Letter to the Editor

Conventional *vs.* extended D2 lymphadenectomy in gastric cancer patients: less is more?—more or less

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Debate in locally advanced gastric cancer patients as a consequence of controversial and sometimes retrieved results in the past decades. According to the recent Japanese Gastric Cancer Association Guidelines (1) and several pivotal randomized studies, a D2 lymphadenectomy should be referred as the standard of care in cT2-T4 as well as cT1N+ neoplasms and the role of splenectomy for tumors invading the greater curvature remains equivocal.

However, according to the latest revision, station #10 has been removed from the definition of D2 dissection in total gastrectomy. On the other hand, the authors did not denied an extensive lymphadenectomy due to unclear evidences about survival benefits. For these reasons, a tentative for a systematic definition of the so called "D2 plus" lymphadenectomy has been carried out even if strong recommendations still lack. According to these guidelines, a D2+ approach could potentially involve station #10, #14v, #13 and #16 on referral to neoplasm location and UJCC's T-status. In this setting, splenic hilar lymph nodes should be harvested with or without splenectomy for cancers of the upper third stomach invading the greater curvature. Superior mesenteric venous lymph node assessment could be justified in case of distal tumors with clinically proven station #6 metastases; posterior pancreatic head lymphoid tissue could be sampled for pyloric or proximal duodenal neoplasms as considered regional lymph nodes in these cases and not M+. Finally, abdominal aortic lymph nodes should be harvested in responsive neoadjuvant regimens for cancers with an extensive lymph node involvement.

These guidelines have certainly raised several questions, as it would result in long-standing conflicts about the oncological efficacy of D2 lymphadenectomy and would re-propose controversial issues about prophylactic splenectomy as well as it would restore a peculiar dimension to the extended lymphadenectomies for stomach cancer; in other words, it would mean, would that mean, have we to newly face with diatribes about results supported by the Medical Research Council (2) or the historic Dutch trial (3)? What has been the usefulness of several subsequent evidence reviews from randomized trials lasting more than a decade? What happened to evidences about the impact of extended lymphadenectomies and distal spleno-pancreasectomies on patients' prognosis? A new beginning or a beginning for the past?

The extension of the lymphadenectomy in gastric cancer, as known, is subordinated to the marked tumor lymphotropism with a radial mechanism and this has given rise to two antithetical positions (4): a historical radical attitude from Eastern countries opposed to a Western conservative one (5), corroborated by epidemiological peculiarities (such as cancer incidence, population's average age, prevalence of clinical stages) and by results that emerged from outstanding trials. This led to a skeptical general by Western surgeons, advocating an unjustified increase in perioperative morbidity and mortality in face of any long-term benefit (3). On the other hand, Western radicalisms burned from several biases that led to misinterpretations. In this regard, it is impossible to

disregard the putative role of splenectomy in course of D2 lymphadenectomy, which has been widely demonstrated (6-8) as the main influencing factor on patients' perioperative outcome rather than lymph node dissections themselves. These evidences marked a watershed between the past and the present, highlighting the need for a profound revision of the Dutch trial which has only taken place in recent years and has clearly shown the risk of locoregional recurrence was significantly lower in patients undergoing D2 lymphadenectomy rather than D1 dissection (9).

The Dutch study, in fact, although conducted on a suitable patient sample, presented several not negligible allocation and procedural issues. The high rates of morbidity (43% *vs*. 25%, P<0.001) and mortality (10% *vs*. 4%) could not and should not have been justified as a consequence of a mere extensive lymphadenectomy. But, only the awareness of the existence of the above confounding factors allowed to clarify that a D2 harvesting was finally associated with a significantly better outcome in patients with gastric cancer (10).

In fact, pioneering Italian phase II trials (11,12) yet highlighted effectiveness of a standardized D2 lymphadenectomy both in the short- and long-term period. Therefore, it seemed to have found the square around a debated and historically problematic topic of criticism and confrontation among scientific communities. However, recent Japanese guidelines somehow rekindle the spotlight on the case. Probably nothing new in some indications, but the common take-home message seems to be to carry out a case-by-case evaluation, without stigmatizing extended lymphadenectomies in locally advanced stomach neoplasms.

