Open Peer Review on Qeios

COMMENTARY

Emphasizing the Vital Role of Robust Peer Review: A Series of Publications Highlighting Potential Errors in Results Reporting and a Plea to Editors

Leticia Bornstein-Quevedo[1], Alfonso Dueñas-Gonzalez[2,3]

1 Immunohistochemistry and Molecular Biology Laboratory, InmunoQ, Mexico City, Mexico

2 Departamento de Medicina Genómica y Toxicología Ambiental, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Mexico

3 Subdirección de Investigación Básica, Instituto Nacional de Cancerología, Tlalpan, Mexico

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Purpose: We present a series of publications on lung cancer in several well-recognized medical journals that present potential errors in the analyses and results of survival data. Our work stresses that a publication in a 'peer-reviewed journal' may not guarantee complete fact-checking or accuracy.

Methods: We gathered publications on lung cancer on which we previously established communication with editors via formal letters to the editor and direct communications with them to comments on these works.

Results: We present our analysis on survival results of eight publications in different journals. We found that these works did not meet the basic survival analysis principles. First, the progression-free survival (PFS) or overall survival (OS) percentages visually estimated from the curves do not match the number of events described in the figures or text at the median follow-up times of reporting. Secondly, death events are more common than progression events are, resulting in higher PFS than OS curves. These two issues may severely jeopardize the authors' conclusions. Surprisingly, the journal editors communicated via formal letters or direct correspondence and did not find mistakes or did not answer. Our work is beyond consideration as to whether these mistakes were deliberate or came from an honest error of the authors.

Conclusions: We state that journal editors should play a more active role in ensuring the accuracy of publications. Inaccurate data can significantly influence physicians' treatment decisions, potentially leading to ineffective treatments. This underscores the importance of our work and the need for improved accuracy in medical publications, as it directly impacts the professional practice of physicians.

Corresponding author: Alfonso Duenas-Gonzalez, alfonso_duenasg@yahoo.com

Introduction

Scientific journals constitute a fundamental part of the progress of science. In medicine, they also directly impact medical care since they inform the medical community about medical progress and are key for formulating patient management guidelines. Therapeutic decisions must be based on the results of clinical studies that provide maximum evidence of benefit. Therefore, research must be conducted with the highest methodological, ethical, and scientific rigor[1][2].

In medicine, a field of immense complexity, often, a physician, having exhausted all therapeutic options recommended by evidence-based guidelines, must turn to studies with lower levels of evidence or even preclinical studies to make informed decisions, such as prescribing drugs off-label. Off-label drug prescription is a common practice in the medical community. Recognizing its importance, medical ethics bodies, the FDA, and most courts consider it essential for optimal patient care[3]. This underscores the critical role of rigorous peer review in scientific journals, preventing the dissemination of unsubstantiated conclusions that could harm patients.

Most scientific journals adhere to globally promoted documents of editorial policies and ethical guidelines, such as the Recommendations of the International Committee of Medical Journals Editors (ICMJE), which contains statements on proper research reporting, reviewing, editing, and publishing, and the Committee on Publication Ethics (COPE) of core practices, comprehensively reflecting on the significant issues in publication ethics[4]. Ethical guidelines and editorial policies aim to ensure that the published works are of good quality. Furthermore, editors and authors generally act in good faith; however, despite the above, there is increasing information about cases of scientific dishonesty that lead to the withdrawal of publication by the author or editor. In Oncology, one of the most representative examples is the positive results of two high-dose chemotherapy studies in breast cancer, which led to thousands of breast cancer patients in the world undergoing this procedure. Several years later, these studies were falsified. Although it ended with a sanction for the researcher, the damage was done[5]

In this work, we present a series of cases of clinical oncology studies that from our analysis these were published with errors in their results. The questionable is that the editors have been informed about these potential mistakes by formal *letters to the editor* or by direct communication by e-mail, and the journals have yet to decide to take action. In principle, these actions from Editors ignoring legitimate concerns do not benefit society and can potentially put patients' health at risk. In all cases, the here presented, potential errors occur in the survival analysis which can lead to erroneous conclusions.

Currently, the most common way to present survival results in oncology studies is with survival curves generated via the Kaplan–Meier method. These curves are compared with the log-rank test to determine whether there are statistically significant differences between groups and with multivariate analysis via the Cox method to determine which factors affect survival[6][7].

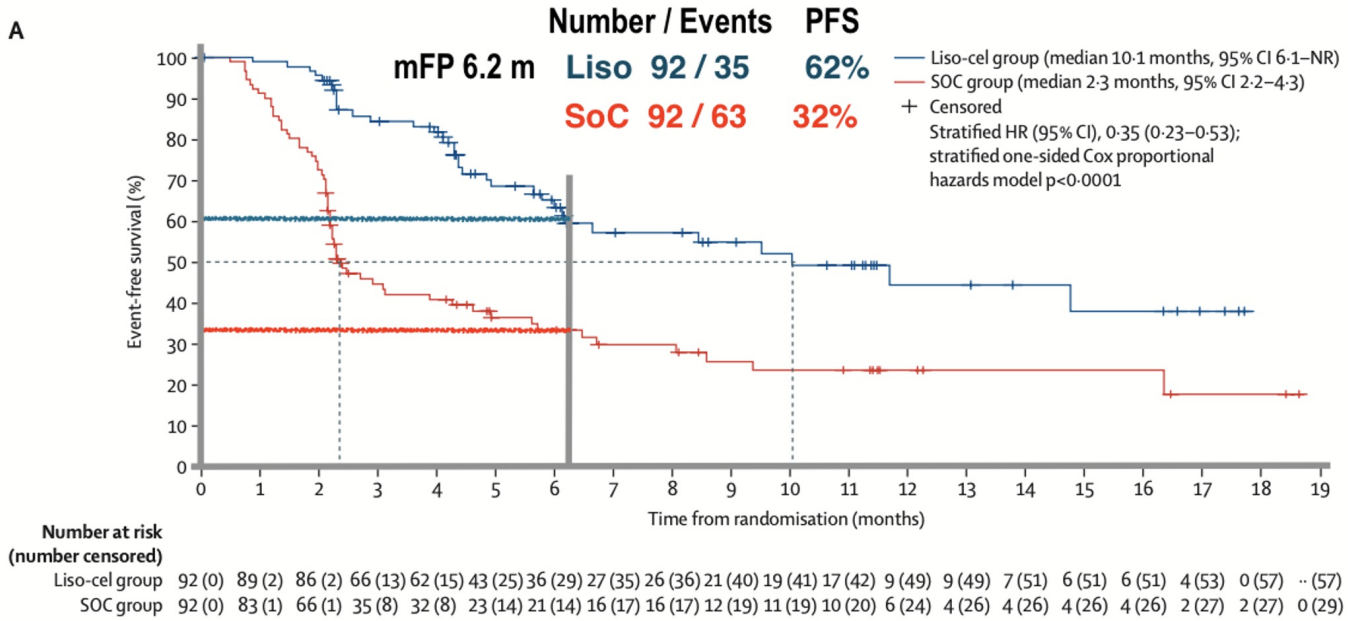
Authors, when presenting survival results, typically do as follows: "The results of this study demonstrate that at a median follow-up of …. months, the median survival is …. months, and the survival probability percentages at 12 and 24 months are ….% and ….%, respectively". These numbers and percentages must correspond with what is drawn in the curves. It is

