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Between evidence and new perspectives on the current state of the multimodal approach to gastric cancer: Is there still a role for radiation therapy?

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Abstract

In patients affected by gastric cancer (GC), especially those in advanced stage, the multidisciplinary approach of treatment is fundamental to obtain a good disease control and quality of life. Although many chemotherapeutics in combination to radiotherapy are adopted in the peri- or postoperative setting, the most optimal timing, regimens and doses remains controversial. In the era of radical surgery performed with D2-lymphadenectomy, the role of radiation therapy remains to be better defined. Categories of patients, who could benefit more from an intensified local treatment rather than more toxic systemic therapy, are still under investigation. Evidence and recent updates of the randomized trials, meta-analysis and prospective trials show that the postoperative radiotherapy plays a fundamental role in reducing the loco-regional recurrence and in turn the disease-free survival in operable advanced GC patients, also after a well performed D2 surgery. Therapeutic decisions should be taken considering the individual patients, but the multimodal approach is necessary to guarantee a longer survival and a good quality of life. Ongoing randomized trials could better define the timing and the combination of radiotherapy and systemic therapy.

Key words: Adjuvant chemoradiation; Locally advanced; Perioperative chemotherapy; Gastric cancer; Combined treatment

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Core tip: This is a review of recent updates from rand-

omized data and prospective phase I/II trial regarding the role of radiotherapy in the multimodal approach of gastric cancer (GC). The actual state of art is still controversial and in particular adjuvant therapy for locally advanced disease remains undefined in different countries. Recent efforts show that a more intensified local therapy such as radiation therapy could have a benefit in increasing the disease-free survival, especially in the category of patients with positive pathological lymph nodes. A carefully multidisciplinary evaluation of the patients with GC is then recommended in the clinical practice.

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INTRODUCTION

In Europe, gastric cancer (GC) remains one of the most common causes of death from cancer, affecting more than 100000 people per year^[1]. The prognosis in patients affected by GC is poor, with longer survival in the Asiatic population^[2]. Surgery is the only known radical treatment, but in a locally advanced setting, a multimodal approach is necessary to improve outcome. D2- vs D1-lymphadenectomy is still controversial because of different findings in the Western and Eastern countries^[3,4]. However, recently available data suggest that D2-lymphadenectomy is the most optimal surgical standard.

A combined therapy including chemotherapy (CT) and/or radiotherapy (RT) is often recommended in a perioperative and/or postoperative setting to improve local control and disease-free survival (DFS). In clinical practice, postoperative chemoradiation therapy (post-CRT) or CT alone can follow radical surgery in patients that have received a previous perioperative CT (peri-CT). In addition, in a postoperative setting, a sequential scheme of RT and CT is sometimes preferred to the combined concomitant regimen. A recent meta-analysis aimed to provide more evidence on the role of post-CRT compared to CT alone after a D2 node dissection and conducted a systematic review of randomized controlled trials by extracting data on survival and toxicity^[5]. A significant reduction of loco-regional recurrence rate ($P = 0.0005$) and prolonged DFS ($P = 0.002$) were demonstrated in the post-CRT group, but no differences in overall survival (OS) and toxicity rates were reported.

In radiation treatment, indications, doses and techniques are often based on the experience of a single center rather than a predetermined guideline. A worldwide consensus on modality, timing, and combination of RT and CT has not been reached yet.

The aim of this review is to explore the current role of radiation therapy according to a definitive multidisciplinary treatment in the era of modern technology, new systemic agents, and radical surgery with D2-lymphadenectomy.

KNOWN EVIDENCE AND UPDATES ON COMBINED THERAPY

Adjuvant therapy

In resectable locally advanced GC, multimodal therapy has been considered a necessity since the American SWOG/INT-0116 trial demonstrated that surgery alone was inferior to surgery and associated adjuvant CRT in terms of survival and disease progression, concluding that resection alone was not enough to obtain acceptable oncological control of the disease^[6]. Subsequently, post-CRT became the standard of care in the United States for locally advanced resected GC patients, and the results of the original trial were also confirmed by updated analysis after long-term follow up^[7]. A significant survival benefit in contrast to surgery alone ($P < 0.001$) was demonstrated for post-CRT, despite the reported high rates of severe toxicity probably due to the conventional two-dimensional (2D) radiation techniques, which include a larger volume of normal tissue in the irradiated target volume. The high incidence of toxicity was also likely accounted for by the high dose bolus schedule of 5-fluorouracil (5-FU) that was previously implemented but is no longer recommended in treatment guidelines such as those of the National Comprehensive Cancer Network. This trial was highly criticized for the antiquated surgical procedure using D0- or D1-lymphadenectomy instead of the radical D2 node dissection (90% vs 10%). However, there is conflicting evidence regarding the choice of D2 vs D1 node dissection; lower loco-regional recurrence rates and cancer-related deaths are demonstrated after a D2 procedure, but no survival advantage and higher complication rates are related to the same approach^[8,9]. As D2-lymphadenectomy is widely used and integrated into current surgical practice for advanced stage GC^[10], does post-CRT still have value in a combined treatment, or is post-CT alone sufficient to obtain the same disease control with less toxicity?

