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Commentary on "Metronomic S-1 Adjuvant Chemotherapy Improves Survival in Patients with Locoregionally Advanced Nasopharyngeal Carcinoma"

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We congratulate Yu and colleagues for their study examining the efficacy and safety of metronomic S1 adjuvant chemotherapy in 474 locoregionally advanced nasopharyngeal carcinoma (LANPC) patients: 64 (13.5%) with and 410 (83.5%) without metronomic S1 [1]. Notably, the metronomic S1 group exhibited significantly improved 3-year locoregional recurrence-free survival (LRFS) (p=0.038), distant metastasis-free sruvival (DMFS) (p=0.002), disease-free survival (DFS) ($p < 0.001$), and overall survival (OS) (p=0.008) rates compared to the group without metronomic S1. The multivariate analysis established that metronomic S1 is an independent prognostic factor associated with better DMFS, DFS, and OS, but not with LRFS. The study's findings warrant conducting a randomized controlled trial in LANPC patients. However, it is critical to stress a significant concern regarding the definitions of endpoints, which may have inadvertently influenced the outcomes in this study.

As a general statistical principle, neither LRFS, DMFS, nor DFS can have better median survival durations or outcome rates at any specified time points except for those obtained for the synonymously used cancer-, cause-, or disease-specific survival results [2,3]. In this respect, Yu et al.'s results contradict this statistical thumb rule. For instance, the 3-year LRFS rate of 100% in the metronomic S1 group is superior to the 98.0% OS rate in the same group. This scenario is theoretically improbable, considering that 2% of cases are already dead at this specific time. This finding is directly linked to the endpoint definitions utilized by Yu et al. The authors fail to consider deaths as an event despite being required to do so by definition, a principle that also applies to DMFS and DFS. However, the "S" in LRFS, DMFS, and DFS signifies "survival status," similar to "S" of OS, indicating that deaths must be considered as events in addition to locoregional failures, distant metastasis, or any relapse, respectively, as shown in Table 1. Thus, the estimates provided by the authors should be regarded as locoregional recurrence–free estimates rather than true LRFS, which are also applicable to DMFS and DFS results. Interestingly, Yu et al.'s methodology is also commonly used by other LANPC researchers for unknown reasons [4,5]. However, this commonality does not justify their endpoint definitions and poses challenges when comparing different studies. Consequently, all survival data should be reanalyzed per established survival endpoint definitions to demonstrate the relevance of the presented outcomes and enable comparisons between similar studies.

Table 1. Standard versus Yu et al.'s endpoint definitions

Characteristic	Event definition	
	Standard definition [2,3]	Yu et al.'s definition [1]
LRFS	Locoregional recurrence	Locoregional recurrence
	Death	Death is not an event
DMFS	Distant metastasis	Distant metastasis
	Death	Death is not an event
DFS	Any kind of relapse	Any kind of relapse
	Death	Death is not an event
OS	Death due to any cause	Death due to any cause

DFS, disease-free survival; DMFS, distant metastasis-free survival; LRFS, locoregional recurrence-free survival; OS, overall survival.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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