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ABSTRACTS

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Controversies in Adjuvant and Neoadjuvant Therapy in Gastroesophageal Cancer

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Introduction: The optimal management of locally advanced esophageal, gastroesophageal junction (GEJ), and gastric cancer remains a subject of active debate. Despite controversy, there is now concensus that surgery alone is inadequate therapy for patients with T3 or node positive disease, and even some advocate for preoperative therapy for T2N0 esophageal or GEJ cancer. Increasingly patients with esophagogastric cancer are treated with preoperative chemotherapy (the more common European approach) or combined chemoradiotherapy (the more common U.S. approach).

Optimizing Postoperative Outcome by Optimizing Preoperative Therapy

Adjuvant therapy improves survival in gastric cancer, with three competing approaches used. 1) The standard use of postoperative 5-FU, leucovorin and radiotherapy in resected gastric or GEJ cancer was established by U.S. INT trial 113, with adjuvant therapy increasing 5 year survival from 27% to 38% with postoperative chemoradiotherapy. Many criticize this trial for inadequate surgery, with most patients having less than a D1 gastrectomy and only 10% undergoing a D2 resection. 2) Pre and postoperative chemotherapy with ECF on the British MAGIC trial improved survival by 13% at 5 years compared to surgery alone for gastric and GEJ cancer, and established a European standard of care. 3) Despite the failure of adjuvant chemotherapy alone to improve survival after gastrectomy, two recent Asian trials treating over 2000 patients have given strong support for the use of adjuvant chemotherapy after D2 resection. These include the ACTS-GC trial using one year of adjuvant therapy with S-1, which improved 3 year overall survival by 10%; and the recently presented CLASSIC trial (1), which improved 3 year disease free survival by 13% with 6 months of adjuvant capecitabine and oxaliplatin. The role of radiotherapy in conjunction with perioperative chemotherapy is now the subject of randomized phase III trials, which are treating patients with chemotherapy with or without radiotherapy in the pre and postoperative setting.

Consistent pathologic measures of improved overall survival (OS) after preoperative therapy and surgery include achievement of a pathologic complete response, therapy treatment effect equaling or exceeding 90%, down staging to a node negative status or earlierT1-2 stage, and achievement of a negative margin R0 resection. Preoperative chemotherapy and chemoradiotherapy have yielded mixed results in achieving these outcomes in esophageal and GEJ cancer. Although the MAGIC and FNLCC 94012 / FFCD 9703 (2) trials reported up to a 14% improvement in 5 year OS with perioperative ECF or CF, EORTC trial 40954 (3) and the U.S INT 113 trial failed to improve OS survival with preoperative CF. An update of the MRC OEO-2 trial employing preoperative CF indicated only a 6% improvement in 5 year OS. Although the MRC authors attributed any improved OS to an improved rate of R0 resection with preoperative chemotherapy, enhanced rates of R0 resection have not been consistently reported in other trials.

The two published preoperative chemoradiotherapy trials that reported improved OS, the Walsh trial and CALGB 97-81, were small and underpowered. The recent CROSS trial (4), treating over 360 EUS staged patients with esophageal squamous cell and adenocarcinoma, reported a nearly 2 year improvement in median survival (49 vs 26 months, p = 0.011), and an 11% improvement in

3 year OS for preoperative chemoradiotherapy with weekly carboplatin and paclitaxel. A pathologic complete response rate of 30% was achieved with an improved rate of R0 resection (67% to 92%, $p < 0.002$). Additional support for the use of preoperative chemoradiotherapy comes from the POET trial reported by Stahl (5), comparing preoperative chemotherapy to sequential chemotherapy followed by chemoradiotherapy: chemoradiotherapy achieved significantly higher rates of pathologic complete response (16% vs 2%, $p = 0.03$) and node negative status (64% vs 29%, $p = 0.01$), and there were trends toward greater median survival (31 vs 21 months), 3 year OS (48% vs 28%, $p = 0.07$), and improved 3 year local tumor control (77% vs 59%, $p = 0.06$) all favoring chemoradiotherapy. In these high risk EUS and laparoscopically staged T3-4 patients, there was no difference in rate of R0 resection (69-70%) between preoperative chemotherapy and chemoradiotherapy.

Despite extensive study, there are no validated predictive or prognostic molecular markers of outcome after preoperative therapy that might potentially guide preoperative therapy. Response on PET scan observed during induction chemotherapy correlates with both response at surgery and survival. The MUNICON trial demonstrated that PET scan non responding patients could be referred to earlier surgery, rather than continue ineffective systemic treatment, without a detriment in survival compared to continuing such therapy (6). Early identification of treatment failure may spare patients from exposure both pre and postoperatively to inactive therapy. Non responding patients also have the potential to cross over to alternative therapies earlier on in treatment. Based on the MUNICON and other PET scan trial results, CALGB has opened trial 80803. Patients with esophageal and GEJ adenocarcinoma will receive induction chemotherapy with either mFOLFOX-6, or weekly carboplatin and paclitaxel. PET responders to induction therapy will then continue the same chemotherapy during subsequent combined chemoradiotherapy, followed by surgery. PET non responders will cross over to the other regimen during radiotherapy, with the hope to optimize pathologic response in non responders by changing chemotherapy during radiation.

The limited efficacy of cytotoxic chemotherapy should lead to the exploration of more innovative molecularly targeted therapies. Targeted agents in ongoing phase III trials in neoadjuvant therapy include bevacizumab added to perioperative ECX chemotherapy in the MAGIC 2 trial in gastric and GEJ cancer, cetuximab added to chemoradiotherapy with paclitaxel and cisplatin in the RTOG 0436 trial in esophageal cancer, and trastuzumab added to chemoradiotherapy with paclitaxel and carboplatin in her2 positive esophageal and GEJ cancer.

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