Molecular pathology-integrated clinicopathological prognostic factors

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Malignant diseases are the main and leading cause of death in Taiwan, contributing to an urgent need of active care for patients with malignant diseases, regardless whether the early- or late-stage of diseases are defined.[1–3] Cancer treatment can be simply grouped into two distinguished therapeutic approaches; one is the highly curative therapy applied either by surgery alone and/or radiation therapy with/without neoadjuvant therapy (NAT) or adjuvant therapy under multi-modality guidance; and the other is the palliative therapy or multidisciplinary decision-making with low possibility of curability, based on the characteristics and patterns of diseases at the initial diagnosis.[4–9] Except of some specific systemic diseases, patients with an in situ or organ-limited diseases have a better chance to be cured accompanied with a long-term survival after the initial primary curative treatment.[2] However, few patients with proposed curable diseases may recur later even though the initial primary active and curative treatment is given, and subsequently die of diseases, suggesting that an accurate and precise evaluation and appropriate and personalized therapeutic plan to those patients with supposedly curable diseases by far-advanced development of new technology or therapeutic strategy is critically important.[10,11] All efforts make the diseases with a maximal chance for curability. The article published in the January issue of the *Journal of the Chinese Medical Association* entitled "The clinicopathological and genetic differences among gastric cancer patients with no recurrence, early recurrence, and late recurrence after curative surgery" attempted to explore this topic, since the authors' enrolled subjects belonged to complete resection of tumors and all of them received the curable surgery claimed by authors.[12]

The authors enrolled 473 patients with gastric cancer (GC) undergoing curative surgery to investigated the impact of genetic alterations and clinicopathological features on disease-free survival (DFS) and overall survival (OS) in these GC patients.[12] DFS was classified as no recurrence, early recurrence (defined by < 2 years) and late recurrence (defined by ≥ 2 years).[12] The authors found that *PIK3CA* amplifications in diffuse-type GC were associated with early recurrence and *ARID1A* mutations were frequently found in patients with single-site recurrence, suggesting that targeted therapy and immunotherapy might be helpful for these patients.[12] The current article is interesting and worthy of further discussion.

The authors' aiming to integrate the molecular pathological factors into the conventional clinicopathological factors to establish a new risk-stratification system in the prediction of DFS and OS and in the guidance of adjuvant therapy in the GC patients is worthy of encouragement, although finally, the authors' efforts may not be successful. None of evaluated molecular pathological parameters, such as microsatellite instability (MSI), *Helicobacter pylori* (HP), Epstein-Bar virus (EBV), and genetical mutations (*PI3K/AKT* pathway, *TP53*, *ARID1A*, and B-Raf proto-oncogene [BRAF]) were useful in the prediction of DFS and OS, and by contrast, only conventional clinicopathological parameters, such as elder population (≥ 65 years), and pathological N (lymph node) category were involved in the OS.[12] Therefore, subgroup analysis was conducted and finally, the authors found the potential role of *PIK3CA* amplifications and *ARID1A* mutations may be related to the certain-type outcomes, such as early recurrence as well as single-site recurrence, respectively.[12]

Recently, technological improvement, the better understanding of tumorigenesis, the continuous innovation of targeted therapy and chemotherapy regimens, the spread of advanced development of surgery and multidisciplinary decision-making have directed patient-tailored strategies, with the aim of improvement of DFS and OS.[9] Among them, a better understanding of tumorigenesis, genetic and epigenetic alternations may provide a brand-new therapeutic approach by developing many uniform and targeted or specific agents in the management of cancer patients when cancer treatment has reached to the plateau.[2,13–15]

Dr Chen's suggestions[12] as targeted therapy and immunotherapy for specific subtypes of GC patients echoed Dr Grothey's mention[15] in 2020, who reported that nothing has changed cancer therapy more in the past 5 to 10 years than the application of immune checkpoint inhibitors, since MSI-H (high)–deficient mismatch repair (dMMR) cancers are sensitive to treatment with immune checkpoint inhibitors, such as programmed death 1 (PD-1) antibodies, with or without adding cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) antibodies with longer durability

