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COMMENTARY

Expanding treatment options for resectable gastric cancer: Is it a countdown for radiotherapy?

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Summary

Chemoradiotherapy (CRT) and chemotherapy in the perioperative or postoperative settings are the different neoadjuvant/adjuvant treatment approaches for resectable gastric cancer. After the results of the ARTIST trial, CRT lost its importance on a large scale in the adjuvant setting. Also, according to the results of the CRITICS trial, CRT does not seem beneficial in the perioperative treatment setting. The beneficial effect of neoadjuvant/adjuvant radiotherapy as a therapeutic option became more questionable as the evidence grows, but still needs further studies to identify its effects on a subgroup of patients who have R1 or <D2 dissection and/or lymph node involvement.

Comment

Gastric cancer is still one of the most diagnosed cancers and the third leading cause of death from cancer worldwide [1]. In other regions of the world except Japan and Korea where routine screening is performed, most of the patients are diagnosed at advanced stage. Because of the highly aggressive nature of the disease, different neoadjuvant and adjuvant treatment strategies were developed. Preoperative chemoradiotherapy (CRT), postoperative CRT, perioperative or postoperative chemotherapy (CT) are the different neoadjuvant/adjuvant treatment approaches to enhance the possibility of survival for resectable disease.

In 2001, a "little" step to move forward was done by Lowy's pilot study [2]. Patients in the study were administered preoperatively 45 Gy radiotherapy (RT) and an additional 10 Gy dose intraoperatively with 5-Fluorouracil (5FU) infusion to T2-4 or node-positive resectable gastric cancer. The total response rate was 73% with an 11% pathological complete response (pCR) however, the study randomized only 24 patients as a single arm.

Five years later from this inspirational study, the results of the phase 2 RTOG 9904 trial demonstrated a higher pCR rate (26%) with preoperative CRT in T2-3 (T4 excluded) or node-positive gastric and gastroesophageal junction (GEJ) adenocancer population [3]. The treatment protocol was preoperative cisplatin and 5FU induction chemotherapy followed by 45 Gy CRT (concurrent with 5FU and paclitaxel) and then surgery. Median overall survival (OS) was 23.2 months, however, this study was also designed as a single arm and only randomized 43 patients.

The main object of neoadjuvant CRT was to complete all treatment process with surgery because of postoperative deterioration of patients' conditions and the high drop-out rates. But the sensitivity of gastric cancer to these treatment options did not allow for routine use of this approach. In

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the absence of satisfactory evidence, preoperative CRT "alone" was not recommended.

As a challenging disease, resectable gastric cancer has high post-surgical relapse rates. Moreover, many patients do not receive preoperative or perioperative treatment because of numerous clinical scenarios. This fact has forced the researchers to develop adjuvant treatment strategies with CRT and/or CT which reduce locoregional or distant relapses.

Intergroup 0116 (INT0116) was a phase 3 prospective study that evaluated the effectiveness of adjuvant CRT versus observation in 556 stage IB-IVM0 gastric or GEJ cancer patients who underwent surgery [4]. Based on outcomes, adjuvant CRT (45 Gy with 5FU and leucovorin) had a survival benefit over surgery alone with a median OS 36 versus 27 months and relapse-free survival (RFS) 30 versus 17 months. The treatment group also had lower rates of local (19% vs. 29%) and regional (65% vs. 72%) relapse rates. In the INT0116 trial, D2 and D1 dissection were performed only in 54 (10%) and 199 (36%) patients, respectively, whereas D0 dissection was performed in most patients (54%). Even Macdonald and colleagues reported no significant differences in RFS or OS according to the extension of the dissection types, so many researchers still criticise this study because of the "low" quality of surgery [4]. In the 10-year update analysis of the study, the hazard ratio (HR) for OS of D2+ subgroup was under the overall HR for treatment benefit unlike D0 or D1 dissection groups [5]. The result could be explained with potential selection bias, small sample size (54 patients), fluctuations of subgroup analysis or the "real effect" of D-dissection type which is a debating subtitle in gastric oncology.

After a decade of criticising the INT0116's surgery quality, another phase 3 prospective ARTIST trial aimed to clarify this discussion [6]. Unlike INT0116, the ARTIST study randomized completely resected gastric adenocarcinoma patients (n=458) with D2 lymph node dissection and compared the adjuvant CRT with chemotherapy (not only observation) in an East Asian population. The treatment protocol was 45 Gy with cisplatin and capecitabine (XP) and 2 cycles of XP before and after in the CRT arm and 6 cycles of XP in the CT arm. There was no significant 3-year DFS difference with the addition of CRT (78.2 vs. 74.2%) but in multivariate analysis, the 3-year DFS in the CRT arm was significantly better compared with CT arm for the node-positive subgroup (77.5 vs. 72.3%, HR=0.68). After a median follow-up of 7 years, there was no OS difference between groups (75 vs. 73% in the CRT and chemotherapy arm, respectively) [7].

After the ARTIST trial there was no reason to combine RT with CT for node-negative patients who underwent D2 dissection. Also, there was no significant OS difference. This fact was based on a highly selected population with good performance status after "high quality" surgery. However, in clinical practice many patients had undergone <D2 dissection and some of them even R1 resection.

