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The "Gastro" Dilemma on the Management of Gastroesophageal Junction Tumours: What Tumorsubsite should they belong to, and what Approach should be Preferred?

Gastroesophageal cancers (including oesophageal, gastric and gastroesophageal junction lesions) are worldwide a leading cause of death being relatively rare but highly aggressive [1]. In the last decades the frequency of the distal stomach cancer decreased, while the incidence of cancer of the cardia and Gastro-Esophageal Junction (GEJ) has been rapidly rising [2,3]. The GEJ anatomically separates the lower oesophagus from the proximal part of the stomach, where the squamous epithelium of oesophagus changes into the columnar epithelium of gastric cardia [4].

Even though the modern surgical techniques gained better results over last decades, outcomes after resection alone are still poor, ranging by 20-30% of survival at 5 years [5]. The integration of pre- or peri-operative multimodal approaches, as Radiotherapy (RT) and Chemotherapy (CT) (eventually combined), seems promising to further improve clinical outcome for such presentations.

One of the main issues about GEJ is the classification: in past, GEJ was alternatively considered a gastric or oesophageal cancer due to their anatomical location at the boundary of these two primary sites [6]. A fundamental classification was proposed by Siewert and colleagues: three types of lesions were defined according to the localization of the lesion's epicentre and detailed on the base of the range of distance from the GEJ [7]. Recently the American Joint Committee on Cancer (AJCC) changed the staging system for GEJ to harmonize some staging aspects for oesophageal and gastric cancer [8]. In the 7th classification, GEJ tumours (i.e. the Siewert type I-II-III) are grouped as a sub site of oesophageal cancer, which epicentre is in the GEJ, or in the distal oesophagus, or as well within the proximal 5 cm of the stomach (cardia) if extending into the GEJ (and distal oesophagus). On the base of the new classification, the three Siewert types together belong to oesophagus.

Radical surgery is the most effective treatment modality, with the aim of the en-bloc removal of primary tumour and lymphatic nodes, obtaining microscopically negative resection margins (R0) [9]. Surgery alone is nowadays mostly confined to the treatment of early localized presentations [1]. The efficacy of neoadjuvant integrated treatments has been widely investigated over last decades.

Over last decades some meta-analyses reported results not clearly significant or borderline significant for the benefit of neoadjuvant radiotherapy, either alone or in combination with concurrent chemotherapy [10]. Quite clear evidence was found about the need for neoadjuvant approach (RT or CT), being apparently showing a trend for benefit using Radio Chemotherapy (RTCT) [11]. The potential of

RTCT for the management of GEJ tumors is also highlighted by the current indications provided by the main International Guidelines, basically recommending the use of neoadjuvant treatment, most of the time represented by RTCT [1,12,13].

A landmark study was recently published in 2012 by van Hagen *et al.* [14] and is currently discussed as reference for the gold standard of the modern treatment of oesophageal cancer, so including the GEJ tumors. Between 2004 and 2008, 366 pts were enrolled for this randomized trial to receive either surgery alone or a RTCT preoperative treatment consisting of RT up to a dose of 41.2 Gy (conventional fractionation, over 5 weeks) plus weekly Carboplatin and Paclitaxel. Pts were eligible if affected by oesophageal carcinoma in general, but the vast majority of them were affected by GEJ lesions: over the 80% of the patient in both arms had the primary lesion sited in the distal third or at the GEJ, and the 75% of the enrolled pts presented an adenocarcinoma. Tolerance to RTCT was good. An R0 resection was obtained for 148/161 pts (92%) vs, 111/161 (69%) in the RTCT and control group respectively. No difference was found in the postoperative complications between the two groups. Two of the most interesting pathological findings should be highlighted: the first is the 29% rate of pCR (47/161pts) in the RTCT group, higher but in line with the previously published evidences for GEJ tumours. The second is the significantly lower presence of pathological nodal involvement in the RTCT compared to the surgery only arm: 31% vs, 75% respectively ($p < 0.001$): the impact of this aspect is enhanced by the mentioned change in the 7th edition of the TNM classification, that tend to highlight the number of involved nodes as a strong prognostic parameter for such tumours. This study highlights the strong potential of RTCT in the modern era, associated, of course, to surgery.

Few studies analysed the direct comparison of RTCT vs, CT alone in preoperative setting: very few of them are randomized and results are sometimes controversial, but tend to stress the high potential of RTCT over CT in term of efficacy, and in particular in term of inducing pathological complete responses (significantly associated to better prognosis) [15].

The main problem interpreting the literature about the issue of the treatment selection for GEJ tumours is the difficulty to have a clear focus on GEJ lesions only: most of the reports (both on oesophageal and gastric tumours, depending on the classification adopted) mix the pure GEJ lesions with either gastric distal, or oesophageal proximal lesions.

A meta-analysis published in 2013 evaluated trials focused on

adenocarcinoma of oesophagus GEJ or stomach only. Authors collected 14 randomized phase III trials comparing surgery alone versus surgery preceded by a CT neoadjuvant treatment (either alone or combined with RT) [5].

The analysis highlighted that administration of CT (globally evaluated as preoperative CT alone + RTCT data) was significantly associated to longer survival (HR 0.81, CI 0.73-0.89; $p < 0.0001$) respect to surgery alone. In particular, when separately analysed by anatomical subsites, the reported results were largest for the GEJ presentations, followed by oesophageal and gastric tumours. Moreover, when compared in direct subgroup analysis, RTCT showed a larger effect than CT in producing the survival benefit (HR: 0.70, CI 0.50-0.99 for RTCT vs. 0.83, CI 0.75-0.91 for CT; $p = 0.38$) but this was not statistically significant.

In conclusion the current and past available evidences about the treatment of GEJ tumours highlight the need for neoadjuvant treatment, in particular seems strongly suggested the use of preoperative RTCT, since it is associated to high efficacy and reasonable toxicity. The urgency for focused trials with a high selective selection only for GEJ tumours will address and eventually confirm what nowadays seem always more to be advocated as a potentially new standard of treatment.

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