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*EDITORIAL