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Comment on "Resection of the Primary Gastrointestinal Neuroendocrine Tumor Improves Survival With or Without Liver Treatment"

To the Editor:

We read with great interest the paper entitled "Resection of the Primary Gastrointestinal Neuroendocrine Tumor Improves Survival With or Without Liver Treatment".[1] The authors revealed that primary tumor resection (PTR) in metastatic gastrointestinal neuroendocrine tumors (GI-NET) was associated with a better survival, with or without liver treatment. The PTR in GI-NET patients with resectable metastases was supported by ENETS[2] and NANETS[3] guidelines. However, the role of PTR in the setting of GI-NET with unresectable liver metastases was controversial. The largest multicenter study, UKINETs study, revealed that PTR improved survival benefit in midgut NETs with unresectable liver metastases.[4] Huttner et al[5] reported PTR in patients with unresected metastatic pancreatic NETs showed an improvement in overall survival (OS). However, these studies did not account for the effect of liver treatment on survival and compare OS between PTR and no PTR in GI-NET with unresectable liver metastases among different primary sites and different grades. The findings of Lewis A et al[1] addressed these issues and may potentially have groundbreaking clinical implication on the treatment of metastatic GI-NET. Based on the importance of this study, we should make a rigorous assessment of the results of the study.

We have several concerns regarding the reported results and their interpretation. The key result of this study was that compared with no PTR, PTR was associated with a better survival in metastatic GI-NET. However, there were several important factors that were unbalanced between PTR group and no PTR group. First, this study did not consider the resectability of primary tumor. The GI-NET patients with unresectable primary tumor were significantly associated with serious complications leading to worse prognosis than GI-NET patients with resectable primary tumor.[3,6] In this study, patients with unresectable primary tumor were more likely to be included into no PTR group. The survival in no PTR group could be weakened by the GI-NET patients with unresectable primary tumor, which may amplify the survival advantage of PTR. Second, the distribution of liver metastasis and extrahepatic metastasis was imbalanced in PTR group and no PTR group, i.e., liver metastasis was significantly distributed in no PTR group (53.3% vs 46.9%, $P<0.001$). The GI-NET patients with liver metastasis had a significantly worse survival than GI-NET patients with extrahepatic metastasis.[1] The obvious tendency of liver metastasis distribution towards no PTR group would worsen the prognosis of no PTR group. Third, grade was missing in 62.1% of no PTR group and in 18.4% of PTR group. The neuroendocrine neoplasms were divided into highly differentiated NET (G1, G2, and G3) and low-differentiated neuroendocrine carcinoma (NEC) according to tumor proliferation and tumor differentiation.[7] Compared with metastatic GI-NEC, metastatic GI-NET patients had a significantly favorable OS. [8] Among those patients with unknown grade data, the distribution of GI-NET and GI-NEC between no PTR group and PTR group was unclear, which may have a significant bias on the outcome. In addition, the GI-NEC patients with more malignant

biological behavior[7] were more likely to be included into the no PTR group, which may amplify the survival advantage of PTR group.

To better investigate the prognosis effect of PTR, we have the following suggestions: 1) remove the cases with unknown grade; 2) resectability of primary tumor and pathological type (NET vs NEC) should be accounted for in the analysis; 3) balance the differences of clinicopathological factors（resectability of primary tumor, liver metastasis, and pathological type）between PTR group and no PTR group using propensity score matching or inverse probability of treatment weighting method approach.[9]

Moreover, there exists some concerns regarding the statistical analysis. First, it would be more helpful if the authors can demonstrate the additional benefit of PTR among liver metastasis GI-NET patients with and without liver treatment (LT). Although OS comparing PTR versus no PTR in GI-NET patients with synchronous liver metastases was separately analyzed in the LT group and no LT group using Kaplan-Meier method, the results were still not convincing because the K-M method cannot adjust for confounders. We therefore recommend to conduct multivariate survival analysis based on the patients with liver metastasis, and incorporate both PTR and LT in the model to reflect their main effects on prognosis. Their interaction should also be included to investigate whether the effect of PTR on overall survival is modified by LT. Second, the clinicopathological characteristics of four treatment combinations (No PTR +No LT, No PTR + LT, PTR +No LT, and PTR + LT) were not compared and balanced in this study, which may bias the survival analysis results. Some methods should be adopted to balance the clinicopathological features. Third, the multivariate analysis of OS did not include the important factors, chemotherapy and grade listed in Table 1.

In conclusion, the work of Aaron Lewis et al[1] was a large effort and may change our concept of PTR in metastatic GI-NET. However, several important issues warrant further investigation.

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