What is the Definition of Cure in Non-small Cell Lung Cancer?

Helen Morgan · Libby Ellis · Emma L. O'Dowd · Rachael L. Murray ·

Richard Hubbard · David R. Baldwin

ABSTRACT

The concept of cure from cancer is important to patients, but can be difficult to communicate in terms that are meaningful. This is because there are a number of definitions of cure that are applied by clinicians, patients and the public, and by policymakers that have a different meaning and significance. In this article, we provide a narrative review of the evidence concerning cure in lung cancer and show how the different definitions may apply in different settings. A better understanding of the various concepts of cure will improve communication with patients on this important topic. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

H. Morgan · L. Ellis · R. L. Murray · R. Hubbard
Division of Public Health and Epidemiology,
Clinical Sciences Building, Nottingham City
Campus, Hucknall Road, Nottingham NG5 1PB, UK

E. L. O'Dowd · D. R. Baldwin (✉)
Respiratory Medicine Unit, David Evans Research
Centre, Nottingham University Hospitals, City
Campus, Hucknall Road, Nottingham NG5 1PB, UK
e-mail: david.baldwin@nuh.nhs.uk

Key Summary Points

Defining cure is not easy, and patients, clinicians and policymakers use the term in different ways.

Despite the high mortality of non-small cell lung cancer, surgery and radiotherapy with curative intent can be offered if the disease is caught at an early stage.

Statistical cure of lung cancer occurs around 10 years after diagnosis.

Long term survival may be easier for patients to understand, and provide a more personalised prognosis.

Clearly explaining concepts like cure and survival are key in communication with patients.

INTRODUCTION

People who develop cancer often want to know if a cure is possible, and by this they mean that they are free from their cancer. However,

defining 'cure' is not as easy as it might first seem and has generated a great deal of discussion and debate. A common definition of cure in cancer is difficult to give, because the public, patients, clinicians and policymakers use the concept in different ways [1]. The first attempt to define 'cure' was in 1963, and referred to a group of disease-free survivors whose annual mortality was equal to that of the general population [2]. More recently, the Siracusa charter defined 'cured' cancer as *'complete clinical remission of a cancer, regardless of the presence or absence of late sequelae of treatments'* [3]. Progress in diagnosis and treatment has resulted in many cancers now being considered curable. Although lung cancer remains the leading cause of cancer-related death worldwide, advances in early diagnosis and treatment of early-stage disease mean that the concept of cure applies to an increasing number of people [4].

The concept of cure in cancer is complex and is considered differently according to personal or professional perspectives. Epidemiologists consider statistical cure, when the mortality rate of the cancer population returns to that of the general population [5]. Clinicians may be more focussed on personal cure, where they consider the likelihood of each individual patient surviving their cancer in the long term [6]. In contrast, patients and the public may be more interested in their quality of life both during and following treatment, and have a different,

personalised approach to what cure means to them. This is termed 'psychological cure'. This article seeks to clarify the concept of cure by exploring the various definitions and show how these apply to non-small cell lung cancer (NSCLC). A narrative review was written, beginning with a comprehensive search of the literature. Relevant articles were identified by searching PubMED, OVID and EMBASE databases. Search terms used are included in Appendix 1 as text words and medical subject headings where appropriate. Relevant articles were identified through screening of titles and abstracts. In addition, reference lists of relevant articles were manually searched. In total 2495 articles were identified, 120 abstracts screened and 65 full papers reviewed. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Table 1 provides a summary of various terms used in this article in relation to cure that are discussed in more detail below. Although they are separate terms, it will be seen that there is considerable overlap when considering matters from a patient's perspective.

Statistical Cure

Statistical cure is used in epidemiology and public health to consider the outcome of the