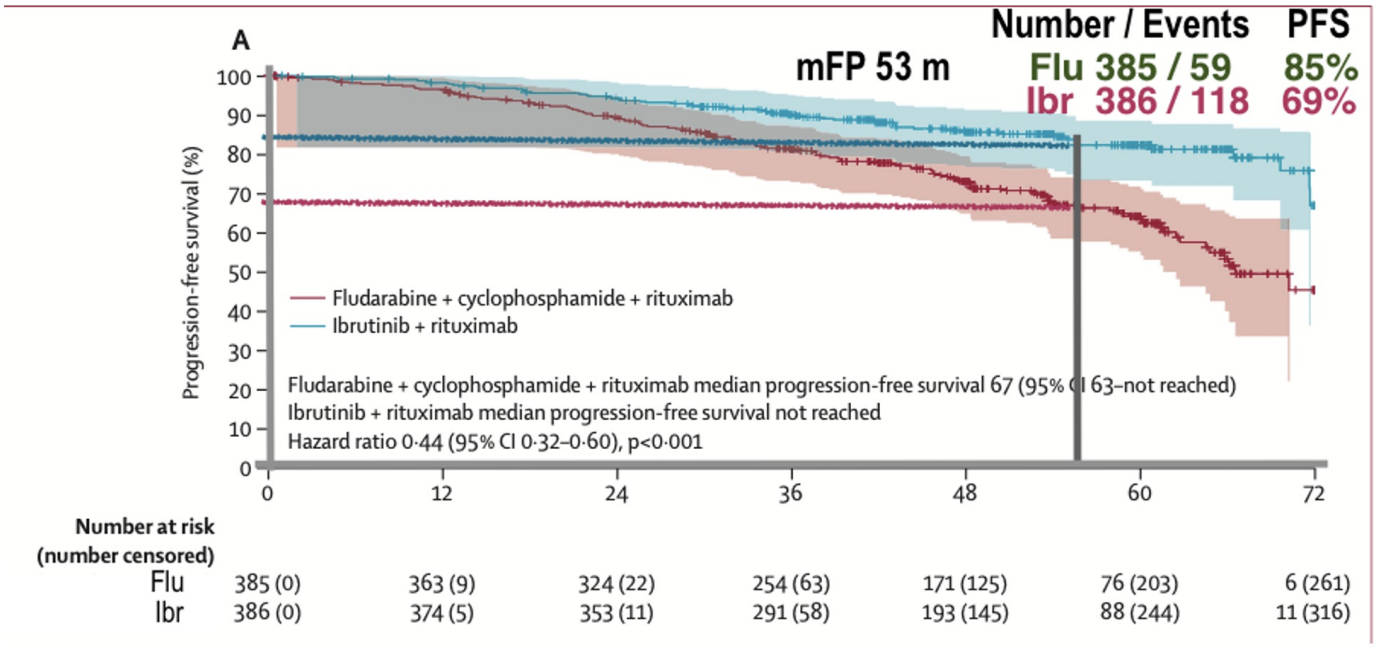
essential to clarify that when a study is reported, it must state the median follow-up time, the total number of events in the study population, and any arm thereof. Hence, the survival percentages obtained by the number of events must correspond to what is observed in a vertical line drawn on the curve on the X-axis (time) on the median survival time.

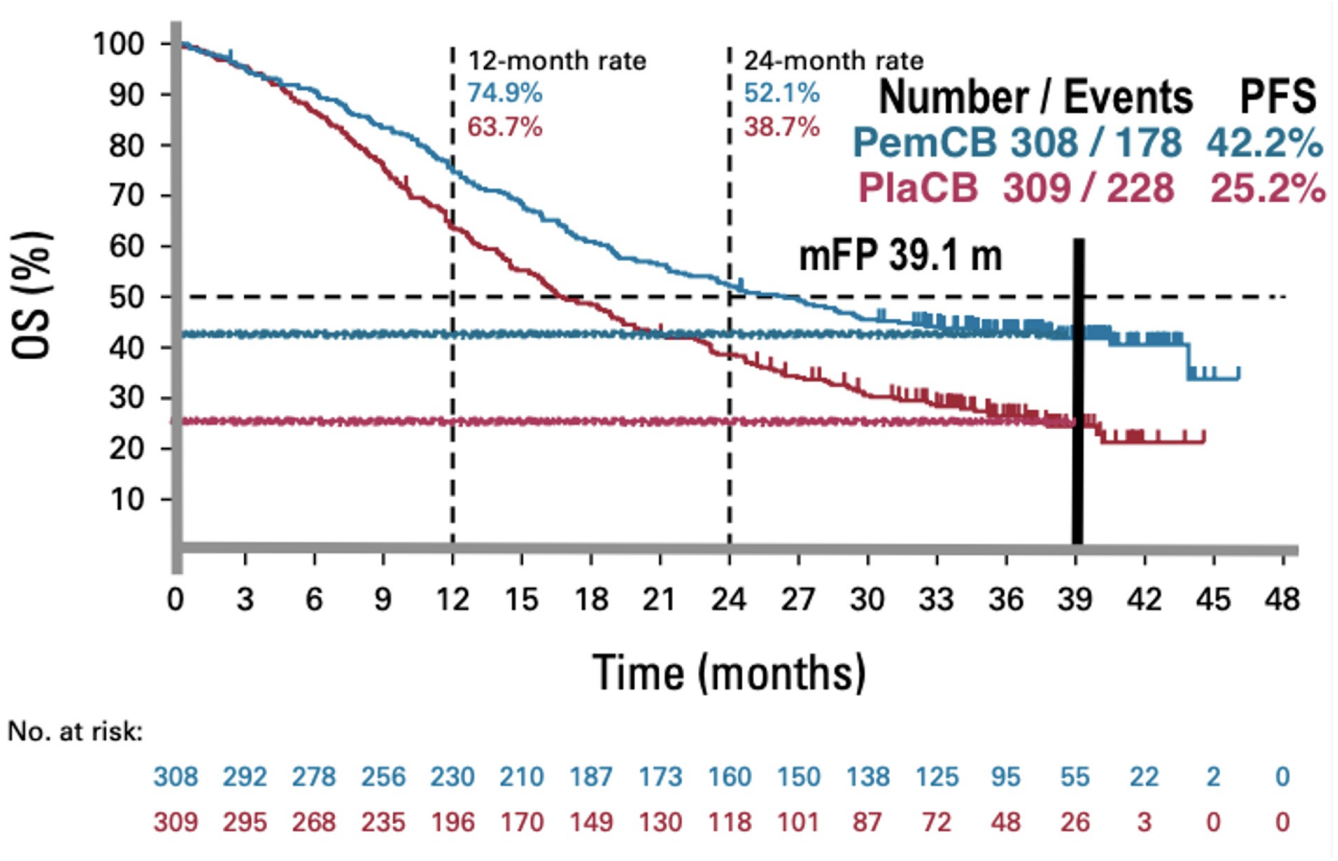
A second fundamental observation is that the two survival parameters most commonly used (endpoints) are progression-free survival (PFS) and overall survival (OS). The first refers to patients who suffer the event (progression), and the second refers to patients who suffer the event (death). Both parameters are usually defined in the time since patients enter the study from the time they suffer the event of interest or are censored (censored refers to patients who leave the study for any reason without having suffered the event at any time during the study or end the study time without having the event). Censoring and event times apply to both PFS and OS. Therefore, the OS curve (median survival time, survival percentages) should always be superior to the PFS curve because a fundamental requirement for relapse or progression is survival. A patient who has died cannot have progression assessed.

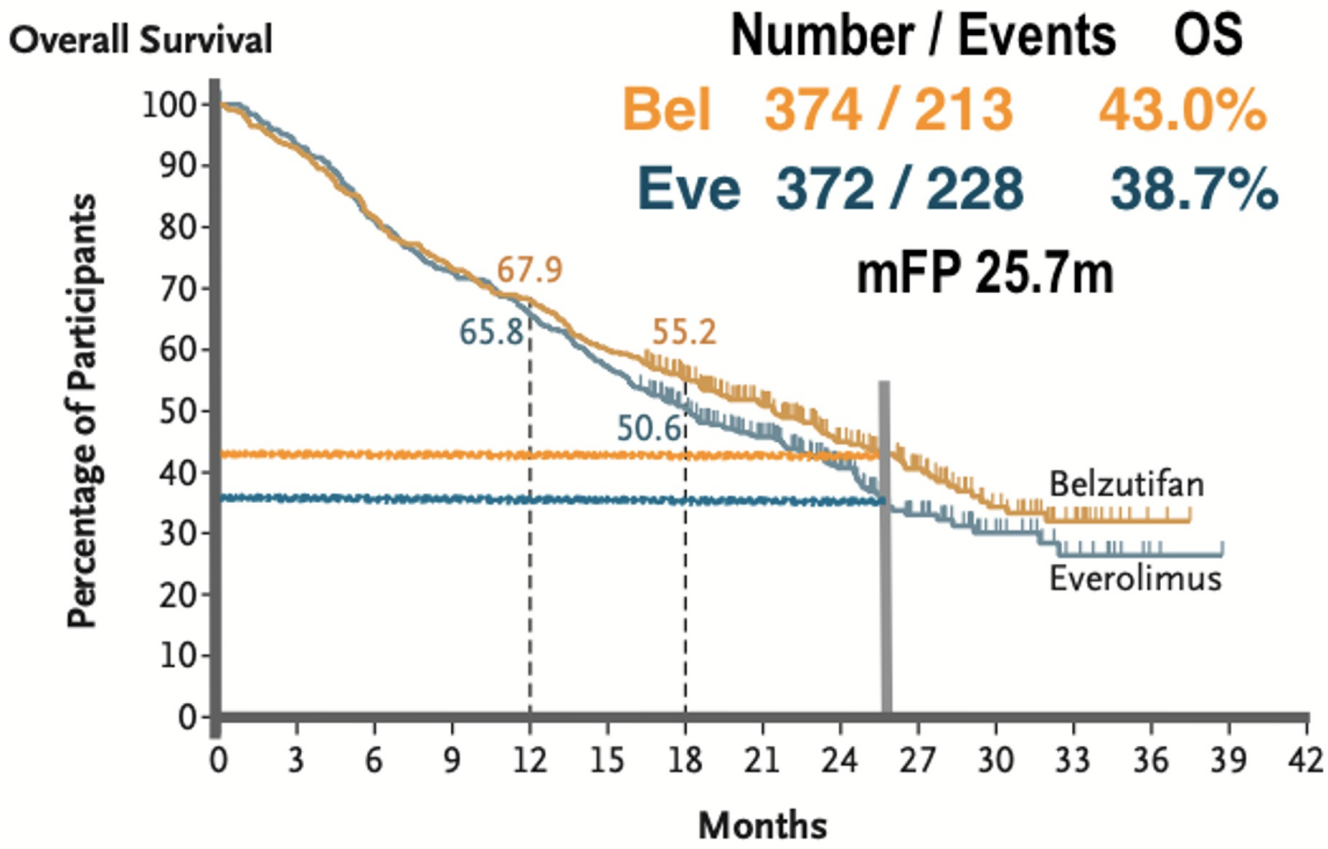
Therefore, in any study, the survival percentage determined by the number of events 1) must correspond to the survival percentage at the median follow-up, and 2) the PFS curve cannot be higher than the OS curve. If the opposite is observed, it means fatal errors (involuntary or involuntary) that invalidate the conclusion. Therefore, the study must be withdrawn since correcting it requires substantial changes and a new revision.

