Neoadjuvant chemotherapy for locally advanced gastric cancer: With or without radiation

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Abstract

The role of perioperative chemotherapy for gastric cancer has been established for gastric cancers in their advanced stage. In most parts of the world, even in Japan and Korea, locoregional recurrence of gastric cancer following curative resection remains a problem. Should radiation be added to chemotherapy to achieve better local and regional control? What is the current evidence? What are the concerns regarding neoadjuvant chemoradiation in terms of safety, efficacy and survival benefit? After a serious review of the literature, the authors conclude that it is still too early to get a definitive answer but radiation seems promising. It may bring a higher pathological response rate. Rationally, more high level clinical trials are needed to confirm the role of radiotherapy in the neoadjuvant setting or to ascertain subsets of patients who may benefit from it. It is of note that surgeons should pay attention to possible complications following radiotherapy, maintain proper nutrition status and minimize the occurrence of postoperative complications. As few data are available in Japan and Korea, interpretation and implementation of neoadjuvant radiation or chemoradiation should be done with caution.

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INTRODUCTION

Early detection of gastric cancer is not easily available worldwide except for in some countries such as Japan and Korea and some ongoing screening programs in areas with a high incidence of gastric cancer[2]. Therefore, locally advanced gastric cancers, usually stage II-III cancers, predominate, which are vulnerable to local/regional recurrence and distant metastasis[2,4]. That is the rationale for neoadjuvant chemotherapy and/or radiation. Downsizing the tumor to facilitate further resection, control of latent lymphatic and hematological micrometastasis and in vivo chemosensitivity assay to avoid unnecessary side effects of ineffective adjuvant chemotherapy may have theoretical benefits[2]. The MAGIC trial[5], which introduces perioperative chemotherapy into guidelines on gastric cancer, did not take an efficacy assessment of preoperative chemotherapy into consideration, compromising the chemosensitivity advantage of preoperative...
chemotherapy. Increasing controversies have come out about the encouraging result from the MD Anderson Cancer Center, who reported a 30% pathological complete response (pCR) rate in a phase II single center clinical trial[9].

Is neoadjuvant chemotherapy the best? Should we add radiation to the preoperative treatment for locally advanced gastric cancer? To gastric cancer located in either distal or proximal gastric cancer or just adenocarcinoma of gastroesophageal junction? What is the potential benefit and what are the potential additional surgical issues? The authors will address these issues.

IS NEOADJUVANT CHEMOTHERAPY THE BEST?
Small size, single arm, phase I and phase II studies of neoadjuvant chemotherapy on gastric cancer have been reported since the last century, usually with high toxic regimens such as etoposide, mitomycin, methotrexate and cisplatin[3]. Neoadjuvant chemotherapy with different regimens, different routes, either regional or systemic, has been carried out widely since the emergence of novel antineoplastic regimens such as oxaliplatin, taxanes, irinotecan, fluoropyrimidines (capecitabine, S-1) and herceptin. The milestone study by Cunningham et al[5] found that perioperative chemotherapy significantly improved progression-free and overall survival in patients with operable gastric, gastroesophageal junction and lower esophageal lesions. The study, referred to as the MAGIC trial, with 503 patients enrolled, demonstrated that the hazard ratio for death and progression were 25% and 34% lower, respectively. However, we cannot find evidence supporting tumor shrinkage and downstaging by perioperative chemotherapy, as concluded by the study. No efficacy response evaluation, either radiographical or histological, has been reported yet. Inclusion of low esophageal lesions, which consisted of nearly 15% of the group, compromised its application in gastric cancer and gastroesophageal junction tumors.

Therefore, there is obviously an urgent need to identify patients who are actually non-responsive to preoperative chemotherapy to avoid useless adjuvant chemotherapy[4,7-9]. Oncologists and surgeons are trying to improve the response rate, especially the pCR rate. One way is to find novel regimens, different combinations, and to incorporate radiation into the treatment modalities. European scholars changed the chemotherapy regimens from epirubicin, etoposide and cisplatin (EEP) to epirubicin, cisplatin and fluorouracil (ECF), and achieved a better pathological response rate[10,11]. pCR rate is an ideal goal for neoadjuvant treatment. For breast cancer patients following neoadjuvant chemotherapy, pCR histology has been identified as an independent prognostic factor[12,13]. Radiotherapy may be of help to achieve a higher pCR rate for gastric cancer[14,15].

