Editorial

Role of the modern radiotherapy in the postoperative setting for esophageal cancer

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Hwang and colleagues recently reported on a propensity score matched (PSM) analysis to evaluate the role of adjuvant radiochemotherapy (RTCT) in esophageal cancer (1). They collected data from 1,095 esophageal squamous cell carcinoma (ESCC) patients. The investigated population both included patients who only underwent to surgery (group 1; 679 patients) and having also received adjuvant RTCT (group 2; 416 patients). The data about patients have been obtained from the Taiwan Cancer Registry database. Finally, 147 balanced patients per group were selected by PSM. The 3-year survival rate was 28.1% in group 1 and 44.9% in group 2, respectively. Interestingly, the multivariate analysis highlighted some factors resulted statistically significant predictors for clinical outcome: postoperative T3 and T4 (pT3/4) [hazard ratio (HR): 2.03, 95% CI: 1.38–2.97, P<0.001], postoperative positive lymph-nodes (pN+) (HR: 1.83, 95% CI: 1.31–2.57, P=0.0004), tumor length over than 32 mm (HR: 1.93, 95% CI: 1.33–2.79, P<0.001), evidence of either microscopical or macroscopical residual (R1 or R2) at resection (HR: 1.75, 95% CI: 1.15–2.66, P=0.009), and administration of adjuvant RTCT (HR: 0.57, 95% CI: 0.42–0.78, P<0.0001). Looking at the patient's characteristics, patients analyzed in group 2 were younger and presenting more advanced tumors compared with group 1. Moreover in the group 2 there were more: T3 and T4 tumors (77.6% *vs.* 28.6%), N+ tumors (76.8% *vs.* 20.3%), M1 tumors (6.3% *vs.* 2.4%), stage III/IV tumors (68.5% *vs.* 15.9%), large-sized tumors (45.6 *vs.* 30.9 mm) and poorly differentiated tumors (32.6% *vs.* 23.4%). The rate of residual tumor at resection margin (R1/2 resection) was also higher in the group 2 (18.6% *vs.* 6.9%). Authors' report that around 45% of the presentations were preoperatively sited in lower esophagus in both groups, but do not specifically account for the junctional presentations. We could summarize that such evidence suggests how postoperative RTCT seems able to compensate for adverse features individuated after surgery, including pT3/4, pN+, more extended tumor length, R1/2, more advanced histological grade. First of all, looking at the presented paper, the reproducibility of the results for all the patients could be questioned since derived from an Eastern population. The issue must be taken in consideration but the presented results are also in line with a previously published experience by Rice and colleagues, highlighting the advantage by administration of adjuvant RTCT over surgery alone in a smaller single-center Western population experiment performed with a similar methodology of propensity-matched comparison for case selection (2). That study involved 31 and 52 patients undergone to postoperative RTCT and surgery alone, respectively; both adenocarcinomas (approximately 84% in both arms) and squamous lesions (approximately 16% in both arms) were included; pT1-4 pN0-1 M0-1 lesions were collected. The trial published by Rice *et al.* strictly aimed to define the clinical efficacy of adjuvant RTCT on the global dataset: no focus on patient's characteristics was driven. Conversely, in the report of Hwang *et al.* a subgroup analysis focused the advantage derived by receiving postoperative RTCT

in specific subset of patients: that is significantly gained for each subgroup including R1/2 resections, T3/4, N+, longer than 32 mm, poorly differentiated lesions. Nowadays, on the basis of some clear literature evidences (3-5) there is a quite wide consensus for the treatment option of esophageal lesions, including for the locally advanced squamous ones: it should be nevertheless noted as the rate of squamous presentations in the CROSS trial is approximately 23%. Thus, the data presented by Hwang and coworkers could allow a reflection whether could there be room for a modification of the indications provided by the currently available guidelines. The last release version of the National Comprehensive Cancer Network (NCCN) guidelines suggests preoperative RTCT as primary treatment option for non-cervical locally advanced respectable presentation (i.e., cT1b-T4 anyN) of ESCC (6). That implies that all the patients should be theoretically referred to preoperative RTCT in the clinical practice. Moreover RTCT is the recommended option when dealing with the case a non-preoperatively irradiated patients if reporting a microscopically or macroscopically non-radical surgery (i.e., R1–2). On the contrary if a patient already received RTCT before surgery, the proposed options include observation only, palliative treatment or best supportive cares. It should be highlighted that the results presented by Hwang and coworkers are based on patient data obtained from Taiwan Cancer Registry database, which is a national population-based database: although interesting and based on a good methodology and big number of collected patients it has not the evidence level of a randomized trial. Thus, three main types of considerations could be addressed regarding the challenges that such evidence arises: may we potentially reconsider the general indication of upfront preference for preoperative RTCT? Should we offer postoperative RTCT to a wider population of patients? Is there room for further integration of postoperative RTCT as an intensification of multimodal treatment?