The randomized Korean trial ARTIST investigated post-CRT vs post-CT alone in resected GC patients who received D2-lymphadenectomy^[11]. The primary endpoint was DFS and they did not find any significant difference between the two arms. The trial was limited by the lower rates of enrolled patients with locally advanced tumors (only 41%), and the higher rates of patients presenting early stage disease with lower risk of loco-regional recurrence after a well-conducted radical surgery such as D2-lymphadenectomy. However, a significant advantage of post-CRT in terms of higher DFS was observed in the subgroup of patients with pathologically positive lymph nodes ($P = 0.0365$). An

update of the data confirmed that post-CRT significantly reduced loco-regional recurrence rates ($P = 0.03$) after D2 resection, especially among the subgroup of patients with lymph node metastases ($P = 0.009$)^[12]. Moreover, in a recent analysis of the above trial, the influence of the metastatic lymph node-ratio, also called the N-ratio (number of positive lymph nodes/total number of resected nodes), was investigated as a possible prognostic factor in terms of DFS in both arms^[13]. On the multivariate analysis, the N-ratio was found to be an independent prognostic factor for DFS. In particular, 5-year DFS rates were 55% and 28% ($P = 0.02$) for N-ratio $> 25\%$ in the post-CRT and post-CT arm, respectively, suggesting an advantage of CRT for selected D2-resected GC patients.

The ongoing ARTIST II trial would further examine the role of post-CRT in the category of patients with resectable GC and pathologically positive lymph nodes after radical surgery. Furthermore, in the multicenter phase III trial CRITICS, patients with resectable GC were randomized to receive either peri-CT followed by gastrectomy with a D1+ lymphadenectomy (minimum of 15 removed lymph nodes, stations 1- 9 and 11) and post-CT, or preoperative CT followed by surgery and post-CRT^[14]. Recently, the surgico-pathological quality and protocol adherence for lymphadenectomy were accurately evaluated in the CRITICS trial, and the surgical quality and centralization were found to be excellent in the Netherlands^[15]. The definitive findings from the CRITICS trial showed a median OS of 43 mo (95%CI: 31-57) in the post-CT group and 37 mo (30-48) in the post-CRT group (95%CI: 0.84-1.22; $P = 0.90$) at a median follow-up of 61.4 mo^[16]. There were 368 (47%) grade 3 adverse events, 130 (17%) grade 4 adverse events, and 13 (2%) deaths. No survival benefits were added with the use of RT in an adjuvant setting. Of the 788 enrolled patients, 233 (59%) of 393 patients started post-CT and 245 (62%) of 395 started post-CRT. Due to the poor postoperative patient compliance in both arms, the authors concluded that the preoperative therapies should be further optimized.

In 2012, a phase III study from South Korea conducted in the National Cancer Center (NCC) reported a longer DFS in locally advanced (98%) D2-resected (100%) GC patients in the arm receiving adjuvant CRT following the Macdonald scheme vs post-CT alone ($P = 0.056$)^[17]. Unfortunately, the study was closed prematurely due to poor accrual. A small multicenter Chinese study, also published in 2012, randomized D2-resected GC patients to receive post-CRT ($n = 56$) delivered with intensity modulated RT (IMRT) or CT alone ($n = 59$)^[18]. In both arms, survival rates and related side effects were not significantly different, but in the CRT group, the median recurrence-free survival was significantly longer (50 mo) than that in the CT-alone arm (36 mo, $P = 0.029$).

Despite clear evidence in favor of adjuvant-combined CRT after a curative-intent surgery, open questions regarding the optimal timing and benefit of RT, and

its combination to systemic therapy remain, especially in the era of extended and well-performed D2-lymphadenectomy.

Two other randomized trials, the Japanese ACTS-GC trial and the Korean CLASSIC trial, demonstrated that the addition of post-CT vs surgery alone offered a tangible benefit in terms of OS and DFS, respectively, in D2-resected patients with stage II/III GC^[19,20]. The first trial showed a significant DFS improvement at 3 years and was subsequently stopped after the interim efficacy analysis, while the second trial was closed after the first interim analysis showed a significantly higher OS in the post-CT arm ($P = 0.002$). Both trials have influenced the type of adjuvant treatment administered in Asian countries, where the use of RT might not be considered fundamental and the related side effects could be synergic to those from CT. The main randomized studies evaluating the postoperative therapy are summarized in Table 1.

