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ORIGINAL ARTICLE

Gastric cancer and adjuvant chemoradiotherapy: when and where, that's the question

I. Kantzou[1,2], G. Sarris[2], M. Poulizi[2], A. Zygogianni[3], T. Liakakos[4], J. Kouvaris[3], N. Bountouroglou[2], V. Kouloulias[1]

[1]Kapodistrian University of Athens, Medical School, 2nd Department of Radiology, Radiotherapy Unit, Attikon Hospital, Athens; [2]Metaxa Cancer Hospital, 1st Department of Radiotherapy, Piraeus; [3]Kapodistrian University of Athens, Medical School, 1st Department of Radiology, Radiotherapy Unit, Aretaieion Hospital, Athens; [4]Kapodistrian University of Athens, Medical School, 3rd Surgical Clinic, Attikon Hospital, Athens, Greece

Summary

Purpose: *Although the incidence of gastric cancer is decreasing, there were still 159,900 new cases and 118,200 deaths in Europe in 2006 representing the 5th highest incidence and 4th highest cause of cancer-related deaths. Postoperative adjuvant chemoradiotherapy has been demonstrated to result in a significant improvement in overall and disease-free survival. We studied the current role of adjuvant chemoradiotherapy in gastric cancer.*

Methods: *Randomized phase III studies and selected phase II studies for adjuvant chemoradiotherapy in gastric cancer were searched in PUBMED using key words. Also, international treatment guidelines as well as review papers were searched and analysed.*

Results: *Based on the published literature, treatment guidelines and reports from international meetings it is obvious that adjuvant chemoradiotherapy in gastric cancer contributes in improved treatment results.*

Conclusion: *Surgical resection remains the cornerstone of curative treatment for gastric cancer. The combination of modern radiotherapy techniques with chemotherapy is feasible, safe and improves overall survival of patients with gastric cancer.*

Key words: adjuvant chemoradiotherapy, gastric cancer, surgery

Introduction

Gastric cancer is a highly virulent disease with an extremely poor prognosis. While the overall incidence in the United States has declined, it has remained constant over the last decade in other parts of the world, including China, Korea, Southeast Asia and the former Soviet Union. While the incidence of distal gastric cancer remains stable in the United States, the incidence of proximal gastric cancers (which are more virulent) is rising rapidly.

The long-term survival of gastric cancer patients is determined by the tumor extension beyond the gastric wall and by the nodal involvement. Tumor confined to the mucosa and submucosa (T1-T2N0M0) has a 5-year survival of at least 70%. Invasion into the serosa increases the risk of lymph node metastases and has a reported 5-year survival rate (in Western series) of 20-30% [1-3].

As a result there is great interest in finding ways to improve the treatment results for this group of patients.

Adjuvant treatments following surgery have been shown to improve survival in several other cancers with similar patterns of relapse. Although many clinical trials have explored the value of neoadjuvant or adjuvant chemotherapy, radiotherapy, chemoradiotherapy and immunotherapy in gastric cancer, these trials have produced conflicting results, making the role of adjuvant therapy controversial.

Results of gastric cancer treatment have tended to be better for studies carried out in Asian countries, possibly related to etiologic or biologic differences in the disease or different practices such as screening for early-stage cancer, the use of extended lymph node dissection and the commencement of chemotherapy immediately after surgery. Attempts to replicate these interventions outside the Asian setting have not been

Correspondence to: Dr. Ioanna Kantzou, Radiation Oncologist. Kondyli 29, Lofos Aksiomatikon, 121 36 Chaidari, Athens, Greece.
Fax: +30 210 5820989, E-mail: ioannakantzou@gmail.com

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successful, raising questions as to whether these trials should be compared with studies conducted in Western countries [4].

In this article we made a thorough review of the current role of surgery and adjuvant chemoradiotherapy and discuss insights and perspectives from the latest clinical studies.

Methods

A Pubmed database search of all randomized phase III studies and selected phase II studies for adjuvant chemoradiotherapy in gastric cancer published until August 2010 was performed. Relevant reports from the latest American Society of Clinical Oncology (ASCO) Annual Meetings and Gastrointestinal Symposia were also included. The following keywords were used in the searches: gastric cancer/carcinoma, surgery, chemotherapy, radiotherapy, adjuvant therapy, targeted therapy. Furthermore, international treatment guidelines as well as review papers by world leaders in the field were considered in the Pubmed database search.

