Editorial Commentary

# Recurrence in complete responders after trimodality therapy in esophageal cancer

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Complete pathological response (pCR) remains one of the most important prognostic factors of long-term survival in esophageal cancer (EC) and gastro-esophageal junction (GEJ) after trimodality treatment including neoadjuvant chemoradiotherapy (CRT) followed by surgery. The pCR is known to be associated with an improved survival and disease-free survival (1-3). Current results of the latest and largest randomized trial on neoadjuvant CRT (neoadjuvant CRT followed by surgery versus surgery alone; CROSS trial) are encouraging in both squamous cell carcinoma and adenocarcinoma subtypes (4,5). With an association of carboplatin-fluorouracil and a radiation dose of 41.4 Gy (23 fractions of 1.8 Gy, 5/week), CROSS trial resulted in a complete pCR rate of approximately 49% for squamous cell carcinomas and of 23% for adenocarcinomas. The pCR has been shown to be associated with an unexpected good long-term survival and some series reported 50% rate of 5-year survival (1,6-8). However, even with pCR, a complete regression with fibrosis and without detectable tissue of tumor (TRG0 Mandard classification) cannot be seen as an absolute and definitive cure. Indeed, some patients will relapse within the two years after completion of the first-line trimodality regimen. Between 20% and 40% of complete responders exhibit recurrence whatever is the histological subtype, within the 24 months after the completion of the trimodality strategy (6,9,10). On this basis, identification of recurrence's predictive factors in complete responders to induction treatment remains crucial. However, few studies have examined risk factors and patterns of recurrence according to histology in this specific subgroup.

In the current issue of the *Journal of Thoracic and Cardiovascular Surgery*, based on a single-institution database, Barbetta *et al.* (11) investigated patterns and risk of recurrence in patients with EC with a pCR after trimodality therapy. Based on a retrospective analysis of a monocentric institutional database, the authors analyzed 233 patients with stage II–III treated with several induction treatment protocols treated over a 20-year period [1997–2017]. They focused on patients who exhibited a pCR. Preoperative staging assessment was based on esophageal ultrasonography (EUS), computed tomography (CT)-scan or positron emission tomography PET-CT (90% before neoadjuvant treatment, 70% after completion of neoadjuvant treatment). The two main goals were to describe the patterns of recurrence and to identify risks factors of recurrence in complete responders. The authors analyzed 233 complete responders (18.6%) among 1,249 patients treated with neoadjuvant trimodality treatment. The study population included 169 adenocarcinomas and 64 squamous cell carcinomas. Platinum-based chemotherapy was the most frequent chemotherapy regimen (92%). Radiation-dose was up to 50.4 Gy in almost 84% of their patients. Absence of viable tumor tissue was the definition

of the pCR even if residual lesions were identified in 33% of patients (Barrett's metaplasia, low and high-grade dysplasia).

With a median follow-up of 42 months (ranging between 0.4 and 213 months), the authors showed that patients with adenocarcinoma presented a higher rate of distant recurrence rather than squamous cell carcinoma. Liver and brain metastases were the two main sites of distant recurrence. In contrast, patients with squamous cell carcinoma presented a higher rate of loco-regional recurrence, especially into the mediastinum with positive lymph nodes. Of interest is the high rate (22%) of early recurrence in complete responders within the 6 months after surgery and especially in adenocarcinomas. On the basis of a multivariable competing risk-regression model, the authors found that poor tumor differentiation remained the sole independent risk factor for recurrence in patients with a pCR whatever the histological subtype, but particularly those with adenocarcinoma.

The central messages of the Barbetta's report can be summarized as follow: (I) patterns of recurrence are different according to histology subtypes: adenocarcinoma patients are more at risk of distant metastasis whereas squamous cell carcinoma patients are more at risk of locoregional recurrence in complete responders; (II) surveillance protocol of recurrence should be more aggressive including every 6 months not only chest-abdomen-pelvis CT (or PET-CT) but also routine axial brain imaging (brain-CT or magnetic resonance imaging) especially for adenocarcinomas; (III) trimodality should be transformed into a quadrimodality regimen including a perioperative chemotherapy in patients demonstrating poor differentiation tumor in adenocarcinomas. This finding should deserve further investigations; (IV) extended mediastinal lymph node dissection should be seen as a standard of care in squamous cell carcinoma regarding the high rate of loco-regional recurrence in this subcategories. Three-field lymph node dissection has to be clarified in this setting (12).

However, the current report presents some limitations that deserve further discussions.

First, because the incidence of adenocarcinoma of esophagus and GEJ has spiked more that sevenfold over the last decades, representing although 72% of the population of the current study, every effort should be made to establish a nomogram to predict the recurrence in adenocarcinoma specifically. Recently, a preoperative nomogram aimed at stratifying patients for the benefit of trimodal treatment in esophageal adenocarcinoma has been reported (13). Among the several investigated variables, signet-ring cell (SRC) histological subtype appears as a strong negative prognosticator of survival associated with early recurrence. Previous studies have shown a dramatic increase in the incidence of the SRC tumours, which has expanded more than 400% in US representing nowadays between 15% and 30% of all esophageal or gastric adenocarcinomas (14-17). Trimodality therapy has been suggested to be one of the independent factors affecting survival and especially in complete responders (18). However, despite their rigorous statistical analysis, SRC histological subtype has not been investigated in the Barbetta's report.

Second, the authors suggested in the univariate analysis of risk factors for recurrence after pCR in overall cohort that total dose of radiotherapy (>50.4 Gy) would be considered as a risk factor even if P value was not significant in multivariate analysis (only variables with P value less than 0.05 were fitted in the final model). Even if this information is weakened by the retrospective nature of the present study and the post hoc determination of the cut-off value of 50.4 Gy, Barbetta *et al.* provided important information for surgeon and oncologist who face trimodality treatment. Given the numerous adverse events observed in patients who received radiation dose ≥50.4 Gy (19), the lack of good evidence supporting a high total radiation dose in term of local control or in term of survival (20), and the risk of recurrence with high radiation dose bring by the Barbetta's study, 50.4 Gy should be considered as an upper limit threshold of total dose of radiation in neoadjuvant setting.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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