While data from these randomized trials gave unclear indications regarding the most optimal adjuvant regimen, a meta-analysis by Fiorica *et al.*^[21] published this year highlighted the importance of post-CRT in increasing survival through the analysis of 10 randomized controlled trials. An increase not only in DFS but also in OS was found in favor of combined CRT, supporting once again the advantages of local therapy in addition to systemic therapy.

Preoperative therapy

It has been proven that both peri-CT and post-CRT have a significant survival benefit over surgery alone^[22], but there has not been a specific randomized controlled trial to test which of these methods is the best choice in the treatment of patients with resectable GC. According to the results of randomized trials, surgery should be performed 3-6 wk from the last day of preoperative therapy. A recent analysis on 5058 patients with resectable gastric/gastroesophageal junction adenocarcinoma published in 2017 by Fitzgerald *et al.*^[23] evaluated the impact of peri-CT vs post-CRT on survival in patients selected from the United States cancer registry treated between 2004 and 2013. They found a 72% survival advantage in patients receiving peri-CT compared with those treated with post-CRT ($P < 0.0001$). Moreover, the survival benefit was higher among patients with positive lymph nodes in the preoperative state which subsequently converted to negative lymph nodes after being treated with peri-CT, suggesting significant tumor downstaging with peri-CT and an important role of the N-status as a significant prognostic factor^[24].

Peri-CT could control micrometastases, increase the chance of a good pathological response, and improve the performance of a curative surgery. In Northern Europe, GC treatment was influenced by the findings described in the MAGIC trial, a major trial regarding the use of preoperative CT published in 2006^[25]. Pa-

Table 1 The main randomized trials in gastric cancer that evaluate the postoperative therapy

| Trial | Year | Randomization scheme | OS | DFS, PFS | Limits |
|-------------------------------------|------|-----------------------------|---|---|--|
| SWOG/INT-0116 ^[6] | 2001 | S-alone vs S + CRT | 3-yr: 50% vs 41% (<i>P</i> = 0.005) | 3-yr: 48% vs 31% (<i>P</i> < 0.001) | Low rates of D2 node dissection, 2D RT technique |
| Update SWOG/INT-0116 ^[7] | 2012 | S-alone vs S + CRT | HR = 1.32 (95%CI: 1.10-1.60; <i>P</i> = 0.0046) | HR = 1.51 (95%CI: 1.25-1.83; <i>P</i> < 0.001) | Low rates of D2 node dissection, 2D RT technique |
| ARTIST ^[11] | 2012 | S + CT + CRT + CT vs S + CT | NR | 3-yr: 78% vs 74% (<i>P</i> = 0.086) | Planned events not reached, lower % of locally advanced tumors |
| CRITICS ^[16] | 2018 | CT + S + CT vs CT + S + CRT | Median OS 43 vs 37 mo (<i>P</i> = 0.09) | | Poor postoperative patient compliance in both treatment arms |
| NCC, South Korea ^[17] | 2012 | S + CRT vs S + CT | NR | 5-yr: 73.5% vs 54.6%, (<i>P</i> = 0.056) | Poor accrual Sometimes 2D RT technique |
| Chinese Study ^[18] | 2012 | S + CRT vs S + CT | 5-yr: 48.4% vs 41.8% (<i>P</i> = 0.122) | 5-yr: 45.2% vs 35.8% (<i>P</i> = NS) | Small series |
| ACTS-GC ^[19] | 2007 | S-alone vs S + CT | 3-yr: 80.1% vs 70.1% (<i>P</i> = 0.003) | 3-yr: 59.6% vs 72.2% (<i>P</i> < 0.001) | Closed earlier due to significant survival benefit in the CT-arm |
| CLASSIC ^[20] | 2012 | S-alone vs S + CT | NR | 3-yr: 59% vs 74% (<i>P</i> < 0.0001) | Stopped after the interim efficacy analysis |

OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival; RT: Radiotherapy; S: Surgery; CT: Chemotherapy; CRT: Chemoradiation; NR: Not reported; HR: Hazard ratio; CI: Confidence interval; NS: Not significant.

tients with potentially resectable GC were randomly assigned to receive preoperative epirubicin, cisplatin, and infused fluorouracil (ECF) or surgery alone. Surgery was scheduled 5–6 wk after the last day of the final preoperative CT cycle. Downstaging and downsizing of the disease were observed in the preoperative CT arm. Also, a significant improvement in 5-year OS (36% vs 23%, *P* = 0.009) and progression-free survival (*P* < 0.001) were reported in the CT group. The main limitations of the study were the low adherence to post-CT (42% received the entire treatment, including post-CT as already planned), and the enrolment of patients with malignancies of the esophagogastric junction or lower esophagus in addition to those with GC. Subsequently, a smaller trial conducted in France, the FNCLCC/FFCD study, demonstrated the advantage of peri-CT over surgery alone in terms of 5-year OS (38% vs 24%; *P* = 0.02) and 5-year DFS (34% vs 19%; *P* = 0.003)^[26]. Although patients with lower esophagus and gastroesophageal junction adenocarcinoma were enrolled, peri-CT was found to be particularly favorable in stomach tumor localization (*P* < 0.01) in a multivariate analysis.