Results

Surgery

Surgical resection is the only modality that is potentially curative. The extent of resection is determined by the preoperative stage [5].

Early gastric cancer, limited to the mucosa, is increasingly being resected endoscopically. Established criteria for endoscopic mucosal resection (EMR) are mucosal cancers < 2 cm, which are histologically differentiated and not ulcerated. These have recently been extended to include larger, ulcerated and undifferentiated tumors but these are being further evaluated because of the potential of nodal disease. Radical gastrectomy is indicated for stage Ib –III disease. If a macroscopic proximal margin of 5 cm can be achieved between the tumor and the oesophago-gastric junction (OGI), subtotal gastrectomy can be performed. Otherwise, a total gastrectomy is indicated.

The extent of nodal dissection has been extensively debated. The current TNM classification recommendations (6th edition) include excision of a minimum of 15 lymph nodes to allow reliable staging. The approach to lymph node dissection is different between Asian and Western surgeons. Systematic node dissection (D2) is actually the standardized procedure in Asia where it shows postoperative morbidity and mortality rates lower than in Western series with higher rates of post-surgical survival [6].

Experience from the Far East has shown in both observational and randomized trials that D2 dissection excising N1 and N2 lymph node tiers is superior to a D1 dissection. While the West until was still debating whether D2 is better than D1, Asians are assessing the role of a more extensive lymphadenectomy, including para-aortic nodes [7,8]. Wu et al. reported superior survival with D2 plus para-aortic node dissection (D3) compared with D1 [9]. The larger JCOG 9501 trial reported equivalent survival comparing D2 with D2 and para-aortic node dissection but with greater morbidity with the more extensive procedure [7]. In the West, two randomized controlled trials have shown little initial difference between D1 and D2 lymphadenectomy [5,10]. Long term follow-up results in the Dutch trial have recently been reported, showing better cancer-related survival after D2 lymphadenectomy [10]. Smaller series from specialized centers have shown equivalent results to the Far East.

The consensus view therefore in the West is that D2 dissection should be the standard procedure performed in specialized centers with appropriate surgical expertise and postoperative care for patients considered medically fit enough to tolerate the procedure.

Resection of the spleen and pancreas is only indicated if there is direct invasion. Splenectomy is indicated for tumors of the proximally greater curvature and gastric fundus, principally to remove splenic hilar nodes. Resection of adjacent organs is indicated when there is definite or suspected transmural invasion and the patient is fit enough for such radical surgery [6].

Additional strategies including pre/postoperative chemoradiotherapy to improve locoregional control as well as overall survival are warranted.

Postoperative chemoradiotherapy

Interest in adjuvant radiotherapy as a treatment is based on the observation that over 80% of patients who die from gastric cancer experience a local recurrence some time post-operation. However, adjuvant radiotherapy alone has been disappointing (Table 1).

To improve the efficacy of radiation, 5-fluorouracil (5-FU) has been used as a radiosensitizer in 3 randomized trials (Table 2). A study by Dent et al. detected only a non-significant trend towards improved survival in patients randomized to adjuvant chemoradiotherapy [11]. Conversely, a study by Moertel et al. detected improved survival in treated patients, but this study has been criticized because randomization took place before consent, and 25% of the patients refused treat-

Table 1. Randomized trials of adjuvant radiotherapy compared with surgery alone in resected gastric cancer

Authors (ref. no.)	*Median follow-up (months)*	*Treatment groups*	*Number of patients*	*Survival (%) 3-year*	*5-year*	*p-value*
Hallissey et al. [13]	NR	Surgery alone RT	145 153	27* 23*	20* 12*	NS (p = 0.14)
Kramling et al. [28]	29.2 (mean)	Surgery alone Intra-op RT	64 51	NR		NS (mean survival 26.9 months for RT vs. 30.8 months for surgery alone)

NR: not reported, NS: not significant, RT: radiotherapy
*Estimated from survival curves

Table 2. Randomized trials of adjuvant chemoradiotherapy vs. surgery alone in resected gastric cancer

