LETTER to the EDITOR **Editorial Process:** Submission:06/04/2026 Acceptance:22/09/2026 Published:28/09/2026

Re: Van Diessen et al. Improved Overall Survival Due to Reduced Waiting Time in Nasopharyngeal Cancer Patients Treated with Chemoradiotherapy in Yogyakarta, Indonesia

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Dear Editor

We read with considerable interest the recent article by Van Diessen and colleagues examining survival outcomes in patients with nasopharyngeal carcinoma (NPC) in the context of reduced waiting times (WT) and modernization of radiotherapy delivery [1]. The authors deserve recognition for addressing structural barriers to oncologic care within a resource-constrained environment and for documenting a notable improvement in 2-year overall survival (OS). Nonetheless, several methodological considerations warrant clarification to ensure rigor and external comparability of the findings.

First, the operational definition of disease-free survival (DFS) employed in this study warrants further elucidation. The manuscript specifies DFS as the interval from completion of radiotherapy to recurrence; however, it remains unclear whether deaths occurring in the absence of documented recurrence were classified as DFS events [1]. Standard oncologic methodology stipulates that DFS encompasses both recurrence and death from any cause as events; otherwise, the metric no longer represents true disease-free survival [2-4]. Both methodological and clinical authorities consistently define DFS as the time to the first occurrence of recurrence or death [2, 3]. If deaths without prior recurrence were censored rather than treated as events, the resulting construct would represent time to recurrence with death handled as a censoring event effectively a recurrence-specific survival metric rather than DFS as conventionally defined. Such a redefinition alters the underlying probability structure: an endpoint requiring patients to be both alive and recurrence-free at time t constitutes a joint state and must therefore be bounded by OS, which reflects survival irrespective of recurrence. Accordingly, DFS constructed according to accepted definitions cannot exceed OS at corresponding time points; deviation from this hierarchy would imply differences in event inclusion or censoring practices. Inconsistent application of DFS definitions across studies further complicates cross-study synthesis, as meta-analytic comparability presupposes equivalence of underlying survival constructs. Explicit clarification of event handling is therefore essential to preserve interpretability, reproducibility, and valid comparison with contemporary oncology literature.

Second, beyond definitional considerations, the conceptual suitability of DFS in this clinical setting warrants closer examination. DFS presupposes the establishment of a clearly defined disease-free baseline a construct that is biologically coherent in the adjuvant setting following complete surgical resection. In contrast, the majority of patients in this cohort presented with locally advanced (stage III–IVA) NPC and were treated with definitive chemoradiotherapy. In such circumstances, patients initiate therapy with macroscopic disease, and radiologic complete response may occur only weeks or months after treatment completion [5, 6]. Accordingly, completion of radiotherapy does not necessarily correspond to attainment of a validated disease-free state. Employing DFS in this context implicitly assumes disease eradication at a fixed post-treatment time point, an assumption that may not reflect the biological trajectory of definitively treated NPC. Progression-free survival (PFS) defined as the interval from treatment initiation to disease progression or death avoids this presupposition and more directly captures disease kinetics under therapy [4 ,7]. Contemporary NPC trials evaluating definitive chemoradiotherapy increasingly adopt PFS as a principal efficacy endpoint [6]. Explicit justification for the selection of DFS, or presentation of PFS as a complementary outcome, would therefore strengthen the biological alignment and interpretive robustness of the analysis.

Third, although the observed improvement in 2-year OS is noteworthy, attributing this change primarily to reductions in WT may oversimplify a complex and multifactorial transition in care delivery. During the study period, several substantial concomitant changes occurred, including expansion of linear accelerator capacity, increased clinical staffing, and a technological shift from two-dimensional and three-dimensional conformal techniques to advanced modalities such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy. IMRT, in particular, has been associated with improved organ-at-risk sparing, reduced treatment-related toxicity, and, in some contexts, improved disease control in head and neck malignancies [8-10]. In the absence of multivariable modeling adjusting for stage distribution, radiotherapy technique, chemotherapy patterns, and treatment era, isolating the independent contribution of WT to OS improvement remains methodologically challenging. Furthermore, OS was

calculated from the initiation of radiotherapy, whereas WT represents the interval preceding this defined time origin. Conditioning survival analysis on patients who successfully initiated treatment may introduce time-related selection biases, including forms of immortal time bias, thereby complicating causal interpretation [11]. Incorporating multivariable time-to-event modeling would substantially strengthen the interpretability of the reported associations.

In conclusion, the documented survival improvements represent meaningful progress in NPC management and underscore the importance of system-level enhancements in oncologic care delivery. Rigorous attention to endpoint definition, biological alignment of survival constructs, and transparent causal modeling is essential to preserve interpretability, reproducibility, and valid cross-study synthesis in contemporary oncology research.

Author Contributions Statement

ET and US conceptualized the correspondence and drafted the manuscript, contributed to methodological analysis, and critical revision. All authors reviewed and approved the final version.

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Reply to the letter to the editor: Re: Van Diessen et al. Improved Overall Survival Due to Reduced Waiting Time in Nasopharyngeal Cancer Patients Treated with Chemoradiotherapy in Yogyakarta, Indonesia

Dear Editor

We thank the authors for their careful reading and for highlighting this important point. We acknowledge that an error was inadvertently made in the disease-free survival analysis, as deaths without documented recurrence should have been included as events. It should include both recurrence and death from any cause as events. Notably, the corrected DFS no longer exceeds overall survival (OS) at any time point, as required by its probabilistic structure. We appreciate this observation, and the corrected disease-free survival analysis, accounting for death as an event, is presented below (Figure 1a-b), (Figure 2a-b).