Currently, there are many systemic agents, including immunotherapy or targeted therapies that could reinforce the effect of well-known and widely used chemotherapeutics. Towards this purpose, the multicenter phase II/III MAGIC B trial aimed to evaluate

efficacy, safety, and OS after randomizing operable patients with GC, gastroesophageal junction cancer or lower esophageal cancer to either combination CT with bevacizumab or lapatinib (for HER-2 positive tumors) or to CT alone^[27]. The primary analysis after phase III concluded showed no significant difference in 3-year OS between the two arms (50.3% in the CT alone group vs 48.1% in the CT plus bevacizumab group; *P* = 0.36)^[28]. More than 70% of the patients in both groups also received post-CT as previously planned, but the main limitation remained the inclusion of both gastric and esophageal tumors.

The intensification of systemic therapy could bring more postoperative complications without any benefit in terms of survival. For this reason, a local approach associated to a well-tolerated CT could compensate for disease control, conserving at the same time a good quality of life with fewer side effects. To date, there is still no randomized trial evaluating peri-CT in a large homogeneous cohort of only resectable locally advanced GC patients. The use of combined therapy (CT + RT) in a preoperative setting has been investigated even less, despite many efforts to evaluate this modality of treatment in other gastrointestinal tumors.

In the German POET trial, patients with locally advanced adenocarcinoma of the lower esophagus or gastric cardia were randomized to receive induction peri-CT or CT followed by CRT before surgery^[29].

Table 2 The main randomized trials in gastric cancer that evaluate the preoperative therapy

| Trial | Year | Randomization scheme | OS | DFS, PFS | Limits |
|---------------------------------|------|---|--|---|--|
| MAGIC ^[25] | 2006 | S-alone vs CT + S + CT | 5-yr 23% vs 36% (<i>P</i> = 0.009) | 3-yr 26% vs 38% (<i>P</i> < 0.001) | Low adherence to post-operative CT, inclusion of gastroesophageal junction or lower esophagus cancer |
| FNCLCC/ FFCD ^[26] | 2011 | S-alone vs CT + S + CT | 5-yr 24% vs 38% (<i>P</i> = 0.02) | 5-yr 19% vs 34% (<i>P</i> = 0.003) | Inclusion of gastroesophageal junction or lower esophagus cancer, small series |
| MAGIC-B ^[28] | 2017 | CT/Beva + S + CT/ Beva vs CT + S + CT | 3-yr 48.1% vs 50.3% (<i>P</i> = 0.36) | NR | Inclusion of gastroesophageal junction or lower esophagus cancer |
| POET trial ^[29] | 2009 | CT + S vs CT + CRT + S | 3-yr 27.7% vs 47.4% (<i>P</i> = NS) | NR | Gastroesophageal junction tumors, closed earlier |

OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival; RT: Radiotherapy; S: Surgery; CT: Chemotherapy; CRT: Chemoradiation; NR: Not reported; NS: Not significant; Beva: Bevacizumab.

Surgery was performed 3-6 wk after induction therapy. The primary end-point was OS, and at 3 years, the median survival was higher in favor of the preoperative CRT group (47.4% vs 27.7%, *P* was not significant), but the predicted statistical survival advantage was not achieved and the study was finally closed prematurely. The authors concluded that a benefit in terms of pathologic complete response was reported in the CRT arm compared to the CT arm (15.6% vs 2.0%). A long-term update of the data in 2017 showed only a trend of significance in OS in favor of preoperative CRT (*P* = 0.055), suggesting an advantage in local control with the addition of RT^[30]. The main randomized studies evaluating preoperative therapy are summarized in Table 2.

Further randomized trials in a preoperative setting are needed to compare the best therapy options. In the meantime, the ongoing phase III randomized TOPGEAR trial (peri-CT vs induction CT followed by CRT) could provide insightful data regarding resectable GC^[31]. An interim analysis showed good adherence to preoperative therapy in both arms, and the treatment could be safely delivered without a significant increase in toxicity or surgical morbidity^[32].

