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EDITORIAL – THORACIC ONCOLOGY

Nomogram for Predicting Pathologic Response Following Neoadjuvant Chemotherapy or Chemoradiotherapy in Patients with Esophageal Cancer

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Esophageal squamous cell carcinoma (SCC) is an aggressive disease, and the majority of patients are diagnosed with an advanced disease stage at the time of initial presentation. For this reason, multimodality therapeutic approaches remain a crucial strategy for esophageal cancer patients in obtaining better prognosis.[1,2] Neoadjuvant treatment with chemotherapy and/or chemoradiotherapy is recommended to reduce the neoplastic burden, reduce the recurrence rate, and increase survival after esophageal resection.[1,2] Neoadjuvant chemotherapy (NAC) and neoadjuvant chemoradiotherapy (NACRT) are both considered effective.[2] Previous studies have demonstrated that addition of NACRT to surgery results in an increase in the R0 resection rate and improved survival, with acceptable perioperative morbidities.[3] Additionally, in patients who respond remarkably to neoadjuvant treatment, an organ preservation approach might be implemented. Patients with complete clinical response, that is, tumor disappearance, may have a better prognosis when compared with patients with partial or no response to neoadjuvant treatment.[4,5] Therefore, it is essential to restage these patients accurately after completion of NACRT, and to provide more information for subsequent treatment. In this way, unraveling the clinical–pathological factors that predict the response to chemotherapy and/or radiotherapy becomes relevant and much sought after. Nonetheless, the better the tumor regression grade (TRG) achieved after neoadjuvant therapy, the higher the 5-year survival rate. Patients with TRG 0–1 after neoadjuvant chemotherapy or chemoradiotherapy could have a theoretically better prognosis than patients with TRG 2–3.[4–6] Unfortunately, there is currently no effective clinical index to predict the efficacy of neoadjuvant therapy, including complete pathological clinical response (pCR), ultimately avoiding a potentially harmful and unnecessary surgical resection. In contrast, the inability to detect residual disease in a timely manner in non-pCR patients remains a major issue that may lead to treatment delay. Although multiple clinical and biological parameters have been associated with an increased likelihood of pCR, none of them can individually predict pCR accurately.[3–6]

In this month's *Annals of Surgical Oncology*, Okamura and colleagues[7] reported a predictive model of therapeutic effect in patients with esophageal SCC who received neoadjuvant treatment. The multicenter, nationwide retrospective study included 4078 patients who received neoadjuvant treatment followed by surgery for esophageal SCC from 85 institutions. They conducted a nationwide survey organized by the Japan Esophageal Society (JES). The authors applied a questionnaire requested information regarding sex, age, body mass index (BMI), pretherapeutic SCC antigen (SCC-Ag) level, pretherapeutic hemoglobin level, pretherapeutic neutrophil-to-lymphocyte ratio (NLR), primary tumor location, cT category, cN category, cM category, details of neoadjuvant treatment, surgery date, surgical approach, resection margins, pathological therapeutic effect, and prognosis. They developed a logistic regression model to predict good pathological therapeutic effects, and a predictive nomogram was generated by applying the logistic regression formula. Patients who

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underwent salvage esophagectomy were excluded from the study. Multivariable analysis revealed that male sex, advanced cT category, and increased pretherapeutic SCC antigen level were independently associated with a worst therapeutic effect. One relevant matter is that this study is real-world research, and the institutions have utilized different neoadjuvant treatment regimens including cisplatin plus 5-fluorouracil (CF), which was the most frequently used combination (60.2%), followed by docetaxel plus CF (DCF, 27.4%), CF with radiotherapy (CF-RT, 4.5%), adriamycin plus CF (3.6%), nedaplatin plus 5-fluorouracil (0.9%), and DCF-RT (0.5%). Intensified neoadjuvant regimens were independently associated with favorable therapeutic effects; DCF-RT elicited the best therapeutic effect, followed by CF-RT and DCF. A predictive model including nine commonly measured preoperative variables was generated. They proposed a nomogram that was also adequately validated internally. The authors concluded that the validated model developed in this study predicts the therapeutic effect in patients with esophageal SCC who received neoadjuvant treatment. They emphasize that the model might contribute to individualized treatment strategies.[7]

The authors need to be commended for a fine study that demonstrates the possibility of predicting the response to neoadjuvant chemo and/or chemoradiotherapy in a large cohort of patients with esophageal squamous cell carcinoma (ESCC).

A nomogram is an advanced and widely applied model that may estimate the predictive therapeutic effect of an individual patient by incorporating multiple variables and their interdependent relationships.[8] Nomograms have been used to stratify and predict therapeutic effect and prognosis precisely in several cancers. It is noteworthy to mention that the presented model considers the clinical and hematological variables, preoperative information, and neoadjuvant treatment strategies, data that can be obtained preoperatively.[7]

Only a few nomograms for predicting therapeutic effect of NAC and/or NACRT, or pCR are currently available in patients with esophageal cancer. In addition, most of them are focused on esophageal adenocarcinoma.[9–12] The main caveats of these studies comprise the small sample size, single-center origin, and retrospective design.[9–12] In this scenario, Okamura's manuscript included data from more than 4000 patients from several Japanese centers, highlighting the possible clinical usefulness of this nomogram, and the authors should pursue an external validation with independent cohorts.[7]

Some studies that evaluated the NACRT response have utilized response evaluation criteria in solid tumors (RECIST) using preoperative imaging evaluation effect. Others have used pathologic criteria, such as the Ryan score to evaluate the treatment effect.[6,12] Okamura et al. have utilized the Japanese Classification of Esophageal Cancer, which is somewhat similar to the Western classification.[7]

Nomograms incorporating clinical data; dynamic hematological indicators, before and after treatment; image analysis from baseline and post therapy, such as conventional parameters derived from computed tomography (CT) or integrated positron emission tomography to estimate treatment response; or radiomics; together with future integration of molecular markers in the nomogram will hopefully improve its clinical utility for assessing patient risk and the ability to predict treatment response after NACRT or immunotherapy.[13–16]

DISCLOSURE I do not have any conflicts of interest.

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