First issue: should we reconsider the indication for preoperative RTCT over the postoperative one? Preoperative RTCT enables early treatment of distant metastases while simultaneously treating the primary disease, facilitates definition of radiotherapy target volumes, and may allow resection of advanced disease. It has, however, some toxicity and, although data about the effect of such toxicity on the clinical global outcome are still unclear (7), it may reduce the ability of some patients to tolerate resection. Postoperative RTCT allows for early surgical debunking, rapidly addresses dysphagia, and allows for RTCT based on accurate pathologic staging, but delays systemic treatment. This is certainly a hard issue since indirect comparison of evidence in literature is not always applicable: often the series administering adjuvant RTCT tend to reserve that to more advanced presentations (also including the presence of surgical residual). Few available reports recently investigated that issue in literature. Looking at them in detail, two have some issues about the characteristics of the involved patients: one only including T4 lesions, administering low radiotherapy dose and not specifying the histology (squamous or adenocarcinoma) (8); or both enrolling the two histology like in the Surveillance, Epidemiology, and End Results (SEER) cancer registry base paper authored by Hong *et al.* (9). Nevertheless these 2 evidences support the role of preoperative RTCT over the postoperative one. Similarly to the paper we are discussing (1), other two reports are national population-based from the Taiwan Cancer Registry: Chen *et al.* collected 234 patients with ESCC, divided into three groups (preoperative RTCT, postoperative RTCT and Surgery alone) (10). They found that bot the RTCT-administering arm were significantly superior to the surgery-only option. In contrast, the survival was similar between the preoperative RTCT and postoperative RTCT groups (P=0.544). Moreover, patients with clinical T3/4 stage tumors and those with a tumor size greater than 5cm were more likely to demonstrate an overall survival benefit from preoperative RTCT compared with postoperative RTCT, suggesting a more founded role for such an approach for these clinical presentations. Hsu and colleagues applied the PSM method to 572 patients with ESCC whose data were collected by the Taiwan Cancer Registry, balancing the analyzed population among who underwent to either preoperative or postoperative RTCT, enrolling T1–4, N0/+, R0/1/2 presentations (11). This analysis did not find a significant difference favoring one approach over the other: interestingly, there was a non-significant trend for preoperative administration of RTCT for all the analyzed clinical outcomes (i.e., overall and disease-free survival).

A randomized trial facing approximately 80 patients in each of its 3 arms (preoperative RTCT, postoperative RTCT, surgery alone, respectively) was provided by Lv *et al.* (12). In their experience local recurrence rate significantly favored the preoperative RTCT over the others options (preoperative 11.3%, postoperative 14.1% and surgery alone 35%, respectively; P<0.05). On the contrary, similarly to the previously mentioned papers, the clinical outcome (specifically the 1-, 3-, 5-, 10-year overall and

disease-free survivals) did not differ significantly, although the preoperative RTCT always had a non-significant favored trend. We can summarize that though there is some conflicting results, there is still not probably enough data (particularly not strong enough) to support the equivalence of postoperative to preoperative RTCT; as most of the authors of the mentioned studies conclude: further evidence are still needed to investigated such a relevant point.

Second issue: should we offer postoperative RTCT to a wider population of patients? We mentioned that the NCCN guidelines currently only advice postoperative RTCT for patients with evidence of residual disease after surgery (R1/2). The paper from Hwang *et al.* actually questions that point since in their experience also pT3/4, pN+, larger sized lesion and poorly differentiated tumors were more likely to demonstrate survival benefit from adjuvant RTCT. Similarly, other published experiences highlighted that some factors other than resection margin status could be associated to an advantage by receiving postoperative RTCT, in particular for the positive nodal status (13,14), specifically in the field of ESCC (15,16) and when presenting extracapsularity (17). It is not clear if such characteristics could be incorporated into new guidelines: if the presence of a certain level of post-surgical residual is clearly associated with a worse clinical outcome, if an adjuvant therapy should be routinely incorporated into the preferable clinical practice in presence of pN+ and/or larger lesions irrespectively if a R0 resection was achieved, need probably a more robust analysis. Finally a third issue can be briefly mentioned: the chance for a further integration of postoperative RTCT to intensification the standard multimodal treatment. A recent report from Hsu *et al.* retrospectively analyzed (by PSM) a group of 64 patients with ESCC cancer who showed poor pathological response to preoperative RTCT: all the investigated population obtained a R0 resection, but showed persistent nodal disease or a postoperative ypT stage greater than or equal to the pretreatment clinical T stage (18). Authors meant to investigate whether postoperative adjuvant therapy could provide a clinical impact by providing to the two groups of patients either surveillance or adjuvant therapy (mostly represented by a second course of RTCT delivering 23.4 to 30 Gy—up to a total dose of 60 to 65 Gy). Compared with those undergoing surveillance, the 3-year disease free survival was significantly improved (45% *vs.* 22.3%; P=0.022), but authors warned about the need for a carefully weighed against a potential increase in the risk of treatment-related death.

Also this last treatment opportunity seems intriguing but strictly needs to be better exploited by a bigger and more robust prospective evaluation before to be recommended for the common clinical practice. Unfortunately it is not always possible to plan and perform a randomized trial with an adequate strength: collecting enough patients can be difficult, and the time needed to plan, set and complete a trial can be conflicting with the urgency of some answers; moreover the rapidity of the scientific evolution could challenge certain schedules or chosen drugs. The rapid and continuous accumulation of new evidences on such an amount of different sources (imaging, genetic, clinical, trials) determines the urgency for solutions able both to quickly interpret the evidences derived from new data and to confirm on independent and wide confirmatory datasets the upcoming results of new hypotheses derived from research (19). The use of large and shared databases for data-mining added to implementation of new technologies applied to data interpretation could be a valid option (20). Being able in the close future to rapidly handle big-data from different sources and to address a research featured by algorithms based on learning machines could enhance our chances to investigate and validate predictive models able to answer highly complex questions. By now, remaining strong the evidence privileging the choice for preoperative RTCT in the routine clinical practice, the experience of Hwang and colleagues suggest us to further study the issue of RTCT, particularly in the perspective of patient selection, timing with surgery and integration with systemic agents, possibly in the setting of randomized controlled clinical trials.

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Footnote

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

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