



Timing of initiation of adjuvant chemotherapy for gastric cancer: A case-matched comparison study of laparoscopic vs. open surgery

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Abstract

Background: Laparoscopic gastrectomy (LG) is reported to be associated with faster recovery than open gastrectomy (OG); however, the influence of the surgical approach on initiation timing of adjuvant chemotherapy (AC) remains unclear.

Methods: This was a single-institutional retrospective observational study. Patients with pathological stage II/III gastric cancer undergoing LG with D2 lymphadenectomy (LG group: $n = 74$) were matched 1:1 with patients selected from 214 similar patients undergoing OG (OG group: $n = 74$), identically matching gender, age, pathological stage, and type of gastrectomy, and comparing AC initiation timing between the two groups. Factors associated with delayed initiation of AC were investigated in a multivariable analysis.

Results: AC was performed in 86.5% (LG) and 83.8% (OG) of patients ($p = 0.64$). The median time interval before AC was significantly shorter in the LG vs. OG group (5.7 vs. 6.6 weeks, respectively, $p < 0.001$), and significantly more patients received AC within 6 weeks (60.8% vs. 27.0%, $p < 0.001$). Independent factors associated with delayed initiation of AC (>6 weeks) were: morbidity (\geq grade 3a; odds ratio (OR): 16.1, 95% confidence interval (CI): 1.86–143), open surgery (OR: 5.17, 95% CI: 2.50–13.1), and postoperative weight loss $\geq 8\%$ (OR: 2.47, 95% CI: 1.07–5.71).

Conclusions: LG may be associated with shorter intervals before AC. Postoperative morbidity should be reduced as much as possible.

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Keywords: Stomach neoplasms; Adjuvant chemotherapy; Laparoscopy; Laparotomy; Gastrectomy; Case-control studies

Introduction

Gastric cancer is the fifth most common and the third leading cause of cancer-related death among malignancies worldwide, with an especially high incidence in East Asian countries.¹ The treatment strategy for advanced gastric cancer differs between Eastern and Western countries. Previously, Western surgeons were against performing D2 lymph node dissection; however, this has recently been recognized as a recommended treatment following the 15-

year follow-up results of a Dutch trial.² In East Asia, gastrectomy with D2 dissection has long been a standard radical treatment, and more recently, adjuvant chemotherapy (AC) is added following surgery for pathological stage II and III gastric cancer because two randomized trials have demonstrated a significant survival benefit.^{3,4} The Japanese ACTS-GC trial showed a survival benefit following one-year postoperative administration of S-1 monotherapy,³ and the CLASSIC trial conducted in Korea and China revealed improved survival with adjuvant capecitabine with oxaliplatin.⁴ Given these findings, many East Asian patients currently receive AC.

The purpose of AC is to eradicate remaining microscopic cancer cells after radical surgical resection. Therefore, AC should be initiated as soon as possible, because surgical stress may cause immunosuppression. Colleoni

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et al. reported that breast cancer patients in the early initiation group (within 3 weeks after surgery) had a significantly better prognosis than did the conventional initiation group. In ovarian cancer, optimal timing of AC was reported as 2.7–3.5 weeks after surgery in recent large-scale study.⁵ In colorectal cancer, Guetz et al. reported that initiating AC within 8 weeks improved survival,⁶ and Biagi et al. reported that each 4-week delay initiating AC was associated with a worsened prognosis.⁷ Therefore, encouraging early initiation of AC in cancer treatment is recommended.

