

**Diabetes mellitus and its effects on all-cause mortality after radiopeptide therapy for
neuroendocrine tumors; Methodological issues**

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Dear Editor-in-Chief,

We have read the paper authored by Umlauft et al., published in *Journal of Nuclear Medicine* in 2017, meticulously and enthusiastically (1). The authors purposed to examine the risk of developing diabetes mellitus (DM) and its effects on all-cause mortality after radiopeptide therapy for neuroendocrine tumors (NET). It was concluded that radiopeptide therapy does not seem to increase the risk of developing DM in NET patients, whereas DM does not seem to increase the mortality of NET patients undergoing receptor-targeted radiopeptide therapy. Although the current study made considerable contribution to the area, some methodological issues must be taken into account to avoid misinterpretations.

First, the authors incorporated all type of mortality in one category; afterwards relationship of DM were examined with this combined outcome. Although, the power of statistical test is improved using the combined outcome, homogeneity of relationships between the DM and cause-specific mortalities must be also taken into account as main assumption. This assumption might be violated in the aforementioned study since the strength of relationships between the DM and all-cause mortality may be different from its relationships with cause-specific mortality (2). Hence, more sophisticated statistical methods have been newly presented to efficiently assess the relationship of exposure with multiple outcomes such as cause-specific mortality (3). Second, the authors compared the hazard of DM among the three treatment modalities using the Cox proportional hazard models; whereas *proportional hazard* assumption as one of the most important assumptions in the Cox model have been violated in this study which is shown in Figure 3c (1). Hence, the variants of this model such as Stratified or Extended Cox regression models must be applied to avoid any misleading findings (4).

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Conflict of Interest

The authors declare no conflicts of interest.

Authors contribution

RP and SS designed the study. RP and SS drafted the manuscript. Critical revision was done by RP and SS.

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