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of response, better safety profile, and improved quality of life associated with immune checkpoint inhibitor treatment compared with chemotherapy making immune checkpoint inhibitors the preferred choice in these MSI-H-dMMR colorectal cancer patients. The aforementioned mention emphasized the importance in using biomarkers (molecular pathology) to identify the specific genetic/epigenetic alternations of cancers to give a uniform therapy, such as targeted therapy or immunotherapy to these cancer patients, which is also claimed by Dr Chen's group.[12]

Furthermore, the benefits of targeted therapy and immunotherapy is limited to particular population with specific genetic/epigenetic alternations, and by contrast, its value can be extended to the general population. A recent study 309-KEYNOTE-775 showed that even though proficient MMR (pMMR) endometrial cancer (EC) patients may have taken advantages of progression-free survival (PFS) and OS under the immune checkpoint inhibitors plus multikinase inhibitors (Lenvatinib as an example) treatment than with chemotherapy (6.6 vs 3.8 months; hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.50–0.72 and 17.4 vs 12.0 months; HR, 0.68; 95% CI, 0.56–0.84, respectively).[16] All highlight the strength of using a new risk-stratification system integrating molecular aberrations into the conventionally clinicopathologic and image system which may offer a better patient-tailored therapeutic plan.[17] Additionally, it is not only associated with a better prognosis but also associated with the decreased therapy-related adverse events.[17] All support the rationale of Dr Chen's effort[12] to integrating the molecular pathological factors into the conventional clinicopathological factors to establish a new risk-stratification system in the prediction of DFS and OS in the GC patients.

Unfortunately, the results of Dr Chen's study[12] seemed to be unsatisfactory in the clinical routine practice, even though the authors claimed that potential value of *PIK3CA* and *ARID1A* in the specific subgroups. Many confounding factors may significantly influence their results, explaining the reason related to the relative disappointments of Dr Chen's study.[12] The severity of diseases in the enrolled subjects showing a great variability with dramatically different pathological tumor-node-metastases (TNM) stages from early stage (I and II) to advanced stage (III) may be one of the most critical and important confounding factor to explain why their efforts cannot work. In fact, stage is the most important and independent prognostic factor for nearly all solid tumors.[2,8] In theory, it is hard to identify any biomarker showing the similar value as stage in the prediction of outcome of the solid tumors. Therefore, it is not surprising to find little assistance of these biomarkers in the prediction of outcomes (DFS, PFS, or OS) of GC patients.

The aforementioned argument has been raised by audience (Drs Li and Chang[18]) who questioned whether surgery alone can be an adequate strategy in the management of advanced-stage GC patients. Dr Chen's study[12] showed 13.5% (n = 64) of GC patients have been treated with adjuvant chemotherapy; however, the current National Comprehensive Cancer Network© (NCCN) guidelines recommend adjuvant treatment rather than surgery alone in patients with pT3-4 and/or N+ GC.[9,18] Only 29% (n = 137) of GC patients did have negative lymph node metastases (N0); and additionally, 29% (n = 138) of GC patients were classified as pT1-2, suggesting the high possibility of risk of undertreatment in Dr Chen's group.[12] Multidisciplinary team or multimodality treatment is encouraged for advanced-stage cancer patients.[2,3,8,9] Since to offer a better chance of survival in the advanced-stage cancer patients is always our goal or our dream, although it is far away from the real world, suggesting the presence of a large discrepancy or a big gap between NCCN recommendation and real-world clinical practice.

Finally, similar to many studies in the literature, the main limitation of the current article cannot avoid many confounding factors.[19,20] For example, in real-world clinical practice which is unlike to the well-established prospective, randomized clinical trial, it is hard to enroll the subjected with little heterogeneous characteristics; therefore, it is difficult to make a strong conclusion.[16] Additionally, retrospectivity in nature may also be a limit. We still highlight the value of Dr Chen's article,[12] since their data are really a reflective in the real world.

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