The following is a series of survival curves from randomized phase III studies published in well-reputed journals (**Figure 1**) in which requirement 1 was met[8][9][10][11][12]. The percentages of the number of events match the curves at the median follow-time.




A
Number / Events PFS
mFP 53 m
Flu 385 / 59 85%
Ibr 386 / 118 69%
Progression-free survival (%)
Fludarabine + cyclophosphamide + rituximab
Ibrutinib + rituximab
Fludarabine + cyclophosphamide + rituximab median progression-free survival 67 (95% CI 63–not reached)
Ibrutinib + rituximab median progression-free survival not reached
Hazard ratio 0·44 (95% CI 0·32–0·60), p<0·001
Number at risk
(number censored)
Flu 385 (0) 363 (9) 324 (22) 254 (63) 171 (125) 76 (203) 6 (261)
Ibr 386 (0) 374 (5) 353 (11) 291 (58) 193 (145) 88 (244) 11 (316)


12-month rate
74.9%
63.7%
24-month rate
52.1%
38.7%
Number / Events PFS
PemCB 308 / 178 42.2%
PlaCB 309 / 228 25.2%
mFP 39.1 m
OS (%)
Time (months)
No. at risk:
308 292 278 256 230 210 187 173 160 150 138 125 95 55 22 2 0
309 295 268 235 196 170 149 130 118 101 87 72 48 26 3 0 0



No. at Risk

Belzutifan	374	347	305	274	254	224	190	143	95	62	36	16	2	0	0
Everolimus	372	347	301	270	244	212	170	124	83	43	23	11	2	0	0

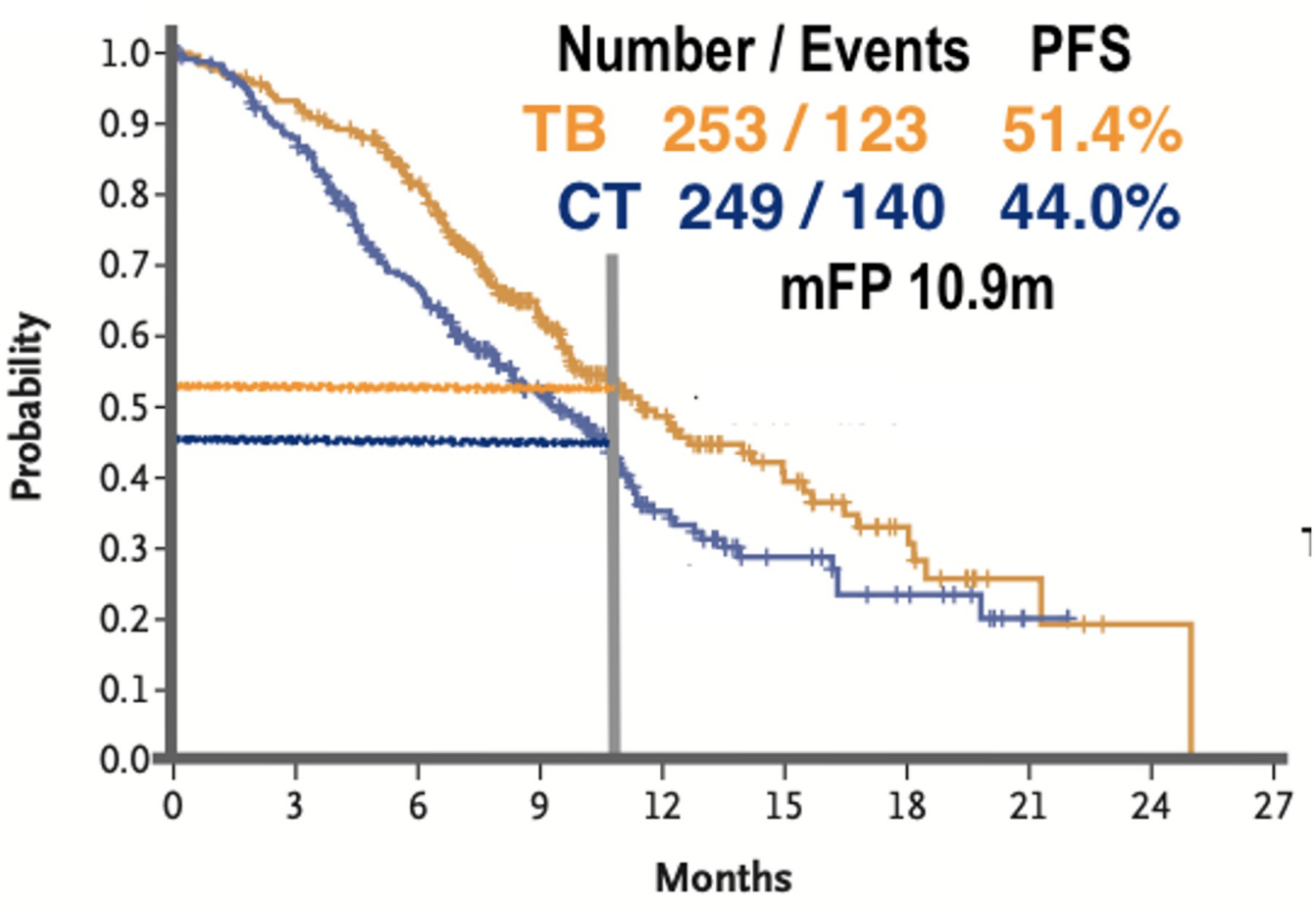


Figure 1. The five curves from different trials published in well-reputed journals (*The Lancet, The Lancet Oncol, J Clin Oncol, NEJM)* , show concordance between the percentages PFS and OS estimated from the number of events with the showed in the curve at median follow-up time[8][9][10][11][12].

On the other hand, **Figure 2** illustrates why OS must always be higher than PFS.