Would the exclusion of station #10 represent a compromise to somehow remedy for the need for splenectomy, defining this "extended" and not D2 lymph node harvesting? Is there a rationale for arbitrary consideration of splenectomy? A very recent meta-analysis published by Zheng *et al.* (13) actually raises many doubts. The Authors conducted a three-arm network meta-analysis including only gastrectomies, gastrectomies with splenectomies and spleen-preserving gastrectomies with lymph node dissection in order to investigate the impact of #10 lymphatics clearance in gastric cancer, and reported comparable rates of 5-year overall survival (HR: 1.0; 95% CI: 0.78–1.3), making therefore them to not recommend a D2 + #10 lymphadenectomy in proximal third gastric cancers.

In reality, a tailored extension of the lymph node dissection involves reasons that are not obvious and recalls the well-known Halstedt criteria for oncological radicality and the need to pursue an oncological R0 radicality; but, in advanced states of disease, up to 33% of ExtraStation micro-deposits are described. Additionally, a greater the number of lymph nodes and a more accurate the staging, could minimize the phenomenon of stage migration. In this view, it does not appear methodologically correct or even ethical to exclude one third of patients with locally advanced gastric cancer from a potentially curative treatment.

This is the case of the para-aortic stations (#16) and the JCOP Study 9501 (14) represents its milestone. This multicenter randomized trial, enrolling 523 patients, identified cohorts of patients achieving satisfactory 5-year survival rates with station #16 dissection.

By contrast, Sasako *et al.* (15), evaluating patients with gastric cancer higher than cT2b, reported no significant differences concerning post-operative morbidity (D2 *vs*. D2 + 16: 20.9 *vs*. 28.1%, P=0.07) as far as no outcome improvement (5-OS: 69.2% *vs*. 70.3%) with an hazard ratio for death of 1.03, suggesting any role in recurrence-free nor in overall survival of para-aortic nodes for locally advanced gastric cancers. Similarly, the Polish Gastric Cancer Study Group (16), reporting their preliminary analysis evaluating the effect of D2 + *vs*. D2, showed comparable morbidity (27.7% *vs*. 21.6%, P=0.248) and mortality rates (4.9% *vs*. 2.2%, P=0.376).

Although there is evidence to support upfront surgery in selected cN+ (16+) patients, a recent Phase II trial of the Stomach Cancer Study Group of the Japan Clinical Oncology Group (17) has definitively clarified its role as a definitive treatment definitive following adjuvant chemotherapy in patients with pre-inductive clinical positive nodes. On the other hand, as reported by Eom *et al.* (18), in the case of infrapiloric lymph node metastases and distal gastric neoplasms, a dissection of the #14v station could represent an independent prognostic factor at stage III disease. But also, tumor histology could drive the need to extent dissection. In this setting, de Manzoni *et al.* (19) stated that D3 lymphadenectomy (including station #13) could somehow revers the negative impact of Lauren's diffuse histotype on locoregional relapses and, thus, advocated to consider an extended lymphadenectomy as a viable option in a histotype-orientated tailored treatment.

Upon these evidences, in conclusions, a putative issue would not be technical but rather would lie in the persistence of long-standing conflicts and in the historical propensity for oncological speculation from Eastern schools dictated by such epidemiological peculiarities of gastric

neoplasms, claiming a natural need for further clinical trials.

What emerges is that there are still no pre-established cut-offs, rather there is strong evidence about the role and necessity of D2 lymphadenectomy, resulting the impelling need for a rationalization of the extent of lymphadenectomies dictated by stages, location and tumors' histology. We have to face with patient-tailored lymphadenectomies which could justify a relative but not significative increase of perioperative risk of complications. The keystone, therefore, would appear to overpass the strict rules of a "D" approach in order to ensure both surgical and oncological radicality for patients.

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