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Response

A case of rich fruit

We thank Mark Crowther and his colleagues for the comments that they have made on our paper.[1] While we welcome their opinions, it is worth noting that systematic reviews and meta-analyses are areas where opinions differ, controversy remains, and comments on published work are common.

Their first point is that our search strategy was incomplete. They observe that a search using both text words and MeSH headings inclusive of conference abstracts results in an increased yield. It is unknown, however, if any of these studies would have been incorporated given our stringent inclusion criteria.

Secondly, Crowther and his colleagues state that our exclusion criteria may have led to bias. While these criteria were clearly delineated and judged by the authors to be clinically and epidemiologically appropriate, we acknowledge the restrictions they may have placed on our review, including the preclusion of potentially valuable data from studies published in non-English language journals and those using serological diagnoses. The former criterion was not possible given our available resources. The latter may have excluded some high-quality studies, but its removal would likely have resulted in the inclusion of many studies of lower quality; the sensitivity and specificity ranges of the enzyme-linked immunosorbent assay (ELISA) test are greater than for the ^{13}C-UBT test and do not discriminate between patients with active infection and those whose infection has been eradicated.[2]

Their third point relates to homogeneity. We did have reservations about quantitatively synthesizing data because of the heterogeneity of results. However, we thought the studies to be sufficiently similar in scope to justify the pooling of their results. While visual inspection of the funnel plot (Stasi et al, Figure 2) does not show the perfect inverted V consistent with the absence of publication bias, the figure does show some decrease in spread with decreasing standard error. It would be implausible to think that a review such as this would be entirely free of bias. The heterogeneity noted is likely to be the result of small sample sizes (and in this analysis many studies are small) and biologic factors. Importantly, our exploration of this variability uncovered the striking correlation between country-specific infection prevalence and response rate illustrated in Figure 4.[1]

We defend our use of the DerSimonian-Laird method to pool data across studies. Crowther and his colleagues suggest that this method increases the weight given to large observational studies, which may be more susceptible to bias. As a random-effects computation, it gives greater weight to smaller studies than conventional fixed-effects methods.[3] Like most pooling methods, the DerSimonian-Laird method does partly weight studies by sample size, which we feel is appropriate. Although it is possible for large-scale observational studies to be susceptible to greater bias, this tendency is largely based on the methodology used, which was controlled for by the threshold established by our inclusion criteria. Furthermore, our investigation dealt almost exclusively with studies of small numbers of patients within a single center, a situation in which random fluctuation assumes a greater, potentially more dangerous role in impacting results.

In summary, we believe the methodology for our systematic review to be sound and support its finding of *Heliobacter pylori* eradication as a viable, noninvasive, and low-cost treatment for ^{13}C-UBT–positive adults with immune thrombocytopenia, particularly in countries with a high prevalence of infection pending the outcome of large-scale randomized trials.

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To the editor:

Differences between nasal and extranasal NK/T-cell lymphoma

We read with interest the results of the peripheral T-cell lymphoma (PTCL) classification project reported by Au et al, which stated that prognosis of extranodal natural killer (NK)/T-cell lymphoma (ENKL) of nasal origin is different from that of extranasal origin.[1] They further concluded these 2 subtypes of ENKL are different entities.

We principally agree with their conclusion, but the prognostic difference they pointed out needs further estimation. Our data on 150 ENKLs (123 nasal and 27 extranasal)[2] also demonstrate the same results if analyzed as a whole (Figure 1A). However, the proportion of localized versus advanced stage of disease is completely different

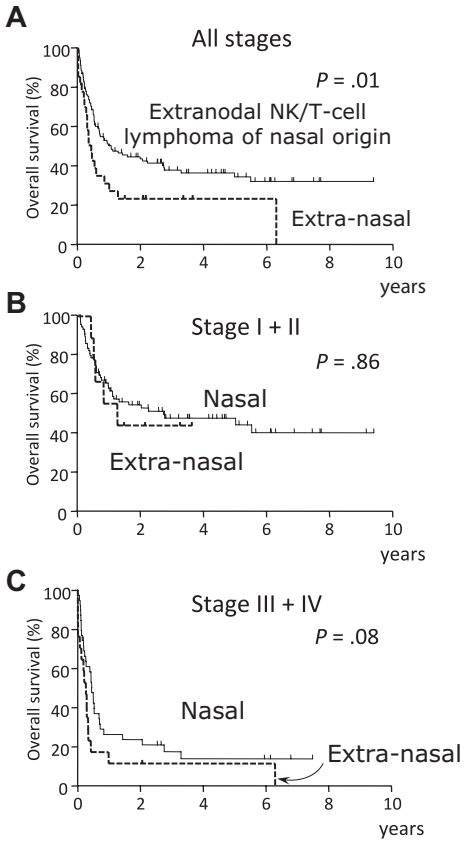

Figure 1. Prognosis of extranodal NK/T-cell lymphoma (ENKL). (A) ENKLs of nasal origin show better prognosis than that of extranasal origin ($P = .01$). (B) When restricted to limited stages (I + II), the prognosis of nasal and extranasal ENKLs are almost the same ($P = .86$). (C) For advanced stages (III + IV), there is no statistical difference ($P = .08$).

between nasal and extranasal origins. Patients who initially presented with localized disease (clinical stage I or II) included 84 (68%) of those with ENKL of nasal origin, but only 10 (37%) of those with ENKL of extranasal origin. This difference is also documented in the literature,[3-5] as well as in the result from the PTCL project.[1] Notably, the prognostic difference disappeared after stratification by clinical stage (Figure 1B,C). We absolutely agree with the notion of Au et al that clinical behaviors of nasal and extranasal ENKLs are significantly different, but we should aware that the prognostic difference is derived from the different extent of each disease.

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Response

Prognosis of stage I/II nonnasal extranodal NK/T cell lymphoma

We thank Suzuki et al for comparing the clinical outcome of their 10 patients with localized (stage I/II) nonnasal, extranodal NK/T cell lymphoma (ENKL) from a Japanese multicenter collection (3-year overall survival; 41%), to the 18 cases with similar disease from our international study (3-year overall survival; 12%).[1] They suggest that low-stage extranasal ENKL may carry a more favorable prognosis.

Due to differences in case selection criteria, it is difficult to resolve this discrepancy in a retrospective fashion. The small number of cases of low-stage extranasal ENKL in both studies means that this is a rare clinical presentation. From our understanding, most of the Japanese cases were dermatologic referrals. This category of cases was not submitted to our retrospective study. Indeed; none of our 18 stage I/II extranasal cases come from the 4 Japanese centers that participated in our study.[1] In contrast, only 2 of the 18 stage I/II cases from our study were cutaneous ENKL. The majority affected the alimentary tract (n = 7) and muscles (n = 5). Such bias may have led to the omission of a Japanese subcategory of limited stage cutaneous ENKL with a good prognosis, that is either not seen or missed in other parts of the world.[2] It is also possible that with more meticulous staging, that is, Epstein-Barr virus (EBV)–encoded early small RNA (EBER) staining of marrow[3] and whole body positive emission tomography (PET) scanning,[4] apparent low-stage extranasal ENKL cases with a poor outcome would actually be upstaged. Given these uncertainties, the prognosis for bona fide low-stage extranasal ENKL (cutaneous and noncutaneous) remains unclear. In this setting, other ancillary variables; such as the size and number of lesions, biochemical and hematologic factors, and EBV DNA load, may also help to predict outcome. Future prospective studies of a larger number of well-characterized cases are needed to resolve this issue.

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