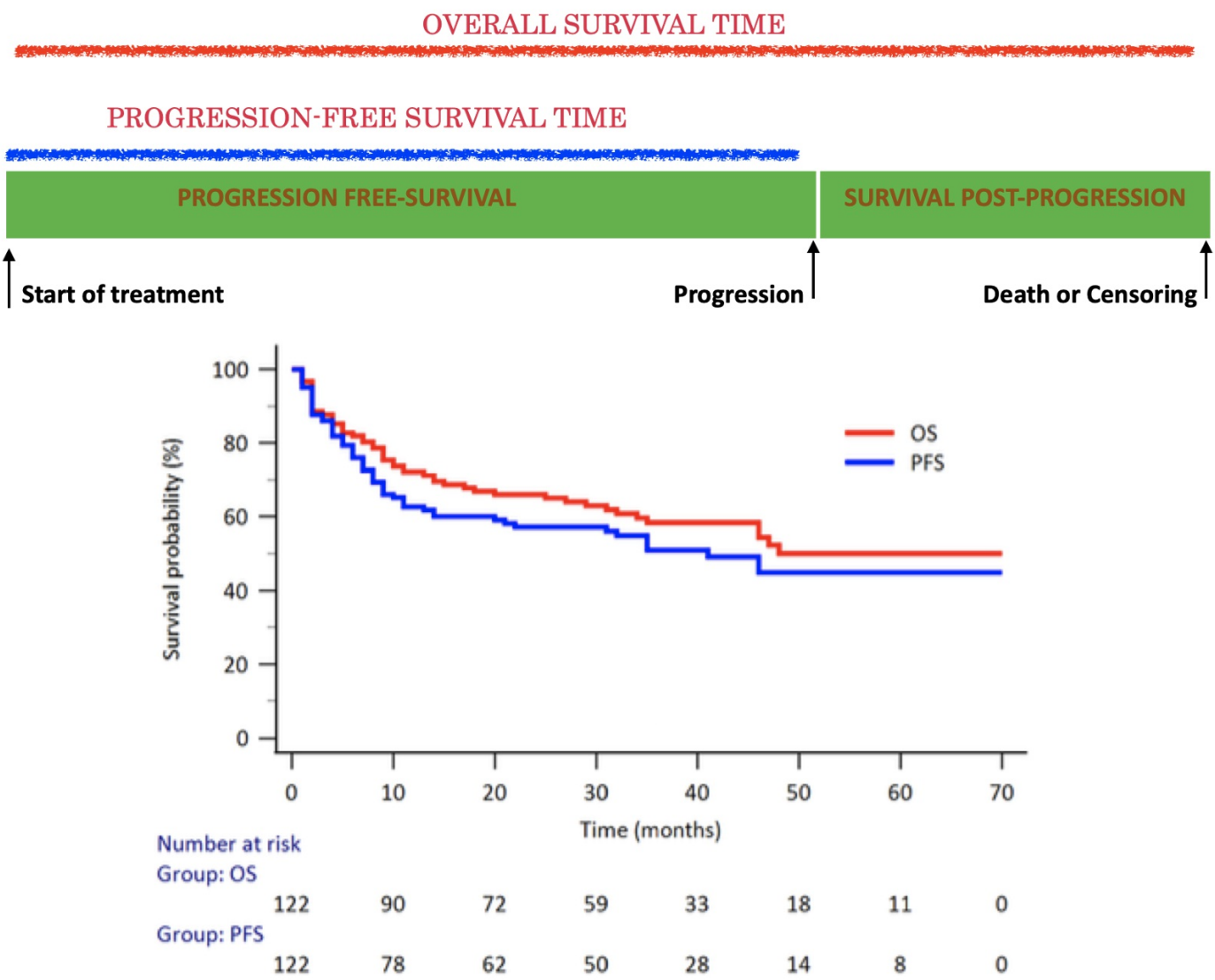


Figure 2. Graphic representation of why OS must always be higher than PFS. The basic principle is that a patient to progress needs to be alive.

Publications series

1. Studies on Prophylactic Cranial Irradiation

Brain metastases (BM) affect up to 50% of patients with non-small cell lung cancer (NSCLC), significantly impacting prognosis and quality of life. Several meta-analyses demonstrate that prophylactic cranial irradiation (PCI) significantly reduces the incidence of BM, offering a potential improvement in outcomes for NSCLC patients. It is worth noting that patients with anaplastic lymphoma kinase (ALK) rearrangements or Epidermal Growth Factor Receptor (EGFR) mutations may particularly benefit from PCI[13].

A recent randomized phase II trial, the PRoT-BM study, published in the***International Journal Radiotherapy Oncology Biology Physics*** supports the idea that certain subgroups of NSCLC patients may experience an OS benefit from PCI[14]. This study included patients with histologically confirmed NSCLC who harbored *EGFR* mutations, *ALK* rearrangements

and had not progressed on systemic therapy. Patients were randomized to either PCI or standard of care (SoC). Among 84 patients, 38 received PCI, and 43 received SoC. PCI reduced the risk of BM from 38% to 7% at 24 months, Hazard Ratio (HR) 95% CI, 0.22-0.78). Notably, with a median follow-up of 43.1 months, OS was significantly improved in the PCI arm (64.5 vs. 19.8 months); HR 0.41, (95% CI 0.22-0.78); p=0.007).

However, the study raises three key issues that must be addressed to validate its findings and support future phase III trials as shown in **Figure 3**.

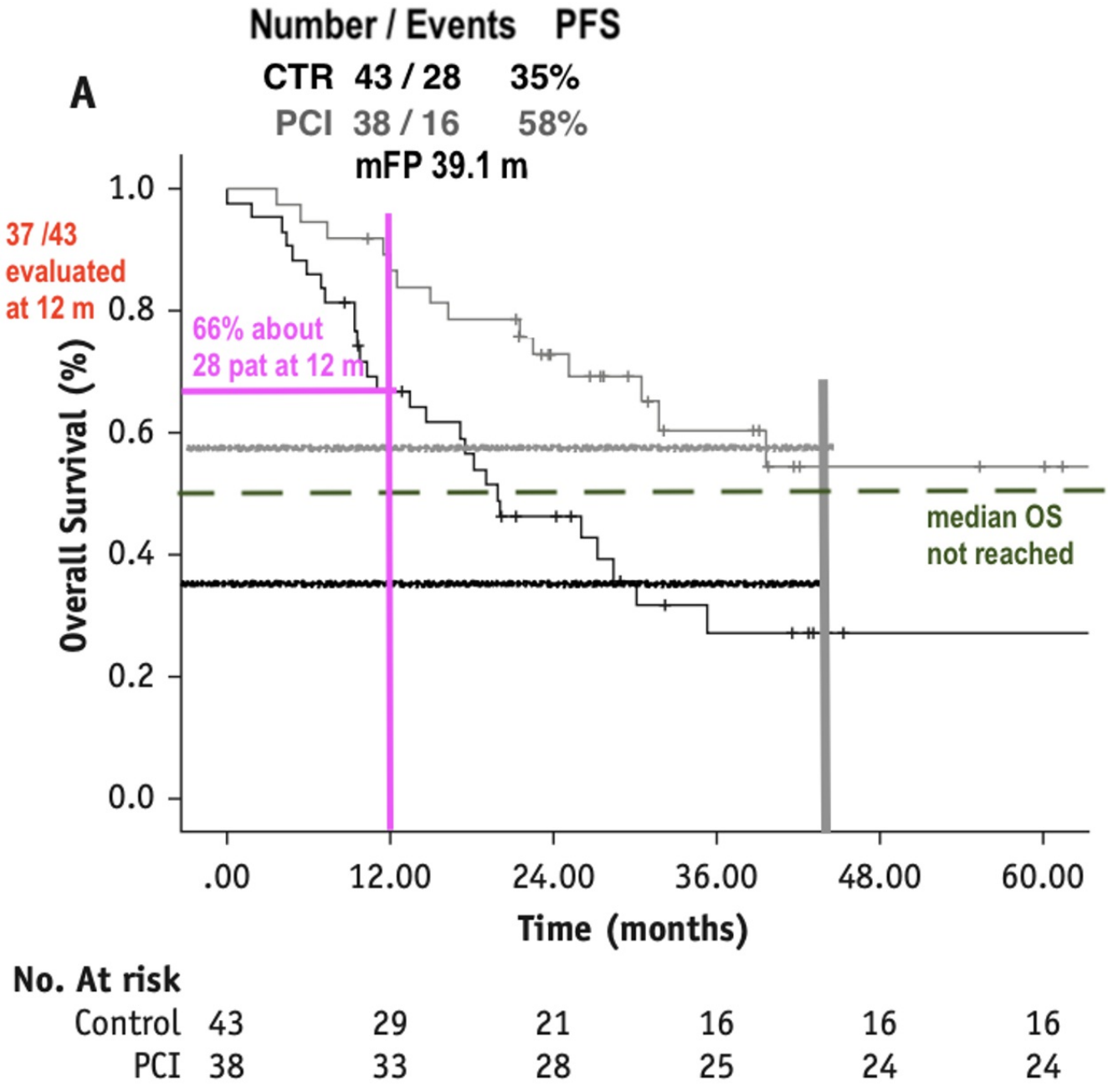


Figure 3. OS curve of the study. Green discontinued line is median survival. Survival rates at 43.1 months were 58% (PCI) and 43% (CTR) grey and black lines. The number of evaluated patients for QoL and neurocognition is lower at 12 months than stated in the text (pink lines).

First, although the median OS for PCI patients was reported as 64.5 months, this endpoint has not yet been reached (discontinued green line). Second, the total number of patients and events, presented in the upper left, indicate OS percentages of 58% for the PCI arm and 43% for the control arm. However, at the reported median survival (43.1 months, gray vertical line), *the survival curves do not align*. Third, the accompanying publication in the same journal reporting quality of life (QoL) and neurocognitive outcomes[15] noted that 37 of 43 patients of the SoC arm completed evaluation at 12 months; however, at that point (pink lines), the survival rate was 66% suggesting that were only 28 patients alive at that time.