Efforts have been made to improve the surgical approach to a less invasive method with less postoperative complications. With the development of laparoscopic techniques in recent decades for the treatment of localized and locally advanced GC, peri-CT has been more recommended principally in Asiatic countries. However, the safety and efficacy of laparoscopic techniques following preoperative CT still need to be verified prospectively^[33]. Surgical randomized trials have reported less postoperative complications such as the occurrence of excessive bleeding after a well-conducted laparoscopic approach in contrast to an open gastrectomy at experienced centers^[34,35]. Unfortunately, these were short-term results and the oncological efficacy in the locally advanced GC remains to be validated in combination with other treatments

necessary for the local and distant control of the disease.

RECENT EVIDENCE OF NOVEL CHEMOTHERAPEUTIC REGIMENS AND MODERN RT TECHNIQUES

In current clinical practice, the multimodal treatment strategy is based on both peri-CT and post-CRT to obtain better outcomes as demonstrated by randomized studies. The role of RT remains controversial and limited due to higher severe toxicity rates, particularly when combined with systemic agents. In the previously mentioned study by Macdonald *et al.*^[6], 273 (97.1%) patients in the CRT arm developed grade ≤ 3 toxicities, mainly represented by hematological and gastrointestinal side effects. Furthermore, 54 (17%) patients discontinued the protocol treatment due to unacceptable toxicity, but this toxicity was due to the use of old RT techniques. Toxicity rates could be reduced with modern RT techniques, which are able to spare normal tissues from higher radiation doses. Also, new chemotherapeutic agents could be combined with RT to obtain better disease control. Meanwhile, data from recent phase I - II studies could be considered in place of randomized data, which is currently lacking.

An American database analysis compared OS between patients who underwent peri-CT to those receiving post-CRT^[36]. A significantly improved OS was found with adjuvant RT on the univariate (*P* = 0.013) and multivariate (*P* = 0.009) analyses in 3656 patients; also, RT had greater benefit among patients with positive surgical margins (*P* < 0.001).

Despite the literature, open questions persist. Could innovative scheduling of radiosensitizers be adopted to increase local control and maintain acceptable levels of toxicity? Could the toxicity profile in a post-CRT setting be improved in locally advanced GC using modern RT techniques? An overview of the phase I - II trials published in the last 5 years has been reported.

Preoperative therapy

Two multicenter phase II trials evaluated by Michel *et al.*^[37] explored the role of CRT pre- ($n = 42$, 50 Gy/2 Gy) or postoperatively ($n = 21$, 45 Gy/1.8 Gy) following induction CT with 4 courses of folinic acid, 5-FU and irinotecan (FOLFIRI). The planned feasibility rates of both approaches were $> 88\%$, while considering unremarkable feasibility rates under 70% . Both studies failed in the primary end-point; in particular, the post-CRT study showed a lower feasibility rate (42.9%) and was prematurely closed. The preoperative study failed with a 73.8% feasibility rate. These results are comparable to the 64% feasibility rate reported by INT-0116, but not to that of post-CRT with capecitabine reported by the ARTIST trial, where the feasibility rate was $> 80\%$, probably reflecting different sensitivities to CT or RT^[11]. The findings from the above phase II studies seem to suggest a higher tolerability for preoperative CRT, but the interpretation of these data should be made with caution due to the use of old RT techniques. The disappointing 8.6% rate of pathologic complete response in the preoperative study would probably suggest a poor effect of irinotecan in contrast to more active agents like cisplatin or paclitaxel.

Effectively, the addition of paclitaxel and carboplatin to a course or preoperative RT showed interesting results in a phase II study by Trip *et al.*^[38]. The design of the study was based on the results of the MAGIC trial^[25], although the treatment protocol was performed in accordance to the CROSS trial^[39], where RT with concurrent weekly paclitaxel and carboplatin was shown to be feasible and improved surgical results in esophageal cancer patients, but was not investigated in GC patients. In the above phase II study, feasibility was 92% and tolerability was good, with 12% severe acute gastrointestinal toxicity and 12% grade 3 leukopenia. Relative high rates of initially unresectable patients (48%) were enrolled, followed conversely by 72% of R0-surgery rates (67% in the unresectable group only). Additionally, this study was limited to a small population ($n = 25$) and despite encouraging results, definitive conclusions on preoperative combined therapy could not be reached.

Another phase II study by Wydmanski *et al.*^[40] enrolled only 13 patients with unresectable GC who were treated with fluoropyrimidine-based preoperative CRT. The study was prematurely closed due to slow accrual (13/40 planned patients). Final results were published due to the favorable outcome in a population that was frequently a candidate only to best supportive care, even if only a small population of limited scientific value was evaluated. Surprisingly, median actuarial OS was 17.1 mo and 1- and 3-year OS were 59% and 48% , respectively; toxicity was mainly characterized by grade ≥ 3 thrombocytopenia (92.3%). The main phase I - II studies evaluating preoperative therapy are summarized in Table 3.

