GASTROINTESTINAL CANCER

CROSS: new standard of care for oesophageal cancer

Surgery remains the cornerstone for the treatment of potentially curable oesophageal cancer. However, for locally advanced tumours, radical resection rates after primary surgery rarely exceed 70%. Moreover, the locoregional recurrence rate after primary surgical resection is also quite high, with locoregional disease recurrence noted in around 30% of patients, regardless of whether patients have distant disease dissemination. The addition of neoadjuvant treatment before surgery can potentially downsize the primary tumour and increase radical resection rates, thus minimizing locoregional recurrence. Importantly, neoadjuvant treatment must be well tolerated by patients, therefore, a carboplatin and paclitaxel regimen with concurrent 41.4 Gy radiotherapy was assessed in a randomized phase III trial.

At 45 months of follow up, authors of the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) reported a significant improvement in 5-year overall survival with the addition of neoadjuvant chemoradiotherapy to surgery compared with that of surgery alone. Now, Shapiro and co-authors present the long-term results of this trial after a minimum follow up of 5 years. In total, 368 patients from eight participating centres in the Netherlands were enrolled.

Long-term follow-up results showed a significant overall survival benefit of neoadjuvant chemoradiotherapy plus surgery (48.6 months) for patients with either adenocarcinoma or squamous-cell carcinoma compared with surgery alone (24.0 months). Similarly, a significant progression-free survival (PFS) benefit was also demonstrated for multimodality therapy in patients with adenocarcinoma and squamous-cell carcinoma. Shapiro summarizes, “a significant reduction in both locoregional and distant recurrence was shown. The significant reduction in

distant recurrence was evident within the first 6 months after patient randomization (which included 5 weeks of neoadjuvant chemoradiotherapy). This result suggests a direct systemic effect of neoadjuvant therapy on distant dissemination.”

Although benefits in PFS and overall survival were demonstrated for the combination regimen, which patient subgroups benefit the most, and which subgroups derive no benefit, remains to be clarified. The encouraging results of the CROSS trial highlight that the improvement in distant disease progression as well as locoregional control might reflect a direct systemic effect of neoadjuvant chemotherapy in this treatment regimen. These advances from the latest long-term data of the CROSS trial indicate that neoadjuvant chemoradiotherapy followed by surgical resection should be viewed as the new standard of care for patients with resectable locally advanced oesophageal or oesophagogastric junctional cancer.

Shapiro comments on the implications of these findings and further planned trials. “In many countries, including the UK, perioperative chemotherapy—according to the phase III MAGIC trial—is considered the standard of care. Currently a new randomized trial is underway: the Neo-AEGIS trial (ICORG 10-14; NCT01726452) is directly comparing the regimens used in the CROSS and MAGIC studies for adenocarcinomas of the lower oesophagus and oesophagogastric junction.”

Shapiro adds that “approximately 30% of patients in the multimodality group had a pathological complete response in their resection specimen—in other words, no residual tumour cells were found in the resection specimen.” This encouraging observation has called in to question the necessity of standard surgical resection after chemoradiotherapy. As a consequence, Shapiro and his

collaborators note that they are “currently performing a phase II feasibility trial in the Netherlands (the pre-Surgery As Needed for Oesophageal cancer trial; preSANO trial) to investigate the most accurate way to detect and predict residual disease after neoadjuvant chemoradiotherapy.” In this trial, patients will be exposed to two rounds of endoscopic ultrasonography with wall-thickness measurements and biopsies of the oesophageal wall, together with PET-CT imaging, after completion of neoadjuvant chemoradiotherapy, but before planned surgical resection. Shapiro continues, “in this feasibility trial all enrolled patients will undergo the planned resection, irrespective of the diagnostic results following neoadjuvant chemoradiotherapy. Therefore, we will have a set of patients for whom we will be able to correlate the full diagnostic package with the final histological results in the resection specimen.”

He concludes, “results from the preSANO trial will show whether we will be able to detect or predict with a high degree of certainty who is a complete responder and who is not. If results from this trial are promising, we will continue with a phase III trial, in which patients will receive either neoadjuvant chemoradiotherapy plus surgery as needed, or the neoadjuvant regimen plus surgery as standard.”

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