Is intraductal papillary mucinous neoplasm associated with extrapancreatic malignancies? Which is the true, prevalence or incidence?

We read with great interest the article by Larghi et al. [1], a multicenter cohort study about prevalence and risk factors of extrapancreatic malignancies (EPMs) in patients with intraductal papillary mucinous neoplasm (IPMN) of the pancreas. They concluded that their prevalence was high, especially for colorectal carcinoma, renal cell and thyroid cancers.

IPMN harbored some genetic mutations in the pancreas and was significantly associated with both synchronous and metachronous pancreatic cancer development [2, 3]. However, the relationship between IPMN and EPM still remained to be solved. There were some retrospective studies evaluating the prevalence of EPM in patients with IPMN and all of them, including the article by Larghi A et al., concluded that their prevalence was high. On the other hand, we reported the prospective study and concluded that the incidence of EPM in patients with IPMN was not high compared with that in general population in contrast to the high incidence of pancreatic cancers [4]. Prevalence is the proportion of a population found to have a disease, whereas incidence is a measure of the risk of developing a disease within a special period of time. The object to be measured was different between them, so it should be interpreted carefully. In focusing on the prevalence, overestimation of EPM could not be eliminated due to the diagnostic bias. As described in the article by Larghi et al. [1], incidence of EPM in their cohort was expected.

Some patients with IPMN may have some germline mutations, like BRCA2 in the article by Lubezky et al. [5], but the majority did not. There were no significant risk factors for developing IPMN. Therefore, if IPMN was really associated with EPM, both the prevalence and incidence should be high. Until the high incidence of EPM in patients with IPMN or genetic mutations for developing EPM was to be elucidated, systemic surveillance should not be justified without certain specific risk factors for developing EPM.

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Concern on quality-of-life analysis in the OPTIMAL study

We read with interest the paper by Chen et al. investigating the quality of life (QoL) in a planned secondary analysis of the ‘OPTIMAL’ study, a randomized trial comparing erlotinib treatment with chemotherapy by gemcitabine/carboplatin (G/C) in patients harboring sensitizing EGFR mutations [1].

The authors used the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire, a well-established validated instrument to measure the QoL [2]. It consists of a series of questions resulting in a score ranging from 0 to 144.

In the methods section of their paper, Chen et al. stated that an improvement of six points in the FACT-L total score can be considered clinically relevant, a threshold based on the methodology used in previous studies [3, 4]. Chen et al. state that each patient who showed at least once an elevation of six points (or higher) in its FACT-L score during the study (at any cycle) was considered as clinically improved, which can introduce bias since the number of cycles is different for the two arms.

Indeed, supplementary Table S1 showed that there is a great imbalance between the two arms regarding the number of patients who completed the QoL questionnaires throughout the duration of the study. Patients in G/C arm completed their questionnaires up to cycle 4 (the usual cycle number for...
chemotherapy), whereas >50% of the patients in the erlotinib arm provided a QoL assessment up to cycle 12 and a substantial number (30%) up to cycle 20. Indeed, even if there was no difference in QoL between the two treatment groups, patients in the erlotinib arm would have had a much higher probability to demonstrate at least once an improvement of six points or more because of their prolonged assessment period. For example, if the probability for at least one individual improvement within four cycles would be 31.5% in both the treatment arms (example data from Figure 5, total FACT-L, G/C arm), the corresponding probability for a 12-cycle assessment period would be $1 - (1 - 0.315)^{12} = 67.9\%$. Thus, the corresponding odds ratio would be $(0.679/1 - 0.679)/(0.315/1 - 0.315) = 4.6$, suggesting that patients in the erlotinib group would appear to have a 4.6 times greater chance to fulfill the success criterion when compared with those from the G/C group, when in fact they have the same probability (31.5% in four cycles equally for both the treatment arms).

Therefore—and although fewer data in G/C arm could also be attributed to more disease progression rate or more severe toxic effects compared with the erlotinib arm—the reported results of clinically relevant improvements in QoL scores and symptoms are seriously biased from this imbalance in the number of cycles. A proper data analysis would need to take into account the number of cycles. Thus, for example, the number of clinical improvements per cycle could be considered as an appropriate alternative outcome measure.

As the results stand, the authors’ conclusion that erlotinib improves the quality of life compared with standard chemotherapy in the first-line treatment of patients with EGFR mutation-positive advanced non-small-cell lung cancer is questionable.

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Reply to ‘Concern on quality-of-life analysis in the OPTIMAL study’ by Couraud et al

In their letter, Drs Couraud, Schuster and Suissa have expressed concerns regarding the validity of the quality-of-life (QoL) analyses from the OPTIMAL phase III study of first-line erlotinib versus chemotherapy for patients with epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) [1, 2]. They highlighted the longer treatment duration for patients who received erlotinib in this study, compared with the four-cycle limit for those receiving gemcitabine/carboplatin (Qilu Pharmaceutical Co. LTD, Jinan City, Shandong Province, P.R. China). They are correct in their assumption that patients in the erlotinib arm would therefore have more opportunity to complete further QoL questionnaires, but it is highly unlikely that this would affect the outcome of the analysis in any meaningful way.

The correspondents argue that this longer duration of treatment offered a greater likelihood of patients showing the six-point increase in score necessary to denote a clinically relevant improvement, but this would only be the case where such improvement actually existed. If there was no benefit with erlotinib, there would actually have been a greater chance of these patients reporting no difference or a worsening of QoL during this period. In fact, this long duration of treatment is directly attributable to the superior tolerability observed with erlotinib compared with standard chemotherapy in this setting, which is reflected in the improved QoL for these patients. Other analyses comparing the QoL with first-line EGFR tyrosine-kinase inhibitors versus chemotherapy have demonstrated similar benefits with targeted versus cytotoxic treatments in EGFR mutation-positive NSCLC [3, 4], so such results are not without precedent.

To address the concerns highlighted above, however, the OPTIMAL investigators have re-assessed the QoL data using only those questionnaires available at the end of cycle 4, i.e. when patients in both arms were still receiving treatment, assuming that their disease had not yet progressed. Table 1 illustrates that QoL was significantly improved with erlotinib versus gemcitabine/carboplatin for Functional Assessment of Cancer Therapy-Lung (FACT-L), Trial Outcome Index (TOI) and Lung Cancer Subscale (LCS) scores at the cycle 4 time point.

These data confirm the results of the overall QoL assessment from this study, demonstrating that the superior QoL benefit