Table 1 Glossary of terms

| Measure	Definition
Statistical cure	The risk of dying or relapsing has become equal to the mortality of age matched general population
Cure point	The length of time from diagnosis to statistical cure
Cure fraction	The proportion of cancer patients who reach the cure point, and their mortality equals that of the general population
Personal cure	When a patient dies from a cause other than their cancer
Personal cure rate	The proportion of patients dying from causes other than their cancer
Psychological cure	A patient feels the chances of their disease returning is sufficiently low to consider themselves effectively cured
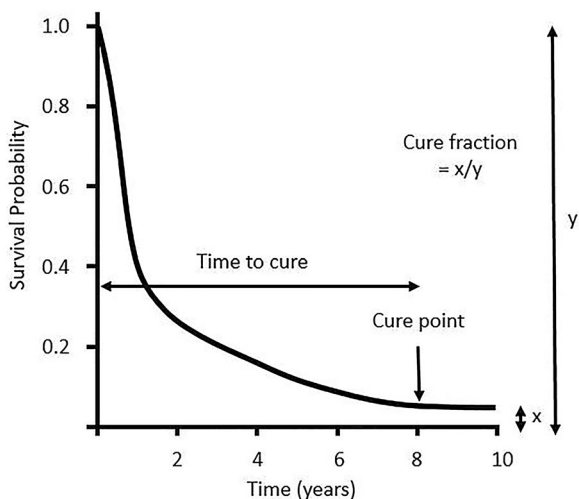
Fig. 1 Graphical illustraion of concepts in statistical cure

whole population of cancer patients. It is useful to policymakers for standardising care across different settings, such as follow-up time [1, 7]. It occurs when the mortality rate of cancer patients returns to the baseline level of the general age-matched population. In other words, if no more cancer patients in a cohort die or relapse from their disease, the risk of death is equal to that of disease-free controls, and statistical cure has been reached [8].

Cure models are used to separate fatal cases from those with the same mortality as the general population [9]. If relative survival is plotted on a survival curve, as patients either die or relapse, they are removed, reaching a time point after which no more patients relapse or die from their cancer or its treatments. At that point, the curve will remain flat. The time point from diagnosis to when this occurs is called the cure point, or time to cure [7, 8]. The proportion of patients still alive is the cure fraction [1]. Figure 1 illustrates these points. A number of statistical techniques can be applied in models to establish the factors that are important in determining cure [10].

In some instances, the relative survival curve may not appear to flatten, implying that either the disease is incurable, or insufficient time has passed for statistical cure to be achieved. Breast cancer patients, for example, can relapse decades after their initial treatment. In these cases,

5-year or even 10-year survival is an inadequate surrogate for statistical cure [8].

Colorectal cancer is the third most common type of cancer and curative treatments are well established, which has allowed examination of statistical cure. As survival of colorectal cancer has improved, many patients will now die from causes other than the cancer, most commonly heart disease [6]. Ninety percent of people with stage I colorectal cancer diagnosed at age 70 will not die of their cancer within 10 years, but instead are more likely to die from other causes: they have been cured [6]. For colorectal cancer, the time to statistical cure has been estimated to vary from 7 to 11 years, based on age, gender and stage of malignancy at diagnosis [1].

For NSCLC, statistical cure is less well established. Attempts have been made to estimate both the cure fraction and time to cure, but the low overall survival has made the calculation challenging. The cure fraction has been estimated to vary between 6 and 11%, with a time to cure of 9 to more than 10 years, where it could be calculated [1]. A study using the Surveillance, Epidemiology, and End Results (SEER) database in the United States calculated a much higher cure fraction of 17%, with time to statistical cure of 9 years from diagnosis [7]. Estimates using the EUROCARE-4 cancer registries found the cure fraction for lung cancer varied from 4.1 to 10.3% across Europe. There was a four-fold variation in cure based on age at presentation, with 16.2% of 15–44-year-olds being cured, compared with 3.5% of 75–99-year-olds [9]. These results are summarised in Table 2.

Whilst the majority of NSCLC does recur in the first 5 years following treatment, these data suggest that the commonly used 5-year survival would be insufficient as a surrogate for statistical cure, and therefore not appropriate as an end point for follow-up [7]. Between 9 and 10.6% of NSCLC patients who are disease-free at 5-years will have a recurrence in the subsequent 5 years [11, 12]. Due to the difficulty in differentiating between a locoregional recurrence and a new primary NSCLC, this may be an overestimation, but does support the notion that 5-year survival cannot be used as an accurate surrogate for statistical cure.

Table 2 Estimates of cure fraction and time to cure

Publication	Cure fraction	Time to cure
Tai, USA, 2005 (Age < 60) [1]	17%	9 years
Francisci, Europe (EUROCARE-4), 2009 [2]	4.1–10.3% (stratified by country)	–
Cvancarova, Norway, 2013 [3]	10.2% (males) 13.7% (females)	–
Dal Maso, Italy, 2014 [4]	6–17% (males) 7–30% (females)	10 years (males) 9 years (females)

NSCLC is a heterogeneous disease, with driver mutations causing both prognostic and predictive changes. Unfortunately, owing to the overall low survival associated with NSCLC, studies looking at the impact of mutations on cure (rather than survival) have not been completed. It is therefore beyond the scope of this article to address how they might impact the cure fraction or time to cure.