The current studies regarding preoperative CRT

are conducted in small cohorts using inhomogeneous therapy regimens and mostly closed prematurely. This treatment setting needs to be evaluated in larger controlled trials with well-selected GC patients and DFS as the primary endpoint.

Postoperative therapy

Many phase I - II studies have been conducted to evaluate the efficacy of post-CRT. In a phase I study by Wang *et al.*^[41], 18 patients with stage II - III GC were treated with 6 cycles of postoperative oxaliplatin, folinic acid and 5-FU (FOLFOX4) before or after capecitabine-based CRT (45 Gy/1.8 Gy + boost 10.8 Gy/1.8 Gy for R+) delivered with IMRT. Severe toxicity was mainly gastrointestinal (33.4%) and hematological (16.7%), and maximum tolerable dose (MTD) for capecitabine was 800 mg/m^2 twice daily. The use of modern RT techniques may increase the safety and tolerance of the treatment, but the real survival benefit of adjuvant CRT remains controversial and could depend on the type of lymphadenectomy (D0, D1 or D2) performed. In the study, the authors themselves admitted to the inferior performance of D2-lymphadenectomy, as compared to that reported in Japanese and Korean trials. Therefore, they encourage the introduction of post-CRT as a standard of care in their center, emphasizing the general concern regarding high rates of side effects when post-CRT was delivered with out-of-date RT techniques.

Thus, it is well known that irradiation techniques could determine the safety of the treatment, especially in a postoperative setting, as demonstrated by many recent phase I - II studies. Zhai *et al.*^[42] treated 30 patients with 2 cycles of adjuvant FOLFOX6 before or after a fluoropyrimidine-based CRT following D2-lymphadenectomy. Acute severe toxicity was characterized generally by neutropenia (40%) and nausea/vomiting (33%). Another study by Wang *et al.*^[43] administered an intensified post-CT-CRT-CT regimen consisting of 1 cycle of FOLFOX, followed by 2 cycles of FOLFOX on days 1 and 22 of RT and 5 additional cycles of FOLFOX after RT in 110 patients with R0 gastrectomy and D2-lymphadenectomy. The most experienced severe toxicities were nausea/vomiting (14.5%) and leukopenia (9.1%). Nevertheless, 3-year OS and recurrence-free survival (RFS) were 77.6% and 67.8% , respectively, and were not superior to those of other trials.

Recently, Liu *et al.*^[44] evaluated the effect of an intensified post-CT with docetaxel, cisplatin, and 5-fluorouracil (DCF) plus CRT, with docetaxel as a radiosensitizer, in a population of 55 resected GC patients. The outcome of this phase II study was promising, showing 3- and 5-year OS of 72% and 61% , respectively. The use of the dose-attenuated DCF regimen employed by Liu *et al.*^[45], which is less aggressive than standard DCF and other CT regimens, and the use of a single agent, docetaxel, as radiosensitizer combined to IMRT could explain the relatively low rate of severe toxicity, when compared to the traditional results of old randomized

Table 3 The main phase I/II trials in gastric cancer that evaluate the preoperative therapy

| Trial | Year/type | N° of patients | Treatment schedule | Median FU | Severe toxicity | Clinical efficacy | Survival | Limits/ characteristics |
|--------------------------|-----------------------|----------------|--|-----------|--|--|------------------------------------|--|
| Matsuda ^[51] | 2014/ Phase I | 9 | SP q15 + RT | NR | Diarrhea (11.1) Anorexia (11.1) | PR (78) SD (22) | NR | MTD: CDDP 25 mg/m ² |
| Michel ^[37] | 2014/ Phase II | 42 | FOLFIRI4→CRT | 38.1 mo | During FOLFIRI (26.2) During RT (19.1) | CR (8.6) Median PFS: 12.3 mo | Median OS: 26.4 mo | Reduced feasibility, 73.8% of patients completed the schedule |
| Trip ^[38] | 2014/ Phase I / II | 25 | CBDCA-PTX + RT | NR | Nausea (4) Anorexia (4) Esophagitis (4) Leukopenia (12) Febrile neutropenia (4) Thrombosis (4) Fatigue (4) | CR (16) PR (52) | Median OS: 15 mo | |
| Wydanski ^[40] | 2014/ Phase II | 13 | 5FU + RT | 30.1 mo | Nausea (7.7) Vomiting (7.7) Thrombocytopenia (92.3) Leukopenia (7.7) | NR | Median OS: 17.1 mo 3-yr OS: 48% | Inoperable patients. High rate of severe thrombocytopenia, with 5FU 325 mg/m ² d1-5 and 29-33 |
| Liu ^[52] | 2017/ Phase II | 40 | SOXx1→S-1 + RT → SOXx1 → surgery → SOXx4 | 26.5 mo | Leukopenia (10) Neutropenia (10) Thrombocytopenia (2.5) | CR (7.5) PR (30) SD (40) PD (12.5) 2-yr DFS: 47% | 2-yr OS: 56% | Treatment compliance: 87.5% |

