

Preoperative chemotherapy in gastric cancer: expanding the indications, limiting the overuse

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Dear Editor

The three main European Oncologic Societies (ESMO, ESSO, ESTRO) have recently published the joint Guidelines for the Management of Gastric Cancer (GC) [1] that should drive daily clinical practice in a region where GC is the sixth commonest cancer diagnosis and the fourth commonest cause of cancer-related death [2]. The Guidelines properly emphasize the role of multidisciplinary treatment. In particular, preoperative chemotherapy (PCHT) has been advocated as the preferred pathway for operable disease with stage >T1N0 [1]. This statement has been made on the basis of the results of the pivotal MAGIC and FFCD trials [3, 4]. Considering that early stages at the presentation are relatively uncommon in Western countries, the current Guidelines have theoretically expanded the application of PCHT to the majority of newly diagnosed GC. However, such an extended application of PCHT may give rise to some issues, in particular in patient selection. The efficacy of PCHT could depend on some tumour features affecting the grade of response. Tumour site, grading, and Lauren's histotype have been proposed as pre-therapeutic factors associated with response in a retrospective study including 410 patients [5], and signet-ring

cell carcinoma has been reported to be less responsive to PCHT [6]. A phase II/III trial comparing surgery versus chemotherapy plus surgery in patients with a signet-ring cell GC is currently ongoing (NCT01717924) and will probably yield clarification on this question. These findings confirm the importance of identifying reliable criteria in order to properly select patients for PCHT.

Another point as regards post-operative morbidity after PCHT is that several studies have proven that gastrectomy after PCHT is safe in terms of complications [3, 4], and a recent meta-analysis showed no differences in post-operative morbidity and mortality rates between patients who did receive and who did not receive PCHT [7]. On the other hand, a recent Korean study including 123 patients who underwent PCHT followed by D2-gastrectomy reported a higher than expected rate of post-operative complications of 29.3 % [8]. Similarly, the EORTC phase III trial, prematurely closed due to low patient accrual, reported a higher rate of post-operative complications in the PCHT arm than in the control arm (27.1 vs. 16.2 %), although the difference was not statistically significant [9]. Importantly, in both studies D2 resection rate was more than 90 %, with a median number of harvested lymph nodes higher than 31. Conversely, in the MAGIC trial, a D2 resection was performed in about 40 % of patients, and in the FFCD trial the median number of retrieved nodes was 19 [3, 4]. These data may suggest that PCHT may increase surgical morbidity in patients treated with an extended surgical approach such as a D2-lymphadenectomy.

Adequate surgery still remains the cornerstone in the treatment of operable GC, and D2-gastrectomy has been recently accepted as the standard surgical treatment also in the Western countries, especially in specialised centres [1]. In the MAGIC and FFCD trials, patients were frequently treated with <D2-lymphadenectomy, whereas a D2-

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lymphadenectomy was performed in 94.2 % of patients in the EORTC trial [9]. Therefore, the main evidence for the efficacy of PCHT ensues from a series of patients who mainly had a “sub-optimal” lymphadenectomy; hence, we could hypothesize that PCHT could fill the survival gap of a limited surgery.

In conclusion, PCHT certainly represents a valuable therapeutic option for GC in Western countries. Expanding the indications for PCHT seems reasonable, but its overuse may be detrimental in unselected patients. Improving the selection of patients for multimodal treatment and not playing down the importance of an adequate surgery represents a challenge to be addressed in the future.

Conflict of interest The authors have declared no conflicts of interest.

References

1. Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24(Suppl 6):57–63.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer.* 2013;49:1374–403.
3. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355:11–20.
4. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol.* 2011;29:1715–21.
5. Lorenzen S, Blank S, Lordick F, Siewert JR, Ott K. Prediction of response and prognosis by a score including only pretherapeutic parameters in 410 neoadjuvant-treated gastric cancer patients. *Ann Surg Oncol.* 2012;19:2119–27.
6. Messager M, Lefevre JH, Pichot-Delahaye V, Souadka A, Piessen G, Mariette C, FREGAT working group-FRENCH. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. *Ann Surg.* 2011;254:684–93.
7. Ge L, Wang HJ, Yin D, et al. Effectiveness of 5-fluorouracil-based neoadjuvant chemotherapy in locally-advanced gastric/gastroesophageal cancer: a meta-analysis. *World J Gastroenterol.* 2012;18:7384–93.
8. An JY, Kim KM, Kim YM, Cheong JH, Hyung WJ, Noh SH. Surgical complications in gastric cancer patients preoperatively treated with chemotherapy: their risk factors and clinical relevance. *Ann Surg Oncol.* 2012;19:2452–8.
9. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. *J Clin Oncol.* 2010;28:5210–8.