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EDITORIAL – GASTROINTESTINAL ONCOLOGY

# Future Treatment Strategy for Esophageal Cancer Based on Prediction of Systemic Recurrence: Significance of Pathologic Nodal Status After Neoadjuvant Chemotherapy

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The main goals of neoadjuvant therapy are to increase the curative resection rate by downstaging the primary tumor and to improve postoperative survival by eliminating systemic micrometastases. Chemoradiotherapy (CRT), the mainstay of preoperative therapy for advanced esophageal cancer in Western countries, has dramatically improved local control by increasing the R0 resection rate. However, distant metastasis is common, and two recent randomized clinical studies comparing neoadjuvant CRT and neoadjuvant chemotherapy (NAC) failed to demonstrate a survival benefit of neoadjuvant CRT despite its favorable local control and R0 resection rates.[1,2]

In recent decades, local control rates have improved markedly because of rapid progress in surgical instruments, surgical technique, and postoperative management. The aim of preoperative therapy should now be shifted from local control to systemic control to improve the treatment outcome for esophageal cancer, which has a high potential for systemic spread. Meanwhile, with the development of new combination chemotherapy regimens including oxaliplatin or a taxane, some clinical trials have reported that NAC reduces the risk of postoperative recurrence and improves survival, as in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial.[3,4]

A review of the role and position of chemotherapy in multimodality therapy would be timely. The findings of several randomized clinical studies comparing neoadjuvant CRT and NAC are currently under way and will provide some guidance in this regard.

Chemotherapy is the only treatment method that can be used to control the systemic spread of esophageal cancer. However, systemic micrometastases cannot always be eliminated by two or three courses of NAC, and chemotherapy must be added postoperatively in some cases. Miyata et al.[5] identified one of the indications for individualization of adjuvant therapy in their investigation of factors related to survival and recurrence among 405 patients with advanced esophageal squamous cell carcinoma whose tumors had been curatively resected after NAC. Their multivariate analysis showed that the number of nodes involved was the only independent risk factor for both systemic recurrence and postoperative survival, suggesting the need for additional adjuvant systemic therapy to inhibit proliferation of residual micrometastases. Pathologic tumor regression grade and ypT stage also had a close association with systemic recurrence but were not independent risk factors. Pathologic nodal status reflects the response of a metastatic lesion to treatment and may be more appropriate for assessment than the pathologic regression grade of the resected primary tumor in predicting the likelihood of residual systemic micrometastases.

In the study by Miyata et al.,[5] 60% of the patients with involvement of three or more lymph nodes experienced systemic recurrences. Their report has two important messages. The first message, as described earlier, maintains that adjuvant therapy should be individualized according to the number of pathologically involved lymph nodes, with adjuvant therapy indicated for patients with three or more positive lymph nodes.



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In multimodality therapy, three significant questions hold the key to success. First, how and what type of preoperative therapy should be used for individual patients based on initial staging by the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) system? Second, how should treatment response be evaluated, and how should the timing of surgery be determined? Finally, how and what type of personalized adjuvant therapy should be administered to patients based on pathologic findings?

The study by Miyata et al.[5] provides the answer to the first part of the last question for patients with NAC. However, the optimal adjuvant therapy for those patients remains unclear. The same regimen as that used for NAC is one of the possibilities for responders to NAC. For nonresponders, however, no evidence currently exists on which to base a recommendation for effective postoperative systemic therapy, so we will need to wait for the results of ongoing clinical trials of immunotherapy, such as the use of anti-PD-1 antibody and various peptide vaccines, and for the development of new therapeutic agents.

The second important message in the Miyata et al.[5] study maintains that the emphasis should be placed on the response of the lymph nodes to NAC rather than that of the primary tumor in patients undergoing curative resection. As already reported, pathologic node positivity was the only independent predictor of overall survival, even in the subanalyses of the MAGIC trial.[6] We previously evaluated the response to NAC by $^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG-PET) in patients with resectable esophageal cancer and PET-positive lymph nodes (PET-N-positive) and identified conversion to PET-N-negative status after NAC as the only predictor of relapse-free survival, with post-treatment PET-N-positive patients showing a threefold higher rate of systemic recurrence (70%) than their post-treatment PET-N-negative counterparts.[7] Without suppression of systemic recurrence, it is impossible to improve the prognosis of patients further with esophageal cancer. The ability of neoadjuvant CRT to decrease the risk of hematogenous metastasis despite a markedly higher locoregional control rate was small but significant in the subanalyses of the Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) trial comparing the outcomes of neoadjuvant CRT with those of surgery alone.[8] Therefore, it may be necessary to review the treatment regimen or method and the standards for evaluating the treatment response in patients with resectable tumors from the perspective of optimal preoperative therapy.

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