CRT: Chemoradiotherapy; RT: Radiotherapy; CR: Complete response; OS: Overall survival; NR: Not reported; PR: Partial response; SD: Stable disease; MTD: Maximum tolerated dose; PD: Progressive disease; DFS: Disease-free survival; PFS: Progression-free survival.

data. The same authors reported a comparable toxicity when the same treatment schedule was administered in a population of 36 medically inoperable GC patients where, as expected, survival was lower. The main phase I - II studies evaluating postoperative therapies are summarized in Table 4.

Despite lower toxicity, good outcomes could also be observed in patients with advanced GC treated with post-CRT and modern radiation techniques, even after D2-lymphadenectomy. Randomized data are needed to support these hypotheses.

Novel chemotherapy

Cisplatin is known to be an active agent against GC and is safely used concomitantly with RT to improve outcome in several cancers. A phase I / II study by Goody *et al.*^[46] investigated the effect of the addition of cisplatin to a fluoropyrimidine-based post-CRT with the aim of identifying the MTD, which was established to be 40 mg/m² weekly. Overall, the acute toxicity rate for all dose levels was 29.1% (37% for MTD group), and 2-year OS and DFS for patients treated at the MTD were 88% and 77%, respectively. Moreover, a very advanced RT technique with 4D-computed tomography planning, daily cone beam-CT, and IMRT were used; compliance was assessed with the European Organization for Research and Treatment of Cancer Quality-of-Life (EORTC) C-30 questionnaire. Unfortunately, the principal limitation of the study was the use of D2-lymphadenectomy only in < 50% of patients and the incomplete planned accrual

that contributed to the reduced power of the study.

In Eastern countries, more evidence is emerging regarding the role of S-1, an oral fluoropyrimidine derivative, in the treatment of advanced GC. Due to the specific characteristics of S-1, it is expected to be well-tolerated by patients and be more effective than 5-FU, as recently demonstrated by a meta-analysis^[47]. In addition, the ARTIST II trial appears to be using S-1 as the concurrent CT agent during radiation. Nevertheless, this drug is not available in Western countries. In some recent studies, S-1 was administered concomitantly to RT, alone^[48-50] or in combination with cisplatin, both in a preoperative and postoperative setting^[51,52]. No excessive toxicities and encouraging outcomes were reported, and an MTD ranging between 70 and 80 mg/m² was identified. Further studies are needed to clearly assess the potential role of this molecule, whose characteristics seem well-suited to be used in combination with RT.

Further molecular characterization of tumors and understanding of disease biology may identify biomarkers and specific markers for trials to optimize radiation timing and the choice of target-oriented therapy^[53]. Similarly, the identification of specific prognostic factors could identify subgroups of patients who could benefit from intensified therapy.

CONCLUSION

In Europe, peri-CT is considered the standard of care in locally advanced GC, while in the United States, pos-

Table 4 The main phase I/II trials in gastric cancer that evaluate the postoperative therapy