Personal Cure

Whilst the epidemiological approach is a useful way in which to understand how statistical cure from lung cancer relates to overall mortality in a population, statistical cure does not readily translate to what an individual patient can expect for the future. This is instead considered by personal cure, which is the time at which an individual cancer patient has no detectable cancer cells, and their life expectancy is no longer shortened by their malignancy [1]. The issue is that, at the time of diagnosis and treatment, an individual can only be given a probability of personal cure based on the statistical cure, and this in turn depends on many factors. Thus, average survival figures have to be used in communicating with patients.

In reality, if detailed information is required by a patient or carer, survival at 1 year and 5 years, and how this is influenced by prognostic markers such as performance status (PS) and stage of cancer, is likely to be easier for patients to understand, and provides a more personalised prognosis. Patients will often want to discuss how different modalities of curative-intent treatment influence this. When talking to lung cancer patients, we must clearly explain our treatment goals to the individual and define precisely what we mean when we use the word 'cure'. In some cases it is perhaps better to avoid discussion of cure and instead refer to the chance of long-term survival [13].

Psychological Cure

Psychological cure is term applied to describe the patients' perception of the status of their cancer as no longer a threat to their life. Patients' opinions on this vary, with some cancer patients finding the concept of cure reassuring, and others feeling the risk of their cancer will always be there, and cure is therefore an inappropriate word. In the case of slowly progressive or indolent cancers, they may never be cured from their cancer, but are still more likely to die of another cause [14]. Patients also highlight the importance of quality of life rather than simply survival time [15]. Some patients refer to a psychological cure, where they acknowledge that there is still a continued risk of a cancer returning, but they feel the treatment they have had is effective enough to prevent the cancer from impacting their mortality, so they are able to continue their lives, considering themselves no longer a cancer patient [16].

In 1985, Dr Mullan, an American physician, published an article describing his experiences as a cancer patient, and 'the goal of cure' [17]. Following diagnosis, treatment and remission, he described the final phase of cancer survivorship as permanent survival or cure. Since then, advances in treatment have meant that many patients now live with metastatic cancer who would not have previously [16]. This change has resulted in an alternative possible outcome of 'extended survival', rather than cure, and affects how many patients feel about their cancer journey.

Communication with Patients and Carers

Surveys have found that shortly after their diagnosis, less than half of newly diagnosed lung cancer patients knew the goal of their treatment, and only 39% were satisfied with the discussion of this [18]. A survey of surgeons reflected this, with 70% explaining what cure meant to their patients and only 40% consistently discussing the possibility of cure preoperatively [19]. The majority of oncologists are hesitant to use the term 'cured' with their patients [3], and report that less than half of cancer patients actually ask whether they have been cured [16]. 'Cancer survivor' is sometimes favoured. It has a wide definition, from someone who has been diagnosed with cancer and has started treatment, to being alive 5 years following diagnosis, regardless of the state of the disease, to a patient who has undergone personal cure, with no chance of their cancer returning [20]. It is important therefore that clinicians try to be as clear as possible on each occasion they communicate.

Communication should follow accepted good practice that include first establishing what the patient knows, what they have been told, and the source and what level of detail they want. The giving of information should be tailored to the patient's needs and preferences within a framework of a necessary minimum to allow treatment and ongoing management to proceed. If used, the terms survival and cure should be explained in a way that can be understood by the patient and their family or carers.

CONCLUSION

Whilst NSCLC continues to have low long-term survival, advances in early diagnosis and treatment are leading to more people being cured. However, the terminology around cure and long-term survival varies between clinicians, policymakers and patients. This can manifest in confusion for clinicians and patients, leading to distress for patients who may feel they have been misled by their clinical teams. Understanding the terms and how these relate to an individual patient is an important aspect of care and forms an essential part of management from diagnosis to treatment and beyond.