Another discrepancy relates to the number of surviving patients. While both studies[14][15] report a median follow-up of 43.1 months (95% CI, 38.8-47.3), the QoL study[15] indicated that 17 patients were alive at the database lock in February 2020, whereas the efficacy study[14] reported 44 deaths. Clarification regarding the exact date of the database lock is needed.

2. Studies on Nitroglycerin

Nitroglycerin a Nitric Oxide donor has been evaluated as an adjunt to anticancer therapy[16]. The trial here discussed was published in 2014 in the Journal ***Radiotherapy Oncology***[17]. It consisted in a single arm study where nitroglycerin was administered during cisplatin vinorelbine after induction and before consolidation chemotherapy. Among the 35 patients enrolled, the median PFS was 13.5 months (95% CI, 8.8-18.2), and the median OS was 26.9 months (95% CI, 15.3-38.5). Interestingly, authors reported that at 48 months of follow-up the PFS percentage is higher than that of OS (38.7% vs. 29%) (**Figure 4**). This is against the principle that OS percentage must always be higher that PFS because a patient to progress needs to be alive.

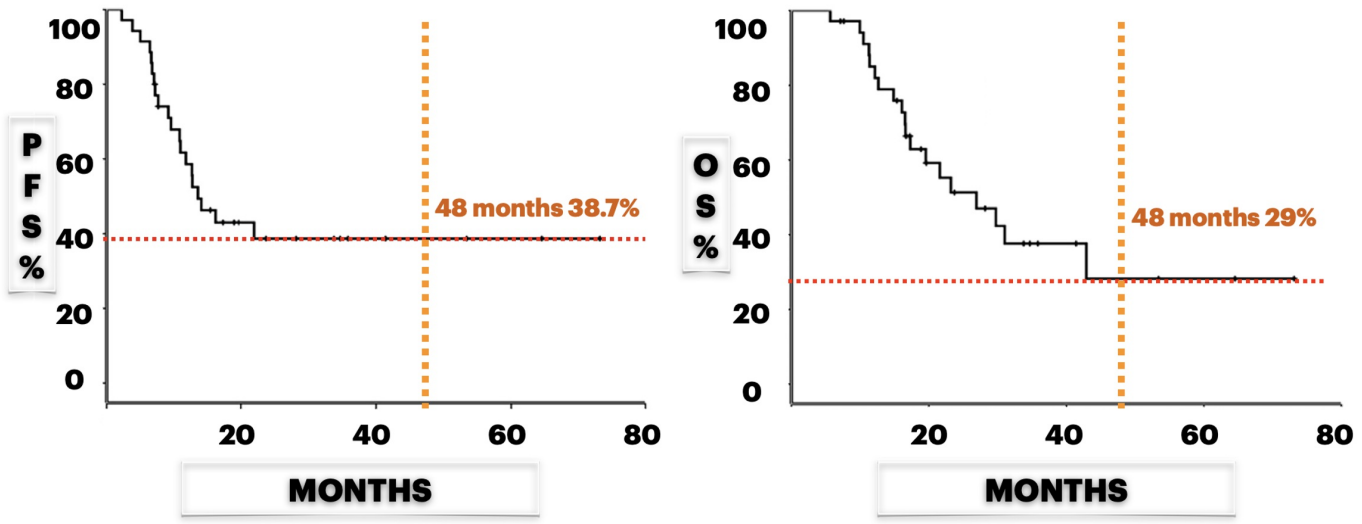


Figure 4. The PFS and OS percentages at 48 months of follow-up.

A second study on Nitroglycerin was a phase II randomized trial published in***International Journal of Radiotherapy***

Oncology Biology Physics [18]. In this study the authors reported that 50 patients were randomized to nitroglycerine, and 46 were to placebo. The results are presented at a median follow-up time of 18.1 months. Compared with radiation alone, the addition of nitroglycerine to cranial irradiation improved intracranial progression-free survival (icPFS) (27.7 vs. 9.6; HR 0.5; (95% CI, 0.2-0.9); p=0.027). Survival curves are as follows: The authors report more OS events than icPFS (62 vs. 43), which is impossible as these data indicate that more patients have died than those evaluated for icPFS (blue discontinued lines). Moreover, the percentages of ICPFS and OS shown in the curve differ from those calculated on the basis of the number of events (gray and black tones lines) (**Figure 5**)

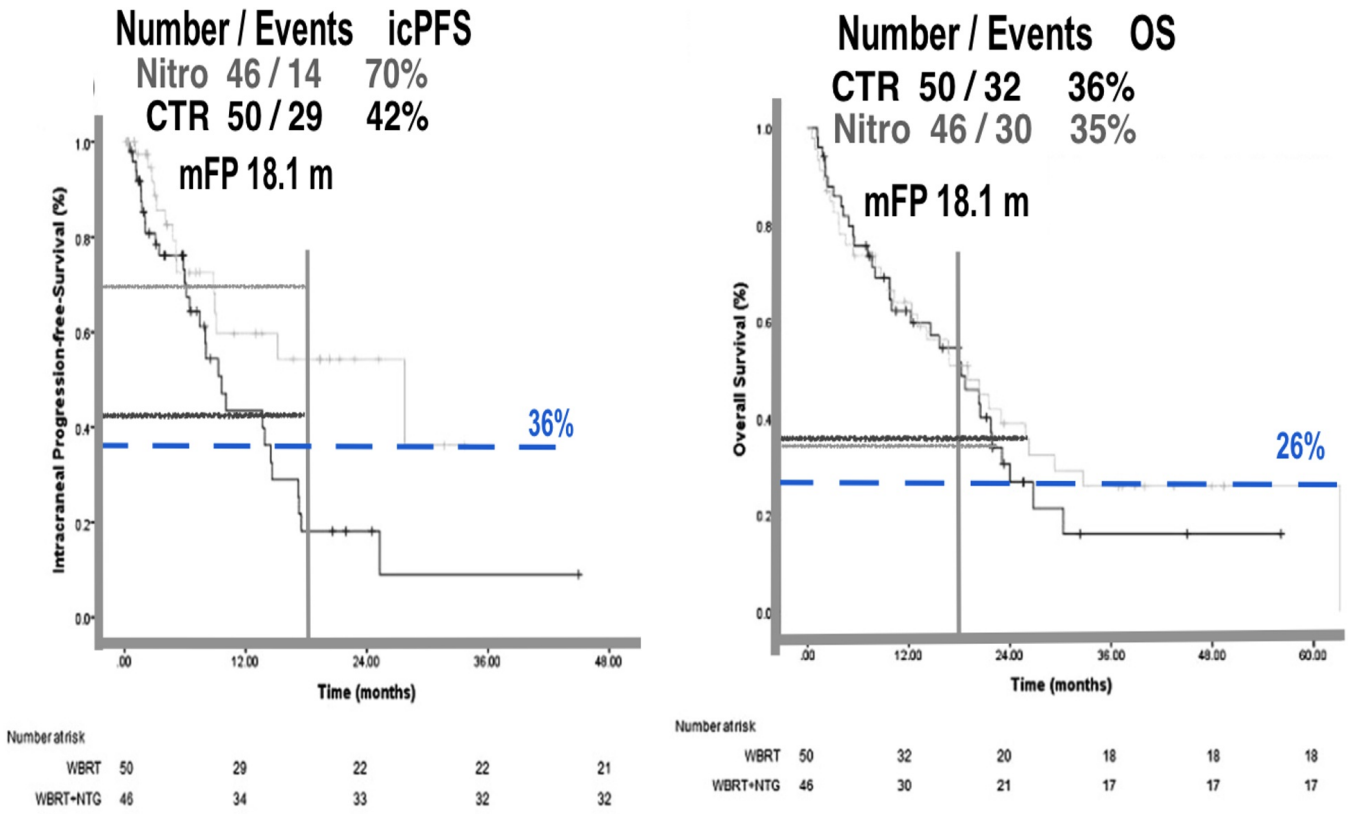


Figure 5. The percentages of ICPFS and OS calculated from the total number of patients and events differ to those showed in the corresponding curves.