| Trial | Year/type | N° of patients | Treatment schedule | Median FU | Severe toxicity | Clinical efficacy | Survival | Limits/ characteristics |
|------------------------|-------------------|----------------|--|-----------|---|----------------------------------|------------------------------|--|
| Michel ^[37] | 2014/Phase I | 21 | FOLFIRIx4→RCT | 26.6 mo | During FOLFIRI (23.8) During RT (9.5) | Median PFS: 22.8 mo | Median OS: 32.9 mo | Parallel study with a neoadjuvant schedule (see above). Study closed for futility (42.9% completed the schedule) |
| Wang ^[41] | 2014/Phase I | 18 | 5FU + RT→FOLFOX4 (8) FOLFOX4→5FU+RT (7) 5FU + RT (3) | 45 mo | Nausea (11.1) Vomiting (5.6) Esophagitis (5.6) Leukopenia (11.1) Neutropenia (5.6) | 4-yr LRC: 93.8% | 4-yr OS: 68.1% | MTD: 5FU 800 mg/m ² twice daily |
| Zhai ^[42] | 2014/Phase II | 30 | FOLFOX6x2→5FU + RT | 21 mo | Nausea (33.3) Vomiting (33.3) Diarrhea (6.7) Hepatic (3.3) Cutaneous (3.3) Neutropenia (40) Sensory (23.3) | 3-yr DFS: 65% | 3-yr OS: 72.7% | |
| Wang ^[43] | 2014/Phase II | 110 | FOLFOXx1→FOLFOXd1, 22 + RT→FOLFOXx5 | 43 mo | Nausea and vomiting (14.5) Diarrhea (0.9) Anorexia (11.8) Fatigue (6.4) Abdominal pain (2.7) Leuko-/neutropenia (9.1) Hemorrhage (0.9) | 3-yr RFS: 67.8% | 3-yr OS: 77.6% | Stage ≤ IIIA significant factor predicting more favorable OS |
| Qiu ^[48] | 2015/Phase I | 21 | SOXx1→S-1 + RT | 26 mo | Nausea (19) Vomiting (19) Fatigue (4.7) Anorexia (14.2) Leukopenia (4.7) | 2-yr DFS: 66.7% | 2-yr OS: 90.4% | MTD: S-1 70 mg/m ² d |
| Shim ^[49] | 2016/Phase II | 46 | SPx1→S-1 + RT→SPx2 | 56.5 mo | Nausea (17.4) Vomiting (8.7) Diarrhea (4.3) Anorexia (15.2) Fatigue (6.5) Neutropenia (28.2) Anemia (6.5) Thrombocytopenia (4.3) | 3-yr DFS: 65.2% | 3-yr OS: 76.1% | Treatment compliance: 73.9% Intestinal-type tumor showed better DFS and OS |
| Goody ^[46] | 2016/Phase I / II | 55 | 5FU-CDDP + RT | 36.4 mo | Hematological (36.3) Constitutional (9) Dermatologic (3.6) Gastrointestinal (18.1) Infection (5.4) Musculoskeletal (1.8) | 2-yr LRR: 16.8% 2-yr RFS: 74% | 2-yr OS: 85% | MTD: CDDP 40 mg/m ² w1,3,5,7 Treatment compliance: 85.5% |
| Liu ^[44] | 2017/Phase II | 55 | mDCFx2→TXL + RT→mDCFx2 | 61 mo | Nausea (63) Vomiting (49) Diarrhea (12) Anorexia (34) Fatigue (31) Neutropenia (60) Thrombocytopenia (51) Thrombocytopenia (15) Anemia (13) Febrile neutropenia (10) | 3-yr PFS: 75% 5-yr PFS: 59% | 3-yr OS: 72% 5-yr OS: 61% | Treatment compliance 76% |

| | | | | | | | | |
|----------------------|-----------------------|----|---|---------|--|-------------------------------------|--------------|--|
| Liu ^[45] | 2017/ Phase II | 36 | mDCFx2→wTXL + RT →mDCFx2 | 35.6 mo | Nausea (63) Vomiting (48) Diarrhea (9) Anorexia (33) Stomatitis (44) Fatigue (27) Neutropenia (53) Thrombocytopenia (62) Thrombocytopenia (16) Anemia (13) Febrile neutropenia (9) | RR: 83% CR: 36% 3-yr PFS: 32% | 3-yr OS: 42% | Inoperable patients. RT was delivered with IMRT technique |
| Wang ^[50] | 2018/ Phase I / II | 73 | S-1 + RT Various adjuvant CT before or after RT | 37.6 mo | Nausea (9.6) Vomiting (5.7) Anorexia (9.6) Esophagitis (3.8) Stomatitis (1.9) Fatigue (1.9) Leukopenia (11.5) Neutropenia (3.8) | 3-yr LRFS: 92.2% | 3-yr OS: 70% | MTD: S-1 80 mg/ m ² |

CRT: Chemoradiotherapy; RT: Radiotherapy; CR: Complete response; OS: Overall survival; NR: Not reported; MTD: Maximum tolerated dose; PD: Progressive disease; DFS: Disease-free survival; PFS: Progression-free survival; LRC: Loco-regional control; RFS: Relapse-free survival; RR: Response rate; LRFS: Local relapse-free survival.

toperative CT has traditionally been used in common clinical practice. As demonstrated by the evidence and the recent updates of randomized trials, meta-analyses and prospective trials, postoperative RT plays a fundamental role in reducing the loco-regional recurrence and in turn, the DFS, in patients with resectable advanced GC, even after a well-performed D2 surgery. A major benefit is noticed in patients with lymph node metastases, suggesting that careful multidisciplinary evaluation of this subgroup is needed. The current results recommend that therapeutic decisions should be made considering individual patients, but a multimodal approach is necessary to guarantee a longer survival and a good quality of life. Ongoing randomized trials could better define the timing and the combination of RT and systemic therapy.

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