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How Long Do I Have, Doc!

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As a graduate of Rawalpindi Medical College and an oncologist in Australia for quite some time, I felt both honoured and humbled when I was requested to write this editorial. Reflecting on my early postgraduate years, I recall being a young doctor, full of energy, vigour, and enthusiasm, with an unwavering belief that we could cure all ailments and 'fix anything'. This youthful optimism nurtured my enduring commitment to improving cancer outcomes. That passion led me through a diverse journey across academic teaching, clinical practice, research, and drug development, ultimately culminating in a focus that brings together the best of early-phase oncology research and patient care.

In those early years, as junior doctors, we were unaccustomed to accepting 'defeat,' encountering failure, or witnessing things go wrong. Accepting death as a possible outcome was perhaps our greatest challenge. Over time, however, maturity and understanding developed that while we must always make the best possible effort to heal—using our knowledge, skills, and experience—we must also recognise when to let go. Death is not a personal or professional failure; it is an inevitable reality to be accepted once all realistic avenues have been exhausted.

Hence, the question, 'How long do I have, Doc?' is one that I must be prepared to answer every day in my practice. I do not carry a crystal ball that can predict the future, nor do I have any special powers; however, oncology has taught me both the science and the art of prognostication. Cambridge defines prognosis as a judgment or the act of making a judgment about what is likely to happen in the future. In medicine, this translates to the process of predicting the likely future course, duration, and outcome of a disease or medical condition. It involves estimating the risks of recurrence or recovery, guiding treatment choices, and managing expectations regarding survival or functional impairment.

Understanding a clinical scenario and predicting a certain outcome (such as survival) must be based on a strong scientific rationale. In oncology, overall survival (OS)—defined as the time from diagnosis or treatment initiation until death—remains the gold standard for demonstrating definitive clinical benefit. As an objective and unambiguous metric, it is the most persuasive and universally accepted endpoint in clinical trials. While OS is ideal, it is also one of the most difficult endpoints to improve in modern oncology. Although many surrogate endpoints, such as progression-free survival, response rates, and quality of life, are frequently evaluated, OS continues to carry the greatest weight for clinicians, regulators, and payers.

In the last 25 years, the overall survival for all cancers has improved by 25% [1]. Cancer diagnosis, once considered a 'curse' (lack of effective treatments and relatively short survival in advanced cancers), is now discussed as a manageable and (potentially) curable disease. Over the last few decades, there has been tremendous development in our understanding of cancer biology and pathogenesis; consequently, a plethora of innovative breakthrough medications targeting various biomarkers and immune and genetically driven pathways have been developed. In addition, early diagnosis, screening, better diagnostic modalities, improved and precise surgical approaches, advances in radiation treatment, and multidisciplinary care have all contributed positively to improving cancer outcomes.

If OS remains the most desired outcome, the goalposts keep changing—a shift that is best understood through a few examples. Median survival for stage IV non-small cell lung cancer (NSCLC) at the turn of the century was remarkably short, often recorded at 6.6–8.5 months. By 2026, the expected overall five-year relative survival rate for lung cancer is approximately 28–30%, and for metastatic (stage IV) disease, it is 10%, representing a five-fold increase from the 2% reported two decades ago. Recent studies have further highlighted this progress. Lorlatinib, an anaplastic lymphoma kinase (ALK) inhibitor, has shown in the randomised Phase 3 CROWN[2] study that for patients with advanced ALK+ NSCLC treated with the drug, 60% remained disease-free at five years, 63% were progression-free, and 76% were alive. Similarly, the KEYNOTE-024[3] study demonstrated that pembrolizumab, an immunotherapeutic agent and programmed cell death protein 1 (PD-1) inhibitor, achieved a durable, clinically meaningful long-term OS benefit in first-line metastatic NSCLC with a PD-L1 tumour proportion score of at least 50%. Kaplan-Meier (KM) estimates of the five-year OS rate were 31.9% in the pembrolizumab group versus 16.3% in the chemotherapy group.