Regarding the second comment, we thank the reviewer for this pertinent observation. In radiotherapy trials, the choice between disease free survival (DFS) and progression free survival (PFS) should be guided by treatment intent and disease stage. DFS is generally preferred in curative or adjuvant settings, where patients typically have no known residual disease after definitive

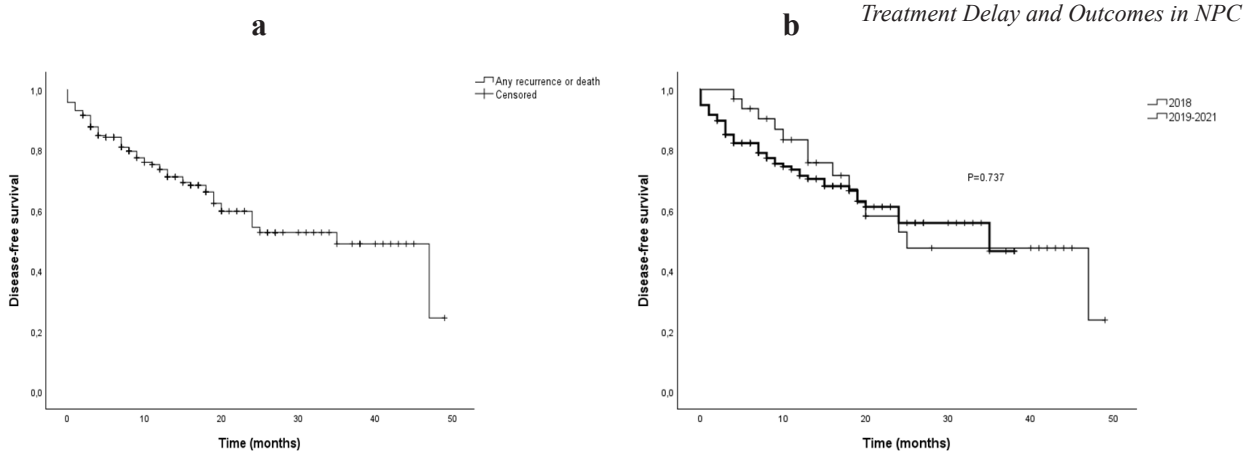

Figure 1a-b. Disease-Free Survival for the 229 NPC Patients, Considering any Recurrence or Death, Overall and in the Comparison between 2018 and 2019–2021, respectively.

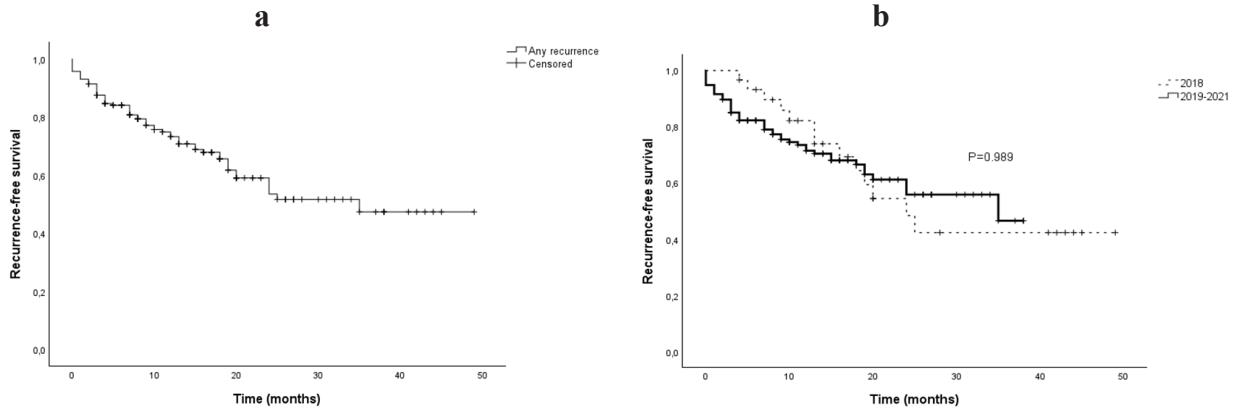

Figure 2a-b. The Renamed Figures, Overall Recurrence-Free Survival, and the Comparison between 2018 and 2019–2021, respectively, for all 229 NPC patients.

local therapy, because it reflects the ability of treatment to prevent recurrence [1]. PFS, in contrast, is more commonly used in advanced or non curative disease, where measurable tumor is present and the goal is to delay progression; it is broader than DFS because it also captures disease progression before death. In radiotherapy practice, the precise definition of the endpoint particularly whether events include death, residual disease at baseline, and how locoregional versus distant recurrences are handled often matters more than the label itself, and we agree that clear specification of these criteria is essential for appropriate interpretation of trial results. Hence, because the goal of treatment in this setting is curative, we prefer DFS as the primary endpoint, both to align with the treatment intent and to enable meaningful comparison with previous trials conducted in the same patient population and hospital.

In response to your third comment, we point out that as discussed in the manuscript, the improvement in 2-year OS observed after 2018 cannot be attributed to reduced waiting time alone. This period also coincided with several system-wide changes in our department, including expansion of staff and linear accelerator capacity, reduced machine workload, implementation of IMRT/VMAT, and more standardized MRI-based target delineation, all of which likely contributed to improved treatment delivery and plan quality. In addition, because OS was measured from the start of radiotherapy, waiting time preceded the survival time origin, which limits causal interpretation and may introduce time-related bias. Since patients who died during the waiting period are excluded, the survival benefit of shorter waiting times might be overestimated. To address this, future studies should consider multivariable regression or other advanced statistical methods to account for these confounding factors. Therefore, the observed association between shorter waiting time and improved survival should be interpreted in the context of these concurrent developments rather than as evidence of a single independent effect.