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# Neoadjuvant therapy of gastroesophageal junction adenocarcinoma: chemoradiotherapy or chemotherapy

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In the Western Countries the incidence of gastroeophageal junction (GEJ) adenocarcinoma has risen significantly since the last decade, with a disparities across race and gender. Although cases of distal gastric adenocarcinoma have steadly declined (1 ).

There are several debate both in regard to their diagnostic classification, as well as their therapeutic management. This is due, to difficulties in determining whether a GEJ cancer is a primary esophageal or gastric lesion, and thus, there is significant variability as to whether these tumors are treated according to esophageal or gastric regimens.

Gastroesophageal cancer is a disease of smokers and drinkers. Gastric cancer is strongly associated with Helicobacter Pylori infection, athrophic gastritis and decreased acid production. GEJ cancer share none of these characteristics; it is associated to high acid production and Barrett's changes in the esophagus. Patients with GEJ cancer tend usually to be obese and have a higher incidence of gastric reflux than the general population. GEJ cancer is more similar to cardia tumor than the other gastric tumor location and probably these two disease should be considered together.

Moreover recent studies revealed two types of carcinogenesis in the distal esophagus and the GEJ, one of intestinal type (about 80%) and the other of gastric type (about 20%). These are characterized by marked differences in morphology, tumor stage at diagnosis, and prognosis. Furthermore, both cancer types show different targetable biomarker expression profiles such as Her2 in the intestinal and EGFR in the non-intestinal pathway indicating new therapy options (2).

In addition, available data on patterns of spread suggested differences in GEJ adenocarcinoma defined in the Siewert classification including three categories of GEJ cancer related to the location of the tumor in the esophagus and stomach (3). This classification has significant surgical implications for the selection of appropriate surgical approaches and extent of resection according to different pattern of nodal spread between type I-II and III tumors. Type I (located more than 1 to 5 cm proximal to GEJ) and II tumors (within 1 proximal and 2 cm distal to GEJ) typically arise in Barrett's epithelium in the esophagus as a result of chronic gastroesophageal reflux disease. Type III tumors (located more than 2 to 5 cm distal to GEJ) are essentially proximal gastric cancer and should be treated as gastric cancer. Recently UICC-TNM staging system (7$^{th}$ ed 2009) gives a new definition of the GEJ adenocarcinoma, as esophageal tumor for all tumor with the epicenter within 5 cm of the esophagogastric junction and also extends into the esophagus, while all other tumours with an epicenter in the stomach greater than 5 cm from the esophagogastric junction and those within 5 cm of the esophagogastric junction without extension into the esophagus are staged using the gastric carcinoma classification.

This updated staging system should be considered for the eligibility criteria in the future clinical trials for gastric cancer and esophageal squamous cell as well as adenocarcinoma (including GEJ adenocarcinoma).

Optimal management of patients with GEJ adenocarcinoma is still a controversial issue. Only very few clinical trials have been designed exclusively for this tumor location and most information on possible impact of adjuvant or neoadjuvant treatment to surgery is currently provided from esophageal and gastric carcinoma trials that usually include also the adenocarcinoma of GEJ. Because of difficulties in administering chemotherapy or radiotherapy soon after a surgical procedures, the higher perioperative morbidity and the disappointing results of trial of adjuvant chemotherapy, many trials have been conducted in order to evaluate the role of neoadjuvant treatment.

**Neoadjuvant Chemoradiotherapy vs Chemotherapy: data from studies of the gastric and esophageal cancer**

To define proper management of GEJ cancer, we need to extrapolate from data derived from patients with gastric or esophageal cancer treated in available clinical trials. Most part of the clinical trials of gastric cancer include about 20% to 25% of patients with GEJ tumors or cardia, therefore is difficult to think these data to be particularly relevant for GEJ cancer. In contrast, more recent trials of esophageal cancer have included a more significant part of GEJ adenocarcinoma, up to 75% of patients.

Most part of these trials evaluated the impact of neoadjuvant chemoradiotherapy (RCT) (4-6) or neoadjuvant chemotherapy (CT) (7, 8) compared to surgery alone. An overall, significant impact on disease control and survival has been reported by a previous meta-analysis (9). Recent update meta-analysis confirmed a strong evidence for a survival benefit of neoadjuvant RCT or CT over surgery alone (10).

The current literature comparing neoadjuvant CRT vs CT prior surgery is limited. In particular the two trials were underpowered and closed early. The first randomized trial was published by Sthal in 2009, the study recruited 119 patients with cT3-4NxM0 adenocarcinoma of lower oesophagus or cardiac. Aimed for 354 patients, the study finished prematurely due to low accrual. Complete pathological response was significantly higher in the CRT group (15% vs 2%), the data on 3-yr OS failed to show an advantage statistically significant. The criticism of this trial include a low dose of radiotherapy and the non-conventional schedule of induction CT (11). The subsequent Australian trial compared two cycles of 5FU and cisplatin with 35Gy of radiation to neoadjuvant chemotherapy alone. The study stopped recruitment for low accrual. This partial results again showed an improvement in the pathological response rate after CRT (13% vs 0%), and no significant difference in OS (12).

However, when data of these studies, that were closed prematurely and clearly underpowered to detect difference in survival, were combined with the pooled results of neoadjuvant CT or CRT from the other analysed studies in the metanalysis (n=2220), the HR from randomized comparisons was 0.88 (p=0.07) in favour of neoadjuvant chemoradiotherapy (10). Importantly, no difference in morbidity was reported between the two treatment approaches

**Conclusion**

In conclusion, based on available evidence, both neoadjuvant chemoradiotherapy or chemotherapy provide significant survival benefit over surgery alone in patients with GEJ carcinoma. A clear advantage of neoadjuvant CRT over neoadjuvant CT, in the few studies evaluating most part of patients with GEJ adenocarcinoma, has not been estabilished and further trials comparing these two strategies should be promoted on this emerging and well defined tumor site.

**References**

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012 CA Cancer Journal for Clinicians 2012; 62, 1: 10-29.
2. Ruschoff J. Adenocarcinoma of the GEJ. Gastric or Oesophageal cancer? Recent Results Cancer Res 2012; 196: 107-13.
3. Siewert JR, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1002 consecutive patients. Ann Surg 2000; 232: 353-61.

4. Hagen van P, Hulshof MCCM, van Lanschot. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. N Eng J Med 2012; 366; 22.
5. Mariette C, Seitz JF, Maillard F, *et al*. Surgery alone versus chemoradiotherapy followed by surgery for localized esophageal cancer: analyisis of a randomized controlled phase III tral FFCD9901Pro. Am Soc Oncol 2010; 28: 4005 (abstract).
6. Burmeister BH, Smithers BM, Gebski V. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomized controlled phase III trial. Lancet Oncology 2005; 6: 659-68.
7. Allum WH, Stenning SP, Bancewiz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009; 27: 5062-67.
8. Kelsen DP, Winter KA, Gunderson LL, *et al*. long term results of RTOG trial 8911: a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin oncol 2007; 25: 3719-25.
9. Gebski V, Burmeister B, Smithers BM. Survival benefit from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analisi. Lancet Oncology 2007; 8: 226-34.
10. Sjoquist KM, Burmesteir BH, Smithers M, *et al*. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncology 2011; 12: 681-92
11. Stahl M, Walz MK, Stuchke M, *et al*. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009; 27: 851-6.
12. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagous? A randomized Phase II trial. Eur J Cancer 2011; 47: 354-60.