Surgery and adjuvant chemotherapy

Abstract It was clearly demonstrated that good local control by either radiotherapy or D2 surgery is essential to cure gastric cancer. D2 surgery can be carried out safely with a large volume of patients and can provide better survival than limited surgery. More extended surgery than D2 cannot provide better survival and causes greater morbidity; therefore, it should not be carried out as prophylactic lymphadenectomy. The effect of adjuvant treatment depends on the type of surgery. Neoadjuvant plus post-operative triplet chemotherapy, postoperative adjuvant chemoradiotherapy, and postoperative S-1 monotherapy now are the standards of care in Europe, the United States, and Japan, respectively.

Key words Gastric cancer · D2 dissection · Adjuvant chemotherapy

Principle of treatment aimed at curing patients with solid cancers

For the majority of solid cancers, treatment aimed at cure comprises good local control and systemic therapy to control occult metastasis. Actually, radiotherapy or surgery including endoscopic resection are the usual methods of local control. For several decades, Western physicians have claimed that advanced gastric cancer was already a systemic disease and that surgery with extended lymphadenectomy could not cure it. However, the results of the Intergroup study (INT0116/SWOG9002) to evaluate the efficacy of postoperative adjuvant chemoradiotherapy demonstrated clearly the necessity and efficacy of good local control to cure gastric cancer. D1 was proven to be insufficient treatment for curable gastric cancer. Thus, either rather simple surgery such as D1 with additional radiotherapy or good D2 dissection is regarded as the basic local treatment for gastric cancer at the moment.

D2 dissection: the gold standard

Dutch and British randomized controlled trials (RCT) failed to prove the survival benefit of D2 dissection over D1. However, these studies are heavily criticized for poor quality control of surgery and postoperative care, unacceptably small hospital volume, high incidence of insufficient nodal dissection (noncompliance), and adoption of the more aggressive option of D2 dissection by routine use of pancreatectosplenectomy. The number of patients treated in an institute each year, which is called hospital volume, showed clear negative correlation with hospital mortality. A certain incidence of morbidity is expected in this surgery in case of a total gastrectomy, thus requiring the knowledge and experience of managing these complications. Mortality after anastomotic leakage was 41.3% and 14.3% in the Dutch trial and the NCCH series, respectively. Similarly, mortality after intraabdominal abscess was 20.9% and 2.7%, respectively. These data suggest experience is mandatory to avoid treatment-related death after major adverse events of surgery.

Eventually, in 2006, a RCT comparing D1 versus D2 (including D3 in the first edition of the Japanese Classification of Gastric Carcinoma) showed for the first time superiority of D2 over D1 dissection in clinical trials. Five-year overall survival was 60% and 54% in the D2 and D1 groups, respectively ($P = 0.041$). This study is a single institutional study with three participating surgeons; thus, generalizability remains uncertain, especially in low-volume hospitals. However, with their experience, D2 can be carried out with quite low hospital mortality (0%) and provide better survival than D1.
Recently, the results of an RCT comparing D2 with more extended surgery, i.e., D2 plus paraaortic lymph node dissection (PAND) was reported. The two survival curves were almost overlapping, while D2 + PAND showed longer operation time and more blood loss and higher morbidity than D2, with statistical significance. It was concluded that prophylactic D2 + PAND should not be carried out for curable advanced gastric cancer. These results led us to conclude that D2 surgery should be regarded as the standard treatment for curable gastric cancer, at least in Japan.

**Adjuvant chemotherapy for curable gastric cancer**

Macdonald et al. reported the results of the Intergroup 0116/SWOG 9008 study in 2001 to evaluate the efficacy of adjuvant treatment comprising 45 Gy administration of radiotherapy and five courses of chemotherapy of fluorouracil (S-FU) and leucovorin. Postoperative adjuvant chemoradiotherapy (CRT) showed statistically significant improvement of relapse-free survival (RFS) and overall survival (OS) for patients with gastric cancer undergoing curative surgery, compared with surgery alone as control. Three-year OS after CRT was 50%, while that of the surgery alone group was 41% (HR = 1.35, 95% CI = 1.09–1.66, P = 0.005). Only 10% of patients underwent D2 dissection in spite of the recommendation of D2 dissection in the protocol, suggesting that poor local control by surgery was salvaged by radiotherapy. After these results were reported, the standard treatment after potentially curative surgery for node-positive patients is postoperative CRT in the United States.