3. Study on Metformin

Metformin has been evaluated as a candidate drug repurposing drug for NSCLC. A study in 224 advanced non-diabetic NSCLC harboring *EGFR* mutations comparing gefitinib plus metformin versus gefitinib plus placebo resulted in nonsignificantly worse outcomes and increased toxicity for the metformin arm[19]. The study here commented, published in ***JAMA Oncology*** in 2019[20] was a randomized phase II clinical trial where 70 patients were randomized to EGFR-Tyrosin Kinase inhibitors (TKIs), and 69 randomized to EGFR-TKIs plus Metformin. At a median follow-up time of 16.9 months, the median PFS (9.9 vs. 13.1), HR 0.60 (95% CI 0.40-0.94), p=0.03 and the OS (17.5 vs. 31.7), HR 0.50 (95% CI 0.28-0.90), p=0.02) were significantly longer in the metformin arm.

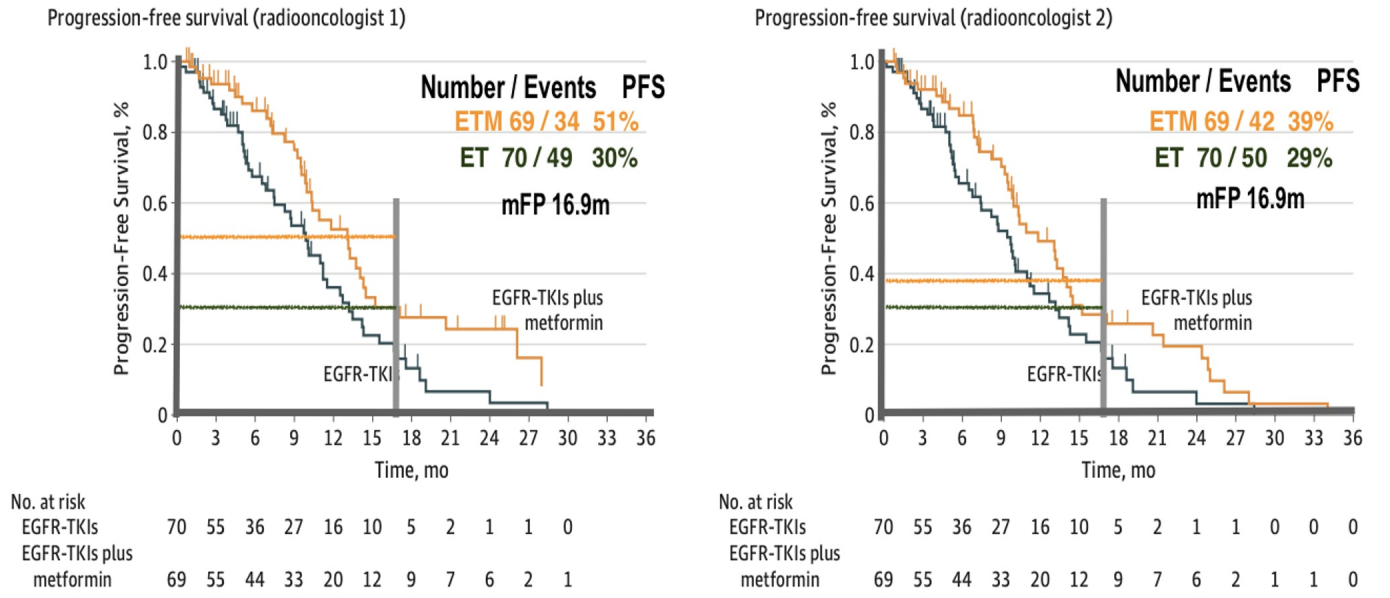


Figure 6. PFS curves and number/percentages of events as evaluated by two radiooncologists.

As shown in the PFS curves corresponding to evaluations of two independent radiooncologists (**Figure 6**). In the upper right of both curves the number and percentages of events are shown. In both PFS percentages patients according to the events do not correspond with the actual curves at the median follow-up time (16.9 months) (vertical red line).

4. Study of pembrolizumab plus docetaxel

The addition of pembrolizumab to docetaxel has shown to increase PFS and OS outcomes as first-line therapy in advanced untreated squamous NSCLC[21]. A recent study comparing pembrolizumab plus docetaxel vs docetaxel alone in patients with previously treated advanced NSCLC was recently published in **JAMA Oncology**[22]. In this study, among 88 patients, 38 and 40 patients were randomized to pembrolizumab plus docetaxel and 40 to docetaxel alone. At a median follow-up time of 8.9 and 7.9 months respectively, authors reported a median PFS of 3.9 vs. 9.5 months for patients receiving docetaxel and docetaxel plus pembrolizumab, respectively (HR 0.24, 95CI 0.13-0.46), p<0.001. The curve is shown in (**Figure 7**). According to the e-Table 2, the authors report 20 progression events out of 40 in the experimental arm, whereas 30 out of 38 in the control arm. Accordingly, the percentages of patients with no progression were 50% and 21%, respectively. However, as seen in the curve at the left, the PFS percentage of docetaxel group at 7.9 months of median follow-up is much lower (8%) that the 21% estimated from the number of events and set before reaching the median follow-up time. Interestingly the data fully coincide in the experimental arm. Just to comparison, the curve at the right shows the PFS curve of the NEJM study[21] that compared these treatments in the first-line. As it should be, the percentage of PFS estimated from the number of events match with the showed in the actual curve.

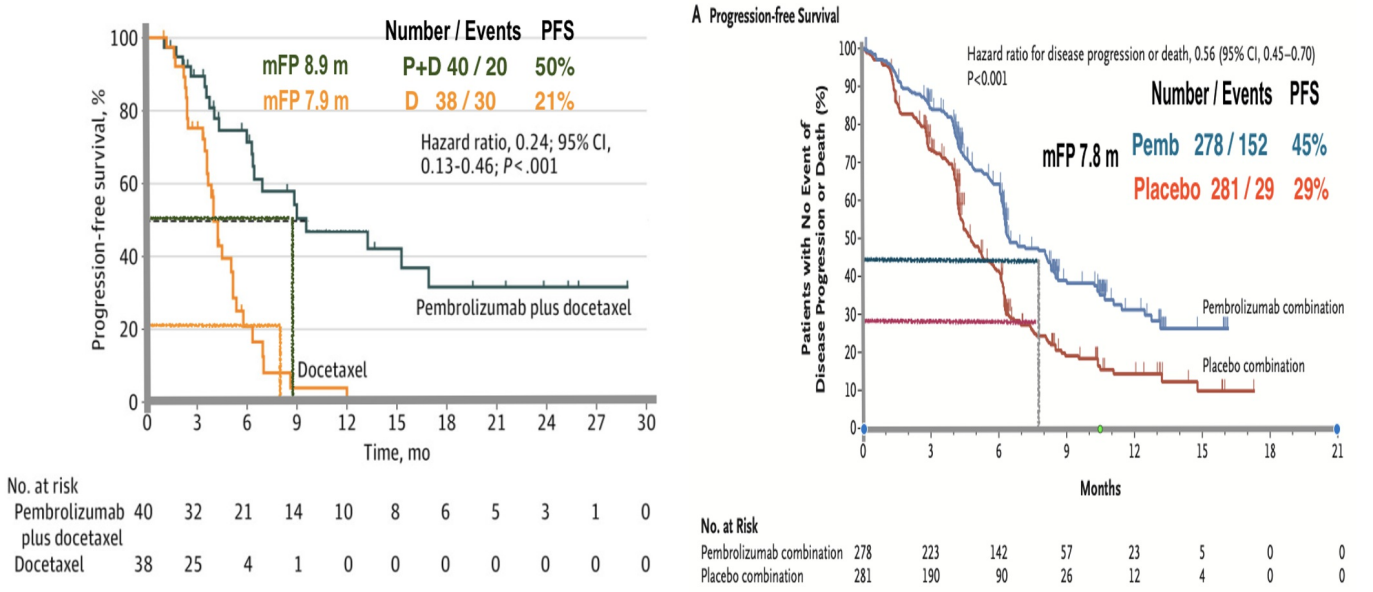


Figure 7. PFS curve of the study at the left, where the estimated percentage for docetaxel is much below the showed in the curve. The curve at the right is a proper example of how the estimated PFS percentages must reflect the percentage estimated with the number of events.

5. A study on early palliative care in lung cancer

Though early palliative care (EPC) is clinically meaningful strategy in the management of advanced cancer, this study aimed to evaluate EPC on patients with advanced NSCLC in a resource-limited setting. The results of PACO trial were published in ***The Oncologist***[23] which studied 146 advanced NSCLC patients. Among these 73 patients were randomized to EPC and 73 to standard of care (SOC). At a median follow-up time of 10.9 months, the authors reported a median OS of 18.1 months (95% CI, 7.9-28.4) for patients with EPC and 10.5 months for patients with SOC (95% CI, 4.7-16.2) (p=0.029). Nevertheless, **Figure 8** shows strong discordance between the OS percentages estimated from the number of events with the OS percentage in the curves.

