Neoadjuvant therapy

Peng-Hui Wang[a,b,c,d,*], Szu-Ting Yang[a,b,c], Chia-Hao Liu[a,b,c]

[a]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Female Cancer Foundation, Taipei, Taiwan, ROC; [d]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, ROC

Malignant diseases are the leading cause of death in Taiwan.[1] Life-saving is the most critical issue for cancer treatment; however, the patients not only wish to be cured from the diseases but also want to have a good to excellent posttreatment recovery as well as had better have their organ-preservation or complete return of the function to maintain good quality of life (QoL) in their remaining life, and these wishes now have become an optimal therapeutic goal for both physicians and patients.[2–4] An accurate and precise pretherapy evaluation and an appropriate and personalized therapeutic plan for these cancer or critically ill patients through the far-advanced development of new technology or therapeutic strategy, such as a minimally traumatic organ-preservation approach and a method for maintenance of physiological and morphological function of targeted lesions can minimize the risk of overtreatment and subsequently avoid the development of severe posttherapy sequelae without compromising the therapeutic efficacy.[5–7] To reach this goal, it is still challengeable. The recent publication in the *Journal of the Chinese Medical Association* entitled "The effect of Mitomycin-C in neoadjuvant concurrent chemoradiotherapy for rectal cancer" may be an example, since the authors investigated the possible benefit of using neoadjuvant therapy (NAT) using concurrent chemoradiotherapy (CCRT), called NAT-CCRT with adding mitomycin-C (called MMT+NAT-CCRT) in the management of patients with clinical T3, T4 or node-positive rectal adenocarcinoma staged (advanced-stage rectal cancer) by magnetic resonance image (MRI) or computed tomography (CT) compared to the NAT-CCRT group.[8]

The authors retrospectively enrolled 191 patients receiving NAT-CCRT (radiotherapy [RT] plus [+] oral tegafur-uracil [UFUR]) and 195 patients fulfilling the above-mentioned criteria (MMC+NAT-CCRT).[8] The authors found that the MMC+NAT-CCRT group had a marginally increased effect to downstage of advanced rectal cancer with odd ratio (OR) of 1.52 (95% confidence interval [CI], 0.99, 2.35).[8] Additionally, the authors found downstage of these patients showed a strongly favorable effect on both disease-free survival (DFS, OR 2.2; 95% CI, 1.53, 3.1) and overall survival rates (OS, OR, 1.73; 95% CI, 1.23, 2.43), although this MMC+NAT-CCRT treatment was associated with an increased low-grade toxicity, particularly neutropenia, genitourinary and dermatological adverse events (AEs).[8] Based on the aforementioned results, the authors concluded that MMC+NAT-CCRT for advanced-stage rectal cancer could provide a better trend to downstage tumor with subsequently improving both DFS and OS rates.[8] The current article is interesting and worthy of further discussion.

First, we give a big hand to congratulate the success of the authors contributing to good care of these advanced-stage rectal cancer. However, we are confused about the authors' recommendation showing MMC+NAT-CCRT treatment should be used with caution in aged patients and patients with impaired bone marrow function.[8] Although the general health and physical condition will be continuously and progressively deteriorated when age process is undergoing, particularly for those elders. It is well-known that the elder population is associated with worse prognosis in almost all diseases,[9] even though it is not consistent to define what is the appropriate cutoff value for elder age.[8,10,11] Dr. Wang's current study used "60" years of age as cutoff value, many studies used "65" as watershed.[10,11]

Second, it is relatively difficult to identify who have an impaired bone marrow function. It is still absent of any marker to predict the hematological toxicity of the patients during the treatment accurately. Furthermore, nearly all antineoplastic agents (chemotherapy [CT] drugs) possess the hematological suppression and other AEs.[12,13] The basic concept should be well informed that the theoretical background of combination of CT and RT is significantly different from CCRT, and the former is given for both systemic and localized therapy, but the latter is limited to localized disease (any CT given to patients based on enhanced therapeutic effect of RT).[12,13] Similar to the principle of statistics applied to the clinical data presentation,[14,15] the theoretical principle is often miss-used in the routine clinical practice. For clinical practice, combination of CT and RT is often associated with more therapy-related AEs, even though both combinations of CT and RT and CCRT will additionally augment the therapy-related toxicity, compared to RT alone.[3] However, the little increase of toxicity of CCRT dramatically improve both PFS and OS; therefore, CCRT becomes the standard curable therapy for locally advanced diseases compared to RT alone does.[16]

Third, it should define the role of "NAT" for any disease treatment.[17,18] The rationale of NAT, one of main components of multimodal therapy, attempts to decrease the severity of the

*Address Correspondence. Dr. Peng-Hui Wang, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail addresses: phwang@vghtpe.gov.tw; pongpongwang@gmail.com (P.-H. Wang).

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complicated diseases (down grade the severity of disease) and follow a definite full-scale clearance procedure, which is often mediated by the surgical approach. The main goal of NAT is the decreasing radicality of surgery and the increasing complete or total surgical resection rates.[19,20] All pursue the better ratio between the therapy-induced AEs and therapeutic efficacy. NAT not only plays an important role as part of multimodal therapies for many kinds of malignant-like or malignant diseases, such as endometrial cancer, endometriosis, cervical cancer, rectal cancer, pancreatic cancer, and esophagus cancer, etc, but also serve as a very good predictor for outcomes.[1,3,4,8,17–20] A recent meta-analysis (125 studies and 11713 localized pancreatic ductal cancer patients, 36.8% for NAT of CT, 15.2% for NAT of CCRT and 48% for combination of CT and RT) showed that the pooled resection rates were 77.4% (95% CI, 71.3, 82.5) for potentially resectable cancers, 60.6% (95% CI, 54.8, 66.1) for borderline resectable cancers, and 22.2% (95% CI, 16.7, 29) for locally advanced cancers, respectively.[20] The study found that achieving surgical resection after NAT was associated with improved survival for patients with potentially resectable (median 38.5 vs 13.3 months), borderline resectable (32.3 vs 13.9 months), and locally advanced (30.0 vs 14.6 months) cancers, respectively,[20] suggesting that NAT indeed and dramatically offer a better chance to total eradication of cancers. Additionally, Dr. Brown also found rates of surgical resection after NAT vary based on anatomical stage.[20] Unfortunately, resection rate of Dr. Wang's study seemed to be 100%.[8] Additionally, the rate of pathological complete response rate was similar (21.0% vs 22.1%) in both groups.[8] Moreover, the drop-out rate was not described in Dr. Wang's study. All contribute to uncertainty whether adding MMC into the standard CCRT as NAT is really beneficial to advanced rectal cancer patients.

Although we concerned with Dr. Wang's conclusion to mention that adding MMC into the standard CCRT for rectal cancer is shown to increase downstaging rate and improve both PFS and OS, since many uncertainties need further clarification, we fully support the concept that multimodal therapy should be discussed between the health-care providers and patients to offer the best between the therapy-related AEs and therapeutic efficacy. With continuous understanding the natural course and behaviors of the malignant diseases, precise, personalized, and friendly therapy may maintain the good QoL after treatment without compromising the therapeutic efficacy, although there is still a long way to struggle.

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