These studies, along with many others, have established the role of targeted and biomarker-driven approaches in achieving significantly higher survival rates for many cancers today.

Modern oncology is evidence-based, and we pick the strongest evidence while justifying a treatment decision. A statistically significant outcome may not always be perceived as clinically meaningful by patients. Quality-of-life measures are therefore routinely incorporated into clinical trials to holistically capture statistical and clinically relevant patient-reported outcomes. Treatment decisions often involve trade-offs between benefits, harms, and inconveniences. With this in mind, we

Published 31/03/2026
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How to cite this article: Alam M. How Long Do I Have, Doc! JRMC. 2026 Mar. 31;30(1).

https://doi.org/10.37939/jrmc.v29i4.3221

performed a review4,[4] of published studies to identify, evaluate, and summarise the benefits that cancer patients judged sufficient to make chemotherapy for NSCLC worthwhile. We found that most patients with NSCLC considered moderate survival gains—such as a 10% absolute increase in survival or six additional months of life—sufficient to justify chemotherapy. Although individual preferences varied widely, the benefits judged sufficient ranged from very small to very large (1% to 50%). Patient preferences and choices are also better understood and appreciated by clinicians and regularly incorporated into the decision-making process.

Another study was performed to derive a model to interpret the survival benefit from interventional clinical trials and formulate this scientific data into a meaningful conversation around prognosis. We searched for randomised first-line chemotherapy trials in advanced or metastatic NSCLC published from January 2000 to April 2008. We recorded the median time to progression (TTP) and median overall survival and extracted the following percentiles (representing scenarios) from each OS curve: 90th (worst-case), 75th (lower-typical), 25th (upper-typical), and 10th (best-case). We concluded that simple multiples of an OS curve's median provided accurate estimates of typical (half to double the median), best-case (triple the median), and worst-case (one quarter of the median) life expectancy scenarios for patients starting chemotherapy for advanced NSCLC[5]. Applying this in real life, for a median OS of 12 months, if 100 patients were to have the same treatment, half of them would survive 6 to 24 months (typical case), whereas a 10% chance each to not benefit (worst case ~2 months) or derive the most benefit (best case~ 36 months).

The prognosis of various tumours widely varies, depending on the stage at presentation, interventions received, and various disease-related factors (e.g., size, grade, invasion, nodal or distant spread, biomarkers, genetic factors, targetable mutations, and many others), as well as patient factors (such as age, performance status, comorbidities, organ dysfunction, and fitness to undergo various procedures and interventions). Many cancers, like testicular and breast, when treated early (stage 1), have a 5-yr survival close to 100%. The 5-year overall survival rate for breast cancer in Australia is 93%, and for prostate cancer, it is 95–97%. This contrasts with some others, like pancreas or high-grade gliomas, where less than 1 in 5 is alive 5 yrs from diagnosis. Any prognostic discussion with these patients and their families would be unique and individualised. While OS remains the desired goal in Oncology, it is also true that individual outcomes from one patient to another may never be the same. Beyond traditional clinical and pathological factors, genomic and biomarker-based tools now assist clinicians in estimating treatment benefits and framing prognostic discussions.

Returning to the question, “How long do I have, Doc?”, the answer is rarely simple or uniform. Prognostic discussions must be evidence-based, avoid precise point estimates, and instead provide ranges and scenarios that support decision-making and future planning. This can often be challenging and daunting, as there may be prohibitions and inhibitions that need to be overcome. At the same time, it has been shown that most patients and families want to know and appreciate the truthful information to be provided, and such conversations have been shown to improve the QoL of patients and carers.

When I convey a prognosis, I remind myself of the nuances of any such discussion, prepare myself for the tangible outcomes, and strive to communicate the information with empathy and compassion, offering hope where appropriate, maintaining a realistic attitude, hoping for the best, and preparing for the unknowns and unexpected. It is indeed an art to convey prognosis, and this art of knowing what the patient wants, how much, and what to say, timing of such discussions, and anticipating the emotional impact must be carefully balanced with a reasonably well-worded scientific rationale based on good evidence.

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