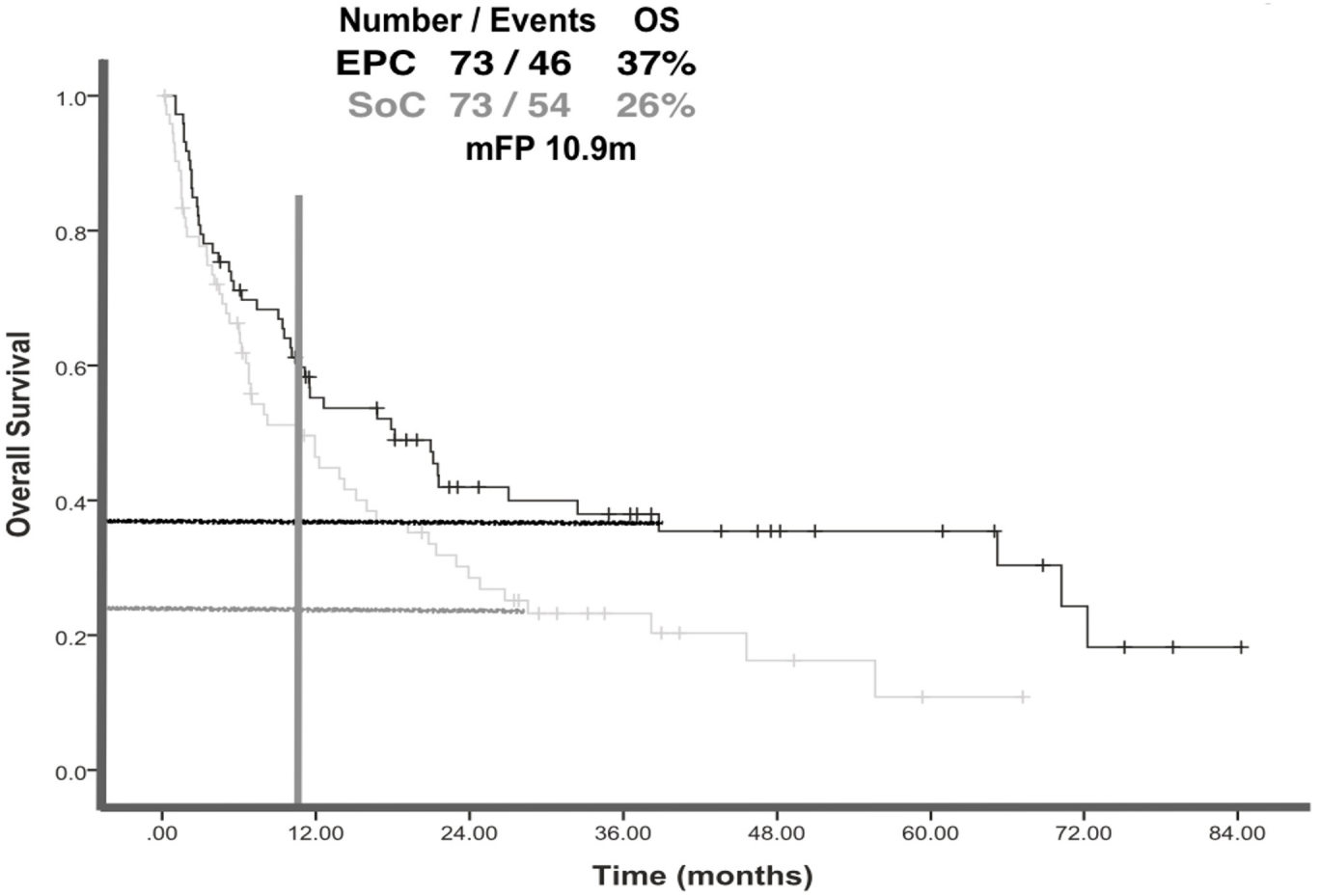
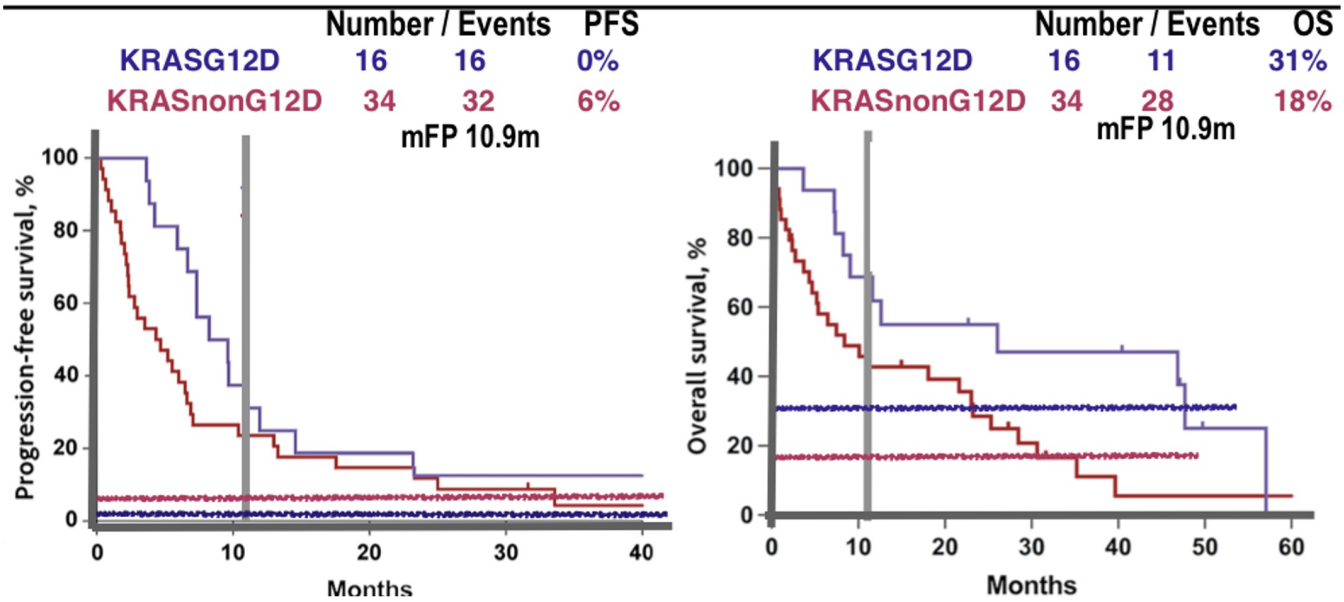


Figure 8. The curves showa substantial mismatch in the survival percentages at the median follow-up time. A similar discrepancy is observed in the curves for the ECOG score (not shown).

6. A study on *KRAS* mutation and prognosis

The *KRAS* gene mutation is the most frequent oncogenic alteration in NSCLC. The recent availability of small-molecule $KRAS^{G12C}$ such as sotorasib[24] bears major relevancy for the study of prognostic impact of$KRAS^{G12C}$ in NSCLC. A recent cohort study on 50 advanced NSCLC with KRAS mutations was published[25]. Authors showed that patients with $KRAS^{G12D}$ mutations had better PFS and OS as compared with those patients with$KRAS^{nonG12D}$ mutations. The median PFS was 8.28 vs. 4.34 months, HR 0.63, (95% CI 0.34-1.18), p=0.100 respectively, while for OS the numbers were 26.09 vs. 8.41, HR 0.46, (95% CI 0.23-0.95), p=0.036.

Nevertheless, **Figure 9** shows strong discordance between the PFS and OS percentages estimated from the number of events with the actual curves. Observations on these PFS and OS findings are being published[26].



Comment

The peer review system, while not perfect, remains a cornerstone of academic rigor. It plays a crucial role in detecting survival data discrepancies, which are often not easily discernible to the untrained eye. When delving into a paper, the question of data trustworthiness inevitably arises. While numerous factors contribute to this, an article's peer-reviewed status serves as a rapid credibility test. However, it is crucial to remember that a 'peer-reviewed journal' label does not guarantee complete fact-checking, impartiality, or accuracy.

Our examination of publications on lung cancer revealed a consistent pattern of survival data discrepancies. These discrepancies, such as the misalignment between the number and percentages of events and the actual survival curves, could significantly distort the conclusions drawn from these studies, raising serious concerns about their validity.

Although there is no consensus on how the median follow-time must be calculated, it is well known that survival results at the time of publication include the whole follow-up times of the first and last patients included in the study, upon which the median survival time is estimated. Naturally, the percentage of events reported at the median follow-up time must be reflected in the survival curve at the median follow-up time. We provide five examples from RCT from reputed journals where this principle is met (**Figure 1**) which appears not to be in the publications we are reporting on. On the other hand, it is essential to understand that in a Kaplan–Meier survival curve, OS survival is consistently superior to PFS curves because a requirement for a patient to be evaluated for progression is survival. Hence, there cannot be more events in the OS curve. This principle is broken in some of the examples reported here.