Authors (ref. no.)	*Median follow-up (months)*	*Treatment groups*	*Number of patients*	*Survival (%) 3-year*	*5-year*	*p-value*
Dent et al. [11]	NR	Surgery alone 5-FU + RT	17 18	NR		NS (estimated survival rate at 140 weeks was 40 vs. 32%)
Moertel et al. [12]	NR	Surgery alone 5-FU + RT	23 39	7* 35*	4* 20*	0.024
McDonald et al. [15,16]	60	Surgery alone 5-FU/LV + RT	275 281	41 50	28 40	0.005
Hundahl et al. [27]	NR	Surgery alone 5-FU/LV + RT	275 281	41 50	28 40	0.005

5-FU/LV: 5-fluorouracil and leucovorin, NR: not reported, NS: not significant, RT: radiotherapy
*Estimated from survival curves

ment. The patients who refused treatment had the best survival of all groups (5-year survival rate 30%) [12]. Furthermore, there was high rate of treatment discontinuation in both studies due to local side effects from radiotherapy.

The Mayo Clinic study randomized 62 patients to surgery vs. surgery plus adjuvant chemotherapy and radiotherapy. Although local control favored the chemoradiotherapy arm, it did not reach statistical significance [13].

The largest trial of postoperative therapy that strongly suggested a benefit from a multimodal approach, combining radiation and chemotherapy after gastrectomy was the Intergroup study 0116 (INT 0116), which enrolled > 550 patients who were randomly assigned to surgery alone or surgery followed by chemoradiotherapy (5-FU /LV plus external-beam radiation, delivered to the gastric bed and regional nodes) [14]. These patients had a clinically significant risk of relapse after gastric resection: 85% had lymph node metastases and 65% T3 or T4 tumors. Median survival in the surgery-only and chemoradiotherapy groups was 27 and 36 months, respectively (long-rank, p=0.005); the corresponding figures for disease-free survival were 19 and 30 months ($p < 0.001$). The benefit of this approach was confirmed by a subsequent update of the results [14,15]. The results of this trial made postoperative chemoradiotherapy the standard of care in the USA among patients with resected gastric adenocarcinoma [16].

In fact the criticism on this study was that only 10% of all patients underwent extensive lymph node dissection (D2) and that in the majority of patients (54%), there were no N1 lymph nodes dissected, suggesting that the positive findings of this trial could be a result of inadequate surgery. Although this suggests that postoperative chemoradiotherapy compensates for suboptimal surgery, a large non-randomized observational study suggested a potential clinical benefit from postoperative chemoradiotherapy after optimal D2 resection. In addition, modern, high-precision radiation techniques and more intensified chemoradiotherapy regimens are likely to further improve the results of postoperative chemoradiotherapy.

In 2005, a phase II study conducted by the AIO/ARO/ACO was published with the aim of developing a novel regimen for adjuvant chemoradiotherapy in cancer patients undergoing potentially curative resection. Eighty-six patients were randomized to receive 5-FU/LV/cisplatin with or without paclitaxel. Radiotherapy with 45 Gy plus concomitantly administered 5-FU 225 mg/m^2/24 h was scheduled in between the two cycles of chemotherapy. Both chemoradiotherapy regimens appeared feasible with acceptable toxicity represented by granulocytopenia, anorexia, nausea and diar-

rhea. The projected 2-year progression-free survival was 64% (95% CI 56-68) for the nonpaclitaxel arm and 61% (95% CI 42-78) for the paclitaxel-containing arm. The authors concluded that treatment should be given in experienced centers in order to avoid unnecessary toxicity [14].

In 2007, two phase I-II studies were published, where a standard radiotherapy regimen comparable to the Intergroup 0116 trial was combined with daily capecitabine with or without cisplatin on radiotherapy days. These studies demonstrated that postoperative chemoradiotherapy with daily capecitabine with or without cisplatin and during weekdays combined with 45-Gy radiotherapy is feasible (after 2 weeks of capecitabine monotherapy) [17,18].

