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GI tumours. Which advances in esophageal cancer?

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Two thousand new esophageal cancers (EC) have been estimated in the 2014, in Italy; and even if the 5-year overall survival has almost doubled in the last ten years however it is still only 13% for males and 17% for females despite the progressive reduction of the squamous cell (SCC) histology in favour of the adenocarcinoma(AC) (1). The substantial advances in diagnosis, staging, treatment and supportive care, clearly had a very little impact on the prognosis, still very disappointing, even for operable patients. Less than 50% of all esophageal cancers are candidate to radical surgery and the 5-year survival after surgery alone is less than 35%, also in controlled trials and in reference Centres (2-4). A meta-analysis on neoadjuvant chemoradiotherapy (nCRT) shows a benefit for combined therapy, with an absolute advantage of 8.7% in the 5-year survival (5). Patterns of failure analyzed in the most recently published studies on nCRT of EC show a significant improvement in local control for patients assigned to neoadjuvant arm, nearly halving the rate of locoregional recurrence: from 29% to15% in the FFCD 9901 study (2), and from 30% to 15% in the CROSS study (4), respectively. However, this reduction translated in an increase of median survival, almost doubled (from 24 to 49.4 months, with an absolute benefit of 13% in the 5-year survival), only in the CROSS study. How could this different outcome in survival be explained, despite the similar effect in the reduction of recurrence? Comparing the two trials, there were more grade 3 or superior toxicities (30% vs 17%) and less radical esophagectomy in nCRT arm (6% vs 14 %) in the FFCD 9901 respect to the CROSS study; moreover, the postoperative mortality rate was superior (11% vs 4%), and the proportion of SCC higher (75% vs 23%) in the former study. Every one of these variables could have contributed to the different outcome in survival and should be considered when planning the treatment. There are some rules that should be followed to obtain the optimal possible outcome for each patient. First, the patient evaluation and the treatment decision should be performed by a multidisciplinary team. Second, the esophagectomy should be carried out by a well trained and experienced team (this stands not only for the surgeons but also for the anaesthesiologists, the nurses, the nutritionists and the rehabilitation trainers). Third, the esophagectomy should be performed when the patient had fully recovered from the toxicity of nCRT, that indication was supported by the evidence that the time between nCRT and surgery could be safely delayed up to 12 weeks (6, 7).

Fourth, the chemotherapy regimen should be decided considering the Centre expertise and the patient comorbidities; since there is no a regimen clearly superior to another in randomized studies, the patient safety and tolerance should direct the choice.

Fifth, all the radiologic images should be carefully examined, compared, discussed and repeated, when unclear, before deciding whether to proceed to surgery or not.

AC are known to have a better postoperative outcome when compared with SCC in relation with less frequent and less severe comorbidities, a lower exposure to alcohol and tobacco consumption, and a lower risk of malnutrition. In addition, AC are usually located in the lower third of esophagus, this meaning

that patients could receive a lower total dose of radiation related to a smaller irradiation field, also with a greater lung volume spared from radiation. This is a critical point with regards to the risk of developing a radiation-induced pneumonitis, and the subsequent decrease of postoperative mortality.

Centre patient volume is a crucial issue when evaluating postoperative mortality (POM). In a recent paper published by the FFCD group (8) a high volume (HV) Centre is defined as one with ≥ 80 procedures over a 10-year period. Factors independently associated with 30 day POM included American Society of Anaesthesiologists (ASA) grade IV, low volume (LV) Centre, anastomotic leakage, postoperative haemorrhage, pulmonary and cardiovascular complications and R2 resection margins. Treatment in a HV Centre with a multidisciplinary esophageal team that follows specific predefined procedures provides an increase in the median and 5-year survival of EC patients. The thirty-day POM in LV was significantly greater when compared to HV Centre (Odds ratio 0.30, 95% Confidence Interval =0.20-0.44; p<0.001). Moreover, in another recently published study from the same group, the nCRT was not an independent predictor of POM (9). All these characteristics, differently distributed in AC and SCC, explain why esophagectomy should always been evaluated in AC, while it could be avoid or reserved as rescue in SCC.

In esophageal cancer the response evaluation is still a difficult and unsolved issue, especially in the definition of the clinical complete remission. The studies on the advantages of using Positron Emission Tomography/Computer Tomography (PET/CT) over Computer Tomography (CT) and endoscopy alone were conflicting. FDG-PET/CT seems to improve the calculation of the RT target volume in patients with esophageal SCC (10). The improvement in staging and restaging and the predictive value of maximum Standardized Uptake Value lack of standardized and reproducible criteria and should be better defined for AC and SCC. Also, evidences and/or guidelines are lacking for the usefulness of serum tumour markers. However, Ca19.9 and CEA could be useful in the decision making process in AC, as reported by our group, in patients with operable AC, for which high CA19.9 and CEA serum levels correlated with occult metastatic disease (p<0.001 and p=0.003, respectively). For this group of patients, high marker levels would encourage a minimally invasive exploration to avoid an inappropriate laparotomy or thoracotomy (11).

However most of the patients with EC die from metastatic disease (70.4% of the recurrence population in the FFCD and 90.5% in the CROSS trial, respectively) suggesting that, without a strategy that will offer a better control in the risk of developing metastatic disease our efforts are not sufficient.

The addition of target molecules, except for trastuzumab with cisplatin and fluorouracil or capecitabine, in the minority of metastatic AD with overexpression of HER2 protein by immunohistochemistry or gene amplification revealed by molecular techniques (fluorescence or chromogenic in-situ hybridisation) (12) has been not very successful till now.

Moreover EC is one of the cancer after melanoma and lung in which the cells expression of mutated immunoreactive peptides is higher The new immune inhibitor checkpoint blockade monoclonal antibodies (anti-CTLA4, anti PD-1 and anti PD-L1) represent a new and very different approach. The EC cells express PD-L1 and PD-L2 in a high percentage of cases and this expression is correlated with the prognosis. Moreover, EC is one of the cancer after melanoma and lung in which the cells expression of mutated immunoreactive peptides is higher (13-15). Other immunologic approaches with vaccination are currently under study, one of the most promising is the adoptive vaccination, using the NY-ESO1 tumor antigen (16). Taking into account all these aspects, the immunology approach could be more effective than expected and be able to change the long term survival also in EC:

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