What is most worrisome is that editors of the journals where these articles are published have been advised either by a formal "Letter to the Editor" or direct letter to the editor in those journals that do not accept correspondence or that the questioned article was published more than three months ago since the observation was made. The data and graphs presented here have been included in such correspondence. However, the editors who addressed these concerns

assured us that the article questioned was reviewed by the appropriate staff and found no irregularities. Some other editors did not answer after a reasonable amount of time and the last case on KRAS mutations and prognosis a letter to the editor is already published but not action has been taken.

This work is a resounding call to action for journals and their editors on regard to the publications here discussed. It is a stark reminder that there is always time to rectify or retract a publication that has not been thoroughly fact-checked or is incorrect. Our observations transcend the debate of whether these discrepancies stem from deliberate data manipulation or an 'honest error.' The issues raised here must be addressed because the ultimate goal of scientific publishing is the advancement of knowledge. In the medical field, it is doubly important because in addition to communicating progress, serves as a basis for developing therapeutic guidelines, and helps doctors make therapeutic decisions. Therefore, what is published is scientifically correct to avoid exposing a patient to an ineffective but potentially risky therapeutic decision.

Statements and Declarations

Data and Software Availability

No data are associated with this article.

Competing Interests

The authors declare not to have conflicts of interest.

Grant Information

The authors declared that no grants were involved in supporting this work.

Author Contribution

The content and ideas expressed in this work are the sole responsibility of the authors.

References

1. ^*Suzuki K, Edelson A, Iversen LL, Hausmann L, Schulz JB, Turner AJ. A learned society's perspective on publishing. J Neurochem. 2016;139 Suppl 2:17-23. doi:10.1111/jnc.13674.*
2. ^*Podolsky SH, Greene JA, Jones DS. The evolving roles of the medical journal. N Engl J Med. 2012;366:1457-61. doi:10.1056/NEJMp1113567.*
3. ^*Meadows WA, Hollowell BD. 'Off-label' drug use: an FDA regulatory term, not a negative implication of its medical use. Int J Impot Res. 2008;20:135-44. doi:10.1038/sj.ijir.3901619.*

4. ^Gasparyan AY, Yessirkepov M, Voronov AA, Koroleva AM, Kitas GD. Updated editorial guidance for quality and reliability of research output. J Korean Med Sci. 2018;33:e247. doi:10.3346/jkms.2018.33.e247.
5. ^Sledge GW Jr. Why big lies matter: lessons from the Bezwoda affair. Medscape Womens Health. 2000;5(1):4.
6. ^Rich JT, Neely JG, Paniello RC, Voelker CC, Nussenbaum B, Wang EW. A practical guide to understanding Kaplan–Meier curves. Otolaryngol Head Neck Surg. 2010;143:331-6. doi:10.1016/j.otohns.2010.05.007.
7. ^Gomes AP, Costa B, Marques R, Nunes V, Coelho C. Kaplan–Meier survival analysis: practical insights for clinicians. Acta Med Port. 2024;37:280-285. doi:10.20344/amp.21080.
8. a, bKamdar M, et al. TRANSFORM Investigators. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomized, phase 3 trial. Lancet. 2022;399(10343):2294-2308. doi:10.1016/S0140-6736(22)00662-6
9. a, bHillmen P, Pitchford A, Bloor A, et al. Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukemia (FLAIR): interim analysis of a multicenter, open-label, randomized, phase 3 trial. Lancet Oncol. 2023;24:535-552. doi:10.1016/S1470-2045(23)00144-4.
10. a, bMonk BJ, Colombo N, Tewari KS, et al, KEYNOTE-826 Investigators. First-line pembrolizumab + chemotherapy versus placebo + chemotherapy for persistent, recurrent, or metastatic cervical cancer: final overall survival results of KEYNOTE-826. J Clin Oncol. 2023;41:5505-5511. doi:10.1200/JCO.23.00914.
11. a, bChoueiri TK, Powles T, Peltola K, de Velasco G, et al. Belzutifan versus everolimus for advanced renal-cell carcinoma. N Engl J Med. 2024;391:710-721. doi:10.1056/NEJMoa2313906.
12. a, bVergote I, González-Martín A, Fujiwara K, et al. Tisotumab vedotin as second- or third-line therapy for recurrent cervical cancer. N Engl J Med. 2024;391:44-55. doi:10.1056/NEJMoa2313811.
13. ^Chalubinska-Fendler J, Kepka L. Prophylactic cranial irradiation in non-small cell lung cancer: evidence and future development. J Thorac Dis. 2021;13:3279-3288. doi:10.21037/jtd.2019.11.36.
14. a, b, cArrieta O, Maldonado F, Turcott JG, et al. Prophylactic cranial irradiation reduces brain metastases and improves overall survival in high-risk metastatic non-small cell lung cancer patients: A randomized phase 2 Study (PRoT-BM trial). Int J Radiat Oncol Biol Phys. 2021;110:1442-1450. doi:10.1016/j.ijrobp.2021.02.044.
15. a, b, cMaldonado F, Gonzalez-Ling A, Oñate-Ocaña LF, et al. Prophylactic cranial irradiation in patients with high-risk metastatic non-small cell lung cancer: quality of life and neurocognitive analysis of a randomized phase ii study. Int J Radiat Oncol Biol Phys. 2021;111:81-92. doi:10.1016/j.ijrobp.2021.04.017.
16. ^Meunier M, Yammine A, Bettaieb A, Plenchette S. Nitroglycerin: a comprehensive review in cancer therapy. Cell Death Dis. 2023;14:323. doi:10.1038/s41419-023-05838-5.
17. ^Arrieta O, Blake M, de la Mata-Moya MD, et al. Phase II study. Concurrent chemotherapy and radiotherapy with nitroglycerin in locally advanced non-small cell lung cancer. Radiother Oncol. 2014;111:311-5. doi:10.1016/j.radonc.2014.01.021.
18. ^Arrieta O, Hernández-Pedro N, Maldonado F, et al. Nitroglycerin plus whole intracranial radiation therapy for brain metastases in patients with non-small cell lung cancer: A randomized, open-label, phase 2 clinical trial. Int J Radiat

Oncol Biol Phys. 2023;115:592-607. doi:10.1016/j.ijrobp.2022.02.010.

19. ^*Li L, Jiang L, Wang Y, Zhao Y, et al. Combination of metformin and gefitinib as first-line therapy for nondiabetic advanced nsclc patients with egfr mutations: a randomized, double-blind phase II Trial. Clin Cancer Res. 2019;25:6967-6975. doi:10.1158/1078-0432.CCR-19-0437.*
20. ^*Arrieta O, Barrón F, Padilla MS, et al. Effect of metformin plus tyrosine kinase inhibitors compared with tyrosine kinase inhibitors alone in patients with epidermal growth factor receptor-mutated lung adenocarcinoma: A phase 2 randomized clinical trial. JAMA Oncol. 2019;5:e192553. doi:10.1001/jamaoncol.2019.2553.*
21. a, b*Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018;379:2040-2051. doi:10.1056/NEJMoa1810865.*
22. ^*Arrieta O, Barrón F, Ramírez-Tirado LA, al. Efficacy and safety of pembrolizumab plus docetaxel vs docetaxel alone in patients with previously treated advanced non-small cell lung cancer: The PROLUNG phase 2 randomized clinical trial. JAMA Oncol. 2020;6:856-864. doi:10.1001/jamaoncol.2020.0409.*
23. ^*Allende S, Turcott JG, Verástegui E, et al. Early incorporation to palliative care (epc) in patients with advanced non-small cell lung cancer: The PACO randomized clinical trial. Oncologist. 2024 Apr 1:oyae050. doi:10.1093/oncolo/oyae050.*
24. ^*de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRASG12C mutation: a randomised, open-label, phase 3 trial. Lancet. 2023;401(10378):733-746. doi:10.1016/S0140-6736(23)00221-0.*
25. ^*Caballé-Perez E, Hernández-Pedro N, Ramos-Ramírez M, et al. Impact of KRASG12D subtype and concurrent pathogenic mutations on advanced non-small cell lung cancer outcomes. Clin Transl Oncol. 2024;26(4):836-850. doi:10.1007/s12094-023-03279-2.*
26. ^*Lopez S. On the impact of KRASG12D subtype non-small cell lung cancer. Clin Transl Oncol. 2024 Jul 8. doi:10.1007/s12094-024-03536-y.*