ADDITION OF RADIOThERAPY IN NEOADJUVANT SETTING MAY BRING SURVIVAL BENEFIT
One recent systematic review and meta-analysis showed a statistically significant survival benefit with the addition of radiotherapy in patients with resectable gastric cancer, without subgroup analysis of pre-, intra- and post-operative radiotherapy[16]. Even although the study confirmed radiotherapy as an armamentarium alternative, it cannot clarify the separate role of different types of radiotherapy, surgical procedures, especially lymphadenectomy, study design, sample size and inclusion criteria which differ remarkably[17-24].

Whether the addition of radiation to the neoadjuvant setting is justifiable remains inconclusive. Skoropad et al[16] reported a randomized controlled trial evaluating preoperative radiotherapy (20 Gy/5 d) plus surgery and surgery alone. With 20 years follow-up, the study failed to demonstrate the survival benefit of radiotherapy but the median survival of the radiotherapy group was longer than the surgical group (28.8 mo vs 20.3 mo), as were the 5, 10 year survival rates (39% vs 30%, 32% vs 18%). Typical “L”-shaped curves were shown. The survival curve of radiotherapy continued to be above that of the surgical group until 15 years after randomization or later. This trend was also seen in gastric cancer patients with T3-4 or N positive lesions yet without intersection. They seem to be due to the decrease of loco-regional recurrences following R0 resection as well as suspicious intraoperative manipulative tumor cell dissemination. This may be the rationale supporting the role of radiotherapy. No data was available regarding the pattern of local and distant failures. Another randomized controlled study with a larger sample size did confirm the survival benefit in selected gastric cancer patients located in gastric cardia[21]. With 370 randomized patients, it indicated a significant survival benefit for neoadjuvant radiotherapy compared with surgery alone (5 year survival rates, 30.1% versus 19.8%, respectively; P = 0.0094). The dosage in this study is 40 Gy compared to concentrated radiotherapy with 20 Gy in the above study. R0 resection was improved by radiotherapy (80% versus 62% for surgery alone; P < 0.001) without increasing morbidity and mortality. Better local control was also indicated (38.6% vs 51.7%, P < 0.025), regional lymph node metastasis 38.6% vs 54.6% (P < 0.005), yet distant metastasis was comparable (24.3% vs 24.7%).

The two studies illustrated above began in the 1970s, using 8-MV photon or telecobalt, now seldom used. Interesting results were from the first multi-institutional trial by Ajani et al[6] with only 32 patients enrolled from three institutions. Linear accelerators were used to deliver a dose of 45 Gy in 25 fractions of 1.8 Gy over 5 wk and the minimum energy allowed was 6 MV photons, with a preferred energy of ≥ 10 MV. Treatment consisted of two cycles of systemic 5-FU, LV and cisplatin followed
by chemoradiotherapy in the form of 45 Gy external beam radiotherapy (EBRT) with continuous infusion 5-FU. High pCR rate of 30% was reached as the primary endpoint. The median survival time for 33 patients was 33.7 mo with a median follow-up of 50 mo, while patients achieving a pCR or pPR had a significantly longer median survival time (63.9 mo). A recent phase III randomized German study incorporated photons into a linear accelerator with an energy no less than 5MeV, comparing preoperative chemotherapy with chemoradiotherapy for locally advanced adenocarcinoma of the esophagogastric junction[25]. Patients with uT3-4NXM0 adenocarcinoma of lower esophagus and gastric cardia were randomized into two groups: induction chemotherapy with PLF followed by surgery; or chemotherapy followed by chemoradiotherapy followed by surgery. Unfortunately the study was closed prematurely due to low accrual. For the 119 eligible patients evaluated, the group with radiotherapy demonstrated a higher response rate (15.6% vs 2.0%). However, it did not translate into a significant 3 year survival benefit (27.7% vs 47.4%, P=0.07). The authors concluded that preoperative chemotherapy may improve survival and should be further investigated. Since patients with a pathological response can generally be translated into long term survival[26,27] and even cure, to achieve a high response rate may be another goal in the management of gastric cancer. In all, more high level randomized controlled studies to address this issue are needed[28].

One recent study from Japan[29] with a small number of enrolled patients investigated the role of neoadjuvant chemoradiotherapy with S-1 and cisplatin (CDDP). The chemotherapy schedule included one cycle repeated after 6 wk. S-1 was administered orally every day on days 1-21 and CDDP was infused on days 1, 8 and 15. Radiation therapy was started concurrently with chemotherapy and repeated daily on days 1-5, 8-12, 15-19 and 22-26. A total of 10 patients were recruited. Seven patients underwent surgery and all had an R0 (no residual tumor) resection without surgical complications. The author concluded that neoadjuvant chemoradiotherapy with S-1 and CDDP may cause surgery to be delayed but shows promise for resectable advanced gastric cancer.