Proper timing of AC in gastric cancer has not been fully evaluated. The latest Japanese guidelines recommend initiating AC within 6 weeks after surgery; however, no persuasive evidence was quoted. Most prospective trials of gastric cancer recommend initiating AC within 6–8 weeks of surgery,^{3,4,8} and two recent studies suggested a correlation between timing of AC and survival, as for other cancers.^{9,10} In 2015, Korean researchers reported that delayed initiation of AC (≥ 8 weeks) is associated with unfavorable survival⁹ and, in 2016, Japanese researchers suggested that beginning S-1 within 6 weeks of surgery is associated with a favorable prognosis.¹⁰

Laparoscopic radical gastrectomy for stomach cancer, which was first reported in 1994,¹¹ was rapidly adopted in East Asia.^{12,13} The advantages of laparoscopic gastrectomy compared with open surgery are reduced blood loss, less postoperative pain, faster recovery, and less wound-related complications.¹⁴ Early on, these benefits were considered in early cancer, but recent reports insist on a benefit in more advanced disease.¹⁵ The outcomes of ongoing randomized studies¹⁶ are necessary to prove oncological validity but acceptable short-term outcomes have been reported in prospective studies.^{17,18} Once laparoscopic surgery is more commonly chosen for advanced gastric cancer, it will be interesting to note whether faster patient recovery affects the timing of initiation of AC. To the best of our knowledge, articles evaluating this issue are limited in number.

The aim of this study was to investigate the influence of the surgical approach on the timing of initiation of AC, comparing laparoscopic and open surgery.

Patients and methods

Study design

Consecutive patients with pathological stage II and III gastric cancer who underwent distal or total gastrectomy with D2 lymph node dissection (R0 resection) at the National Cancer Center Hospital East between May 2010 and January 2015 were included in this single-institutional retrospective observational study. Patients who underwent laparoscopic gastrectomy (LG group: $n = 74$) were matched 1:1 to 74 patients selected from 214 patients with the same cancer and grade who

underwent open gastrectomy (OG group) matched for gender, pathological stage, and type of gastrectomy.

At the early phase of the study period, laparoscopic gastrectomy was employed only for clinical I, then the indication for that has been gradually expanded up to clinical T3N1. The choice of operative approach was decided after our multidisciplinary oncological team discussion, which consisted from surgeons, medical oncologists and gastrointestinal endoscopists, finally with informed consent with patients. During the study period, postoperative patient management has been consistent, following a unified clinical approach for gastrectomy. The criteria for discharge included sufficient oral intake of more than half of the served diet without vomiting or nausea, stable inflammatory parameters in blood examinations, being afebrile, and feasible performance status. The first visit to our outpatient division was performed 3 or 4 weeks after discharge. When patients were diagnosed as pathological stage II or III, their conditions were rechecked and patients were consulted to the medical oncologist that day. Medical oncologists evaluated patients' performance status and laboratory findings, then made a decision on the timing of initiation and dosage of AC; surgeons were not involved in this decision. Medical oncologists aimed to start AC within 6 weeks after surgery as recommended in the Japanese guidelines,⁸ but AC was postponed when patients were not fully recovered from surgery. Types of AC were: 1) S-1 monotherapy, 2) capecitabine plus intravenous oxaliplatin (XELOX), 3) S-1 plus intravenous cisplatin, or S-1 plus intravenous oxaliplatin (SOX) for patients at high risk of recurrence. XEROX and SOX were also being used as part of a separate clinical trial, during our study,^{4,19} for which initiation within 6 weeks was recommended. This study was approved by the Institutional Review Board of the National Cancer Center, Japan (IRB file No.: 522, approval date: April 24, 2016).

Data collection

The primary endpoint of this study was initiation timing of AC. The secondary endpoint was the completion rate of AC. We also evaluated the factors associated with delayed initiation of AC using multivariable analysis. We collected the following from the electronic medical record for analysis: patients' characteristics, type of surgical procedure, postoperative complications, pathological stage, body weight change after surgery, and the initiation timing or administration status of AC. Patients' performance status was categorized according to the classification of the Eastern Cooperative Oncology Group. Tumor staging followed the 7th classification of the International Union Against Cancer,²⁰ and histological subtypes followed the Japanese Gastric Cancer Classification guidelines.²¹ Grading of postoperative complications was classified according to the Clavien-Dindo criteria.²² All postoperative complications occurring within 30 days were included

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