In 2009, a phase II study conducted by the RTOG was published, aiming at the evaluation of two paclitaxel and cisplatin-containing chemoradiotherapy regimens as adjuvant therapy in resected gastric cancer (RTOG-0114). The conclusion of the study was that though paclitaxel-cisplatin appeared to be safe and the median disease-free survival favorable, the disease-free survival failed to exceed the lower bound of 52.9% for the targeted 67% disease-free survival at 2 years and could not be recommended as the adjuvant arm for future randomized trials [19].

In 2010 a phase I-II study was published in Annals of Oncology with the aim to demonstrate that postoperative chemoradiotherapy in gastric cancer with weekly cisplatin and daily capecitabine is feasible at the defined dose level [20]. The results of this study demonstrated that postoperative chemoradiotherapy with capecitabine is feasible at the defined dose level and the schedule of this study is currently being tested as the experimental arm in a phase III multicenter study (chemoradiotherapy after induction chemotherapy in cancer of the stomach/CRITICS), in which patients are randomly assigned to receive 3 courses of epirubicin, cisplatin and capecitabine (ECC) and then surgery followed by 3 more courses of ECC (arm 1), or 3 courses of ECC and then surgery followed by chemoradiotherapy with cisplatin and capecitabine (arm 2).

Discussion

Currently the treatment of choice for operable gastric cancer has not yet been defined [21,22]. INT 0116, which used 5-FU and LV, was the first to show that adjuvant chemoradiotherapy provides a survival benefit for patients with resected gastric cancer [14-16]. However, toxicity remained significant, and the survival benefit was modest. Recent attempts have been made to combine other chemotherapeutic agents in both adjuvant and neoadjuvant setting, including epirubicin and cisplatin.

RTOG-0114 was an attempt to introduce both paclitaxel (P) and cisplatin (C) into two adjuvant treatment arms utilizing different doses and schedules. In addition, one arm (PC) did not include 5-FU as part of the adjuvant treatment [19].

The overall hematologic toxicity of PCF was comparable to that observed on INT 0116, but grades 3 and 4 gastrointestinal toxicity of 68% observed in this arm significantly exceeded the 32% incidence of grade 3 and 4 gastrointestinal toxicity observed in INT 0116.

Based on the study endpoints, PCF cannot be recommended because of excess toxicity and PC cannot be recommended since it failed to achieve an improvement in disease-free survival over what would be expected from conventional 5-FU and LV. In addition, the local-regional failure of 33% in PCF and 26% in PC does not represent an improvement in local control when compared with INT 0116. The conclusion of the study was that PC cannot be recommended as the adjuvant arm for future randomized trials when combined with radiotherapy.

A phase I-II study of postoperative chemoradiotherapy in gastric cancer with dose escalation of weekly cisplatin and daily capecitabine chemotherapy demonstrated that postoperative chemoradiotherapy with weekly cisplatin and daily capecitabine is feasible at the defined dose level and this schedule is currently being tested as the experimental arm in a phase III multicenter study (CRITICS study) [20].

In the radiotherapy part of treatment only modifications in clinical target volume delineation have been introduced. More sophisticated 3D conformal and intensity modulated radiotherapy techniques are used in comparison with anterior-posterior (AP-PA) techniques being used in the past and in the INT 0116 study [23,24].

Questions remain about the optimal type and sequencing of chemotherapy and implementation of new radiotherapeutic and surgical techniques [25,26]. Currently, the combination of modern radiotherapy with weekly cisplatin and daily capecitabine is tested in the CRITICS study, a large multicenter, randomized, phase III study in which all patients receive 3 preoperative courses of ECC, then have gastric surgery followed by another 3 courses of ECC or chemoradiotherapy. In the experimental arm (chemoradiotherapy), cisplatin and capecitabine are used. Surgery requires at least a D1 resection with a minimum of 15 lymph nodes removed in this study. Quality assurance of surgery and radiotherapy will be part of this study.

In conclusion, an optimal and standardized surgical resection of the primary tumor and the regional

lymph nodes remains the therapeutic cornerstone in patients with localized, non-metastatic gastric cancer. The combination of modern radiotherapy with weekly cisplatin and daily capecitabine in the postoperative setting is safe with manageable toxicity in patients who have had gastric surgery and this multinodal treatment is currently being tested in a large, randomized, phase III study.

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