WHAT WILL WE DO TO ALLEVIATE SURGICAL CONCERNS FOLLOWING RADIATION?

Surgeons are always concerned about the safety and efficacy during the perioperative period and the timing of curative resection[30,31]. It has been established that resection remains the main armamentarium; missing it may place gastric cancer patients with limited survival opportunities.

Radiation may lead to direct and indirect injuries. Ionizing radiation injuries cells by transferring energy to critical biological macromolecules, including DNA, proteins and membrane lipids, which may also react with high-energy free radical intermediates. Ultimately, free radicals produced may cause the same results. Pathological changes include edematous, thickened and hyperemic mucosal manifestation in the early stage, and fibrosis to a different extent in the late stage[32,33]. Those micro and macro changes will certainly make normal surgical plates, especially those between draining lymph nodes and surrounding vasculatures. Of the most concern, the prepared Anastomosis may be performed on radiated tissues. The fragile, edematous, hemorrhagic tissues may be easy to tear, making anastomotic leakage a nightmare for surgeons. Fortunately, the concern may not translate into clinical reality. One early study from May 1984 to July 1988 evaluated 67 patients treated with intraoperative radiation (IORT)[34]. The most common nonfatal complication was anastomotic leak (n = 5). When compared with historical controls undergoing comparable surgery at this institution prior to the availability of IORT, complication rates were similar. The result has not yet been challenged within different controlled clinical trials. In the phase III German trial, only hospital mortality was reported, one in the chemotherapy group (1/49) and two in the chemoradiation group (2/45)[35]. Median days on intensive care and total hospital stay did not differ (20 d vs 22 d), suggesting the anastomotic leakage rate may not be high. Even in a setting where both pre-operative and intraoperative radiotherapy were used, the rate of anastomotic leakage was only 2% (n = 1)[36]. In the large randomized clinical trial by Zhang et al, there was also no statistical significant difference between two groups; 1.8% and 4% in radiation and surgery groups, respectively[37]. Similar results have been obtained on neoadjuvant chemoradiotherapy for esophageal squamous carcinoma[38].

Yet, surgeons should not be so optimistic about the rate of anastomotic leakage following radiotherapy as there are still hints from several studies[39,40,41]. Necessary prophylactic measures should be taken for selected high risk patients, evaluated during or after surgery. In our experience, key points to prevent the occurrence of anastomotic leakage are to reduce the tension at the anastomotic site, make mucosa to mucosa anastomosis contact, avoid a tear in the muscular layer of the esophagus, especially when it is thin, retain necessary blood supply, and maintain drainage.

Anorexia, nausea and fatigue are almost ubiquitous problems during gastric radiation therapy. Nutritional and gastrointestinal support may be of great importance to complete the full course. Nearly 20% of patients may fail in completing planned radiation therapy. Malnutrition may in turn affect the safety and outcome of the surgery[42]. Anastomotic leakage may be among the related complications. Other complications included late gastritis, uncomplicated gastric ulcers, or ulcers complicated by perforation and hemorrhage, acute pancreatitis and so on[43].

FUTURE DIRECTIONS

Data on neoadjuvant radiotherapy for local and advanced gastric cancer are limited[44]. Therefore, it is too early to
get a definitive answer. Rationally, we still have to investigate with high level clinical trials to confirm the role of radiotherapy in the neoadjuvant setting, to investigate different drugs as a radiosensitizer or as a combination, and to ascertain subsets of patients who may benefit. It is of note that surgeons should pay attention to possible complicated circumstances following radiotherapy, maintain proper nutrition status and minimize the occurrence of postoperative complications.

Of note, the limitation of this review is that few data from Japan and Korea are available regarding the role of radiotherapy for gastric cancer as radiotherapy is not widely accepted in those two countries, especially in the neoadjuvant setting. Surgical procedures with regional lymphadenectomy have been well standardized, leading to a much lower local recurrence rate. Ethnic differences among countries are still controversial. Whether neoadjuvant radiation could provide additional oncological benefit in Japanese or Korean patients, even in certain subgroups, is still waiting for more evidence. Clinical studies on neoadjuvant treatment should be based on the standardization of surgical procedures and sufficient sample size.

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