AB006. Management of T2 oesophageal cancer

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Abstract: Optimal treatment strategy for patients with oesophageal cancer is a matter of a debate. We are more and more aware that oesophageal cancer is not a uniform clinical entity, and that optimal treatment may be different depending on tumour histology, stage, grade and location. Unfortunately, adequately powered prospective randomised trials are lacking, and therefore the current practice is still based on moderately reliable evidence. As there are no prospective randomised studies concerning specifically the treatment of T2 oesophageal cancer, the only available evidence comes from non-randomised analyses of institutional or national databases. There were five such studies published, all with the inherent drawbacks of retrospective analyses. The treatment strategies included: surgery alone, surgery ± adjuvant chemotherapy, and neoadjuvant chemotherapy or radio-chemotherapy followed by surgery ± adjuvant chemotherapy. Also, these studies used different chemotherapy regimens and different radiation doses and quality of surgery was not reported. All these studies have found no difference in survival between the different treatment regimens. They all, however, pointed out the high inaccuracy of clinical assessment of T2. This assessment is highly dependent on the quality of the diagnostic work-up, and again, the above-mentioned studies did not include precise data in his regard. It seems likely that the cT2 assessed in 1990s using endoscopy and 8-row CT is not the same as cT2 determined in 2018 using contemporary high-resolution CT, PET scanning and endoluminal ultrasound. There are also factors associated with a higher risk of understating the T stage, e.g., larger size of the tumour, high grade and lymphovascular invasion. In a recently published study a decision analysis model for two treatment strategies was presented: a upfront surgery ± adjuvant chemotherapy for upstaged patients and neoadjuvant chemoradiotherapy followed by surgery. The authors concluded that induction chemoradiation is beneficial if the probability of pathological upstaging exceeds 48%. The findings of the above-mentioned five studies can be probably summarised with the statement, that although there are no data showing benefit from any treatment strategy, the inherent weaknesses of their methodology makes any conclusions disputable. In the last two years, there were two other important studies published, comparing effectiveness of the neoadjuvant therapy followed by surgery *vs.* definitive chemoradiotherapy in the treatment of oesophageal cancer. Importantly, they both included only squamous cell carcinoma (SCC), stage cII–III. So, only a subgroup of patients included had T2 disease. Both these studies have shown significant benefit from the trimodality treatment. Whether this is due to the histological type of cancer (SCC only), more advanced disease (stage II and III) or more accurate pre-treatment staging, remains unknown. And finally, the prospective randomised study that provided us with high-quality evidence regarding the role of trimodality therapy of oesophageal cancer, which is the CROSS trial. This study included 366 patients, 75% of them with adenocarcinoma (AC) and 23% with SCC. The study protocol allowed enrolment of patients with T1N1 or T2–3N0–1 disease, and finally T2 was found in 15% in trimodality group and in 19% in the surgical group. The CROSS trial has shown highly significant survival benefit from the trimodality regimen, for both: AC and SCC patients, although this benefit was more pronounced in the SCC group. There was no separate analysis provided for the T2N0 subgroup. It should be noted that the CROSS trial utilised novel protocol of the neoadjuvant therapy, that included carboplatin and paclitaxel for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions). This regimen is better tolerated than the previously used, with fewer toxicity and 94% of patients who could undergo surgery after completion of neoadjuvant therapy. It is generally believed, that the CROSS trial paved the way for the modern trimodality therapy of oesophageal cancer. While planning the treatment of a patient with oesophageal cancer, three important issues should be taken into account, besides the effectiveness of particular modalities. Firstly, the above-mentioned inaccuracy of the pre-treatment determination of T was in >70% of patients with cT2N0. Secondly, assessing response to the induction therapy, it should be remembered that cCR is not pCR (in 63% of patients with cCR persistent tumour can be found in the specimen). Thirdly, if a salvage oesophagectomy becomes necessary due to relapse after planned definitive chemoradiation, the results are worse in terms of mortality, anastomotic dehiscence and pulmonary complications, as

compared to elective surgery. I could summarize the current concept of treatment of the T2N0 oesophageal cancer with the following statements: (I) scientific quality of the available evidence is suboptimal, and we have to build our treatment strategies on the basis of indirect deduction; (II) on the basis of the results of the CROSS trial, and given the inaccuracy of the clinical determination of the T2, trimodality therapy seems optimal for most of the cT2N0 patients; (III) upfront surgery may be optimal option for cT2N0 patients with low probability of pathological upstaging; (IV) further adequately powered, randomised studies are necessary to confirm the role of the trimodality therapy in particular subgroups of patients with oesophageal cancer; (V) advanced systemic therapies, and particularly immune therapies, should be investigated as a part of combined protocols.

Keywords: Esophageal cancer; staging; esophagectomy; multimodality treatment; decision making

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