ACKNOWLEDGEMENTS

APPENDIX 1: SEARCH TERMS USED IN THE SYSTEMATIC REVIEW

Lung	Lung
	Pulmon*
	Bronch*
	Respiratory

Appendix continued

Cancer	Cancer*
	Carcino*
	Neoplas*
	Malignan*
Cure	Cure*
	Curative
	Statistical cure
	Personal cure
Non-small cell	Non-small cell
	NSCLC
	Adenocarcinoma
	Squamous cell
Survival	Surviv*
	Outcome*
Radical radiotherapy	Radical radiotherapy
	SABR
	Stereotactic ablative radiotherapy
	CHART
	Continuous hyperfracctionated accelerated radiotherapy
Surgery	Surgical
	Surger*
	Resect*

The * means that any susequent letters included a word in the search

REFERENCES

1. Tralongo P, Surbone A, Serraino D, Dal Maso L. Major patterns of cancer cure: clinical implications. Eur J Cancer Care. 2019;28:6.

2. Easson EC, Russell MH. Cure of Hodgkin's disease. 1963.

3. Tralongo P, Maso LD, Surbone A, Santoro A, Tirelli U, Sacchini V, et al. Use of the word "cured" for cancer patients—implications for patients and physicians: the Siracusa charter. Curr Oncol. 2014;22(1):38–40.

4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

5. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. Biostatistics. 2007;8(3):576–94.

6. Yu B, Tiwari RC, Feuer EJ. Estimating the personal cure rate of cancer patients using population-based grouped cancer survival data. Stat Methods Med Res. 2011;20(3):261–74.

7. Tai P, Yu E, Cserni G, Vlastos G, Royce M, Kunkler I, et al. Minimum follow-up time required for the estimation of statistical cure of cancer patients: verification using data from 42 cancer sites in the SEER database. BMC Cancer. 2005;5(1):48.

8. Jakobsen LH, Andersson TML, Biccler JL, Poulsen LØ, Severinsen MT, El-Galaly TC, et al. On estimating the time to statistical cure. Bmc Med Res Methodol. 2020;20(1):71.

9. Francisci S, Capocaccia R, Grande E, Santaquilani M, Simonetti A, Allemani C, et al. The cure of cancer: a European perspective. Eur J Cancer. 2009;45(6):1067–79.

10. Othus M, Barlogie B, Leblanc ML, Crowley JJ. Cure models as a useful statistical tool for analyzing survival. Clin Cancer Res. 2012;18(14):3731–6.

11. Okada M, Nishio W, Sakamoto T, Harada H, Uchino K, Tsubota N. Long-term survival and prognostic factors of five-year survivors with complete resection of non–small cell lung carcinoma. J Thorac Cardiovasc Surg. 2003;126(2):558–62.

12. Maeda R, Yoshida J, Hishida T, Aokage K, Nishimura M, Nishiwaki Y, et al. Late recurrence of non-small cell lung cancer more than 5 years after complete resection. Chest. 2010;138(1):145–50.

13. Effinger KE, Link MP. For patients with cancer, cure is not enough. JAMA Oncol. 2015;2(2):1–3.

14. Khan NF, Rose PW, Evans J. Defining cancer survivorship: a more transparent approach is needed. J Cancer Surviv. 2012;6(1):33–6.

15. Yang P, Cheville AL, Wampfler JA, Garces YI, Jatoi A, Clark MM, et al. Quality of life and symptom burden among long-term lung cancer survivors. J Thorac Oncol. 2012;7(1):64–70.

16. Miller K, Abraham JH, Rhodes L, Roberts R. Use of the word "cure" in oncology. J Oncol Pract. 2013;9(4):e136–40.

17. Mullan F. Seasons of survival: reflections of a physician with cancer. New Engl J Med. 1985;313(4):270–3.

18. Gabrijel S, Grize L, Helfenstein E, Brutsche M, Grossman P, Tamm M, et al. Receiving the diagnosis of lung cancer: patient recall of information and satisfaction with physician communication. J Clin Oncol. 2008;26(2):297–302.

19. Winner M, Wilson A, Yahanda A, Kim Y, Pawlik TM. A cross-sectional study of patient and provider perception of "cure" as a goal of cancer surgery. J Surg Oncol. 2016;114(6):677–83.

20. Khan NF, Harrison S, Rose PW, Ward A, Evans J. Interpretation and acceptance of the term 'cancer survivor': a United Kingdom-based qualitative study. Eur J Cancer Care. 2012;21(2):177–86.