Cunningham et al. reported the results of the MAGIC trial to evaluate the efficacy of perioperative chemotherapy (three cycles each before and after surgery). The chemotherapy used for this trial was a combination of epirubicin (50 mg/m², day 1), cisplatin (60 mg/m², day 1), and S-FU (200 mg/m²/day, continuous i.v., day 1–21) (ECF). This treatment showed statistically significant improvement of both PFS and OS compared with surgery alone as control; 5-year OS was 36.3% and 23.0% in the perioperative chemotherapy and surgery alone groups, respectively. These results are highly appreciated in Europe and Great Britain, where at least neoadjuvant chemotherapy is regarded as the standard of care. However, several points can be criticized in this study. There are 100 participating hospitals with no active quality control of surgery. Therefore, only about 56% of curable patients underwent D2 dissection. Second, more than 14% of patients had adenocarcinoma of the esophagus, requiring a different type of surgery. Third, shortly after randomization, 9 of 253 patients allocated to surgery alone either did not undergo surgery or no information about surgery was available for them. If the quality of eligibility assessment is reasonable, it is impossible that so many of the randomized patients did not undergo surgery. Fourth, among 198 patients who underwent surgical resection, the pathological T stage was unknown in 5 patients and pathological nodal stage was unknown in 42 patients. These facts suggest strongly that the quality of this trial was much poorer than that of the INT 0116 study and JCOG studies. As they did not report the OS of curable patients separately in the surgery alone group, comparison with other clinical trials that included exclusively curable patients is almost impossible. However, the tumors resected in the control group were not more advanced than those included in the INT 0116 or JCOG studies.

In this century, six other articles reporting the results of RCTs on adjuvant chemotherapy with surgery alone as control could be found in the Western world. Only one of these, with a small sample size, showed a statistically significant difference of OS between adjuvant chemotherapy and surgery alone.

There have been five articles reporting the results of RCTs in Japan, having surgery alone as the control arm, after 2000. The first three failed to prove the efficacy of adjuvant chemotherapy. One of them, JCOG9206-1, showed some difference that might have been significant if the sample size had been large enough. Nakajima et al. reported the results of the N-SAS-GC study to evaluate the efficacy of UFT for pT2 pN1-2 patients. Although this study was positive to show the efficacy of high-dose UFT for patients with T2N1–2, the number of enrolled patients was just 38% of the projected sample size, and the OS and RFS of the control arm was about 10% worse than the other Japanese study, JCOG9206-1, for the same population in the same decade. Therefore, confirmation is needed to apply this result to clinical practice. The most recent study, ACTS-GC, showed clearly the benefit of S-1 monotherapy as postoperative adjuvant chemotherapy for stage II/III patients who underwent D2 dissection. In the subgroup analysis, all the subpopulations showed the same tendency (HR < 1), showing applicability for all stage II/III patients. Grade 3/4 adverse events were less than 7%; 6 months compliance was about 80% and that at 1 year was 65%. S-1 monotherapy after curative surgery was therefore feasible and effective to improve the OS and RFS of patients with this stage. Now, this treatment is regarded as the standard of care of stage II/III gastric cancer patients in Japan.

The role of radiotherapy after D2 dissection is controversial. Theoretically, it means duplication of local control for possible lymph node metastasis. Subgroup analysis of the INT 0116 study showed no benefit of CRT in the patients who underwent D2 dissection, although the interaction was not statistically significant because the number of those undergoing D2 dissection was too small. One Korean institution is carrying out a RCT comparing D2 surgery alone versus D2 + CRT to evaluate the efficacy of CRT after D2 dissection. As the control arm of this study remains surgery alone, the results must be carefully interpreted. If the results of this study show a clear benefit of chemoradiotherapy after D2 dissection, we might consider some trials comparing D2 + CRT versus D2 + chemotherapy.

In conclusion, standard treatment for curable advanced gastric cancer in Japan is D2 surgery followed by adjuvant chemotherapy by S-1 for 1 year.