJ. Survival and quality of life at least 1 year after pneumonectomy. *J. Thorac. Cardiovasc. Surg.* 144(5), 1139–1143 (2012).

- **Compares the health related quality-of-life of patients who undergo pneumectomy with the general population and shows that it is lower in the former group.**

31. Hattori A, Matsunaga T, Takamochi K, Oh S, Suzuki K. Locoregional recurrence after segmentectomy for clinical-T1aN0M0 radiologically solid non-small-cell lung carcinoma. *Eur. J. Cardiothorac. Surg.* 51(3), 518–525 (2017).
32. Koike T, Koike T, Yoshiya K, Tsuchida M, Toyabe S. Risk factor analysis of locoregional recurrence after sublobar resection in patients with clinical stage IA non-small cell lung cancer. *J. Thorac. Cardiovasc. Surg.* 146(2), 372–378 (2013).
33. Ostroff JS, Krebs P, Coups EJ *et al.* Health-related quality of life among early-stage, non-small cell, lung cancer survivors. *Lung Cancer.* 71(1), 103–108 (2011).

- **Demonstrates that lung cancer survivors may experience an impairment in physical functioning which could negatively have an effect on their quality-of-life.**

34. Sarna L, Cooley ME, Brown JK *et al.* Women with lung cancer: quality of life after thoracotomy: a 6-month prospective study. *Cancer Nurs.* 33(2), 85–92 (2010).
35. Nomori H, Mori T, Shiraishi A *et al.* Long-term prognosis after segmentectomy for cT1 N0 M0 non-small cell lung cancer. *Ann. Thorac. Surg.* 107(5), 1500–1506 (2019).
36. Maeda R, Yoshida J, Hishida T *et al.* Late recurrence of non-small cell lung cancer more than 5 years after complete resection: incidence and clinical implications in patient follow-up. *Chest* 138(1), 145–150 (2010).
37. Maeda R, Yoshida J, Ishii G *et al.* Long-term outcome and late recurrence in patients with completely resected stage IA non-small cell lung cancer. *J. Thorac. Oncol.* 5(8), 1246–1250 (2010).

- **Demonstrates that some patients with NSCLC may be at risk of late recurrence.**

38. Verstegen NE, Lagerwaard FJ, Hashemi SM, Dahele M, Slotman BJ, Senan S. Patterns of disease recurrence after SABR for early stage non-small-cell lung cancer: optimizing follow-up schedules for salvage therapy. *J Thorac Oncol.* 10(8), 1195–1200 (2015).
39. Butts E, Gococo-Benore D, Pai T *et al.* P08.05 Risk factors associated with recurrence following curative therapy for stage I NSCLC. *J. Thorac. Oncol.* 16(3), S283 (2021).
40. Kelsey CR, Marks LB, Hollis D *et al.* Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. *Cancer* 115(22), 5218–5227 (2009).
41. Lee BE, Port JL, Stiles BM *et al.* TNM stage is the most important determinant of survival in metachronous lung cancer. *Ann. Thorac. Surg.* 88(4), 1100–1105 (2009).
42. Wada H, Toyoda T, Kaiho T *et al.* P2.16-44 Long-term outcome of pulmonary segmentectomy for c-IA non-small cell lung cancer. *J. Thorac. Oncol.* 13(10), S848–S849 (2018).
43. Senthi S, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol.* 13(8), 802–809 (2012).
44. Andreano A, Peake MD, Janes SM *et al.* The care and outcomes of older persons with lung cancer in England and the United States, 2008–2012. *J Thorac Oncol.* 13(7), 904–914 (2018).
45. Driessen EJ, Aarts MJ, Bootsma GP, van Loon JG, Janssen-Heijnen ML. Trends in treatment and relative survival among Non-Small Cell Lung Cancer patients in the Netherlands (1990–2014): disparities between younger and older patients. *Lung Cancer.* 108, 198–204 (2017).
46. Hechtner M, Eichler M, Wehler B *et al.* Quality of life in NSCLC survivors - a multicenter cross-sectional study. *J Thorac Oncol.* 14(3), 420–435 (2019).
47. Grutters JP, Joore MA, Wiegman EM *et al.* Health-related quality of life in patients surviving non-small cell lung cancer. *Thorax* 65(10), 903–907 (2010).

- **Highlights the importance that adverse events have on survivors of NSCLC.**

48. Pennell NA, Neal JW, Chaft JE *et al.* SELECT: a phase II trial of adjuvant erlotinib in patients with resected epidermal growth factor receptor-mutant non-small-cell lung cancer. *J. Clin. Oncol.* 37(2), 97–104 (2019).
49. Winton T, Livingston R, Johnson D *et al.* Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N. Engl. J. Med.* 352(25), 2589–2597 (2005).
50. Zhong WZ, Wang Q, Mao WM *et al.* Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1–N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. *Lancet Oncol.* 19(1), 139–148 (2018).

51. Pignon J-P, Tribodet H, Scagliotti GV *et al.* Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J. Clin. Oncol.* 26(21), 3552–3559 (2008).
52. Lee J, Kim HK, Park BJ *et al.* Recurrence dynamics after trimodality therapy (Neoadjuvant concurrent chemoradiotherapy and surgery) in patients with stage IIIA (N2) lung cancer. *Lung Cancer.* 115, 89–96 (2018).
53. American Cancer Society. Cancer treatment & survivorship facts & figures 2019–2021 (2019). www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2019-2021.pdf
54. Merrill RM, Hunter BD. Conditional survival among cancer patients in the United States. *Oncologist.* 15(8), 873–882 (2010).
55. Department of Health (Quality Health) United Kingdom. Quality of life of cancer survivors in England: report on a pilot survey using patient reported outcome measures (PROMS). Health, Do (2012). https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/267042/9284-TSO-2900701-PROMS-1.pdf
56. Coebergh JW, Janssen-Heijnen ML, Post PN, Razenberg PP. Serious co-morbidity among unselected cancer patients newly diagnosed in the southeastern part of The Netherlands in 1993–1996. *J. Clin. Epidemiol.* 52(12), 1131–1136 (1999).
57. Sugimura H, Yang P. Long-term survivorship in lung cancer: a review. *Chest* 129(4), 1088–1097 (2006).

10.2217/lmt-2023-0003