Evaluation of JWA and XRCC1 expressions in gastric cancer

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Abstract: Recently surgery in combination with chemotherapy, and radiation therapy largely improved the clinical outcomes in comprehensive treatment of gastric cancer. However the overall survival rate of gastric cancer patients is still poor in terms of the stages of the disease. In order to achieve a more satisfactory prognosis, proper individual treatment plans should be developed due to the new guidance tools. In this respect, previously proposed actual biomarkers cannot provide expected benefit. Supporting evidences suggested that potential prognostic properties of JWA and DNA repair enzyme X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1) seem promising. Since endogenous and exogenous factors may induce DNA damage and subsequent gastric cancer development, assessment of JWA and XRCC1 expression status may be favorable. For the validation of the guidance of JWA and XRCC1 expression in all cases randomly, further investigations are necessary in a large series of gastric cancer patients. Because of the ethical considerations, actual standard methods should be used in addition to the JWA and XRCC1 evaluation in gastric cancer cases. Consequently screening for gastric cancer is still cost-effective in countries with high risk as well as moderate risk populations.

Key Words: Gastric cancer; chemotherapy; JWA; X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1)

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Gastric carcinoma is the fourth most common cancer worldwide (1) and the second in Asia while more than half of the world's gastric cancer cases appear in Eastern Asia (2). In the West, the gold standard for diagnosing cancer is to detect depth of tumor invasion into the gastric wall, whereas in Far East, it is more important to detect cellular atypia or structural atypia, regardless of invasion (3). Accepted by all, the classical independent prognostic factors influence the five-year survival rate are serosal invasion, extragastric lymph node metastasis, liver metastasis, stage of disease, resection margin, and operative curability in gastric cancer patients (4). Last ten years treatment modalities for gastric cancer have been changed on a large scale. Curative endoscopic submucosal dissection provides the five-year overall survival rate of 97.1% for early gastric cancer (5). Among these, approximately 22.4% developed lymph node metastasis, which is associated with a poor five-year survival rate of only 72.7% (6). Unfortunately, the rate of early gastric cancer detection varies by country, and recently, the best early gastric cancer/advanced gastric cancer ratio is 2.9 (7). Furthermore, after endoscopic resection of early gastric cancer, overall, the rate of residual/recurrent tumor is 33.3% (8). Still overall survival rates in patients with early gastric cancer were 94% and 90% at five and ten years, respectively (9). Thus screening for gastric cancer is cost-effective in countries with high incidence. Even in populations with moderate frequency risk stratification may increase the cost-effectiveness of screening (2). As it can mostly be diagnosed at an advanced stage, the overall survival rate is 20-40% (10). Actually in patients with stage I-III gastric cancer, no improvement in long term survival could yet be seen (11). For localized gastric cancer, the treatment strategies alter country by country.

While in western countries, preoperative chemotherapy or adjuvant chemo-radiation is favored, D2 gastrectomy followed by adjuvant chemotherapy is a routine approach in Asia (12). Gastric Cancer Working Group reported that R0 resection with D2 lymph node dissection has produced the best survival data and also post-operative adjuvant chemotherapy including S-1 (tegafur, 5-chloro-2, 4-dihydropyrimidine, and potassium oxonate) is recommended after surgery. Adjuvant chemotherapy for gastric cancer, fluorouracils plus platinum is the most widely accepted first-line regimens, whereas taxanes or irinotecan are mostly used in second- and third-line settings (2). Indeed the outcome of gastric cancer is extremely complex and varies with the stage of disease as well as in patients with similar pathological features. Even in early stages, although appropriate surgery and adjuvant chemotherapy, prognosis may be poor. It is evident that in order to arrange proper individual treatment plan, we need new guidance tools.

In this respect, literature survey suggests that combinations of carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9), and CA72-4 are the most effective ways for staging before surgery or chemotherapy. However, the positive rates are 21.1% for CEA, 27.8% for CA19-9, and 30.0% for CA72-4 (13). It was shown that positive expression of the breast and ovarian cancer susceptibility gene 1 (BRCA1) exists with the significantly prolonged overall survival in stage II-III gastric cancer patients. Although response to platinum-based adjuvant chemotherapy is a good prognostic factor, the BRCA1-negative patients benefit more from platinum-based adjuvant chemotherapy (14). Patients with BRCA1 expression have a better prognosis in gastric cancer, contrarily, patients without BRCA1 expression can benefit from platinum-based adjuvant chemotherapy. Because of this dilemma BRCA1 expression in gastric cancer is open to debate.

Conversely, an apparent concordance was defined considering the potential prognostic properties of JWA and X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1) with the low expression rate in resectable gastric cancer patients. Low expression of JWA and XRCC1 are also significantly associated with gastric cancer and unfavorable TNM stage. This result is in accordance with the positive predictive effect of low expression of JWA and XRCC1 on survival in adjuvant platinum-based-chemotherapy received patients. However in the series of cases of Wang *et al.* it was not mentioned whether the rate of R0 resection and D2 dissection were performed (15). It is argued that JWA and XRCC1 low-expression provides an advantage in terms of both progression of gastric cancer with unfavorable TNM stage and response to platinum-based-chemotherapy with favorable survival.

Prolonged and excessive generation of reactive oxygen and nitrogen species are assumed to contribute to the development of carcinogenesis by inducing oxidative DNA damage when combined with low DNA repair capacity (16). XRCC1 is one of the prominent base excision repair (BER) enzymes and plays an essential role in the removal of endogenous and exogenous DNA damage (16-18). Capella *et al.* and Ratnasinghe *et al.* found relationship between Arg allele of XRCC1 at codon 399 and gastric cancer (19,20), while Huang *et al.* in Polish people and Duarte *et al.* in a Brazillian population could not demonstrate the similar findings (21,22). However in our previous study, we have found that the individuals carrying homozygous Gln allele have increased risk of gastric cancer 2.540 folds (23). Contrarily, in Far East populations, no association between XRCC1 Arg399Gln polymorphism and gastric cancer has been shown (24,25). Wang *et al.* did not investigate the gastric cancer patients for the presence of XRCC1 polymorphisms. On the other hand, mechanistic studies have demonstrated that JWA regulates XRCC1 expression at both the transcriptional and post-translational levels (26) and JWA displays a key role in protecting cells from oxidative stress induced-DNA damage via increased levels of XRCC1 (27). It seems reasonable to pay attention to status of JWA and XRCC1 expression in addition to classical methods during the evaluation of gastric cancer patients. However the contribution JWA and XRCC1 instability to the life expectancy should be checked in TNM stage-matched gastric cancer groups following surgery plus chemotherapy.

Taken together all these data, individual genetic susceptibility and alteration in serum markers are not determined precisely at prognostic level in gastric cancer patients, yet. Therefore further investigations are necessary due to the complexity of personal cancer progress and to select the most beneficial surgical intervention and chemotherapeutic regimens.

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