In similar East Asian populations with completely resected tumors and D2 dissection, two phase 3 trials demonstrated the effect of adjuvant chemotherapy [8,9]. ACTS-GC randomized 1059 stage II or III (with excluding T1 tumors) gastric adenocarcinoma patients to 1-year adjuvant S-1 treatment or surgery-only groups and demonstrated the efficacy of adjuvant S-1 with a significant 3-year OS advantage (80.1 vs. 70.1%) [8]. The other phase 3 CLASSIC study, also randomized 1035 stage II or III gastric adenocarcinoma patients to adjuvant chemotherapy or surgery-only arms, but the treatment protocol was 3-week cycles of capecitabine and oxaliplatin for 6 months. The results favored the adjuvant chemotherapy arm with a significant 3-year DFS difference to surgery-only group (74 vs. 59%, HR=0.56) [9]. After 5-year follow-up these results consolidated with 5-year estimated OS advantage of chemotherapy group (78 vs. 69%) [10].

These two studies strengthened the adjuvant treatment options for completely resected gastric adenocarcinoma patients with D2 dissection. However, the results of the studies need to be validated in Western populations. Moreover, there is still a lack of evidence to use adjuvant chemotherapy for patients who underwent D0 and D1 dissection.

In the middle of neoadjuvant and adjuvant processes, the "central" role of surgery -with its quality and extension- is doubtless for curable treatment. The "gravity force" produced inevitably by this central position leads to develop perioperative treatment strategies. Of course, with CT and CRT combinations.

The effectiveness of perioperative chemotherapy versus surgery alone has been demonstrated in the UK Medical Research Council study (MAGIC) with 5-year OS rates 36 versus 23% [11]. This milestone study randomized 503 stage 2 or higher gastric, GEJ and lower esophagus adenocarcinoma patients and the treatment was administered both preoperatively and postoperatively with 3 cycles of epirubicin-cisplatin-5FU (ECF). Significant toxicity profile and drop out rates during the treatment process were remarkable, such that 54.8% of the patients started postoperative chemotherapy and 103 of 250 patients completed the whole treatment protocol.

Similarly, in the French multicenter trial (FNCLCC/FFCD) perioperative chemotherapy (cisplatin and 5FU) significantly increased the curative resection rate (84 vs. 73%), 5-year OS (38 vs 24%) and disease-free survival (DFS) (34 vs. 19%) compared to surgery alone [12]. However, due to lack of accrual, the study terminated prematurely.

After the MAGIC study the ECF regimen became standard protocol in clinical practice for patients who are candidates for perioperative chemotherapy. But neither MAGIC nor FNCLCC/FFCD trial had a subgroup analysis for D1 or D2 dissection types.

More recently, the first results of the FLOT4 study (NCT01216644) were presented in the ASCO 2017 Congress [13]. This phase 3 trial (716 patients with T2-4 or node-positive resectable gastric or GEJ adenocarcinoma) reported the most effective survival outcomes of perioperative treatment ever with FLOT regimen (docetaxel, oxaliplatin, leucovorin and 5-FU) compared to standard ECF or ECX protocols (median OS 50 vs 35 months; median PFS 30 vs 18 months). The OS advantage favored the FLOT regimen in all subgroups, including node negative and positive patients. These promising results have a great potential to change the clinical practice for all eligible patients to perioperative chemotherapy with an acceptable toxicity profile and similar surgical morbidity and mortality.

Finally, in April 2018, Cats et al. reported the results of the phase 3 CRITICS trial [14]. The study randomized 788 stage IB-IVA resectable gastric (83%) or GEJ (17%) adenocarcinoma patients. The design of the CRITICS study combined the two different treatment approaches (MAGIC and INT0116 trials) and aimed to compare postoperative CRT with CT alone in resectable gastric cancer patients having preoperative CT. Both treatment arms received 3 cycles of epirubicin, cisplatin (or oxaliplatin) and capecitabine preoperatively. After surgery, the perioperative CT arm received 3 additional cycles and the other arm (postoperative CRT) received 45 Gy of radiotherapy with concurrent 5FU and cisplatin.

The study randomized patients once before the preoperative chemotherapy start to avoid selection bias and there was no difference in OS, event-free survival (EFS) and locoregional control between two arms. As a feature of a high-quality phase 3 prospective trial with one randomization process, these results depend on statistical analysis of intention to treat population.

After the results of the ARTIST trial, CRT treatment lost its importance on a large scale in the adjuvant setting. For many clinicians, with CRITICS trial, CRT also won't be a part of perioperative treatment. But of course, with some question marks...

As mentioned before, the ARTIST trial excluded D1 dissection and also showed 3-year DFS advantage of CRT in a subgroup of patients who had lymph node involvement. In the CRITICS trial, R0 resection was performed to only in 80-82% and 11-13% of the patients had <D1 dissection. Unfortunately, the study didn't include per-protocol results of lymph node dissection subgroups in the postoperative setting in both CRT and CT arms. This point still needs clarification.

One of the other studies that clinicians eagerly await the results is the ongoing phase 3 TOPGEAR trial (NCT01924819). This study may answer whether adding preoperative CRT to perioperative chemotherapy (ECF) will be beneficial or not [15].

The other important point that is both CRITICS and the ongoing TOPGEAR trials administered ECF chemotherapy which is less effective compared with the new FLOT regimen [13].

In conclusion for resectable gastric cancer, FLOT regimen is the new mainstay treatment option for eligible patients to perioperative treatment. Neoadjuvant/adjuvant radiotherapy becomes a non-beneficial therapeutic option as the evidence grows, but still needs further studies to identify its effects on a subgroup of patients who have R1 or <D2 dissection and/or lymph node involvement.

Conflict of interests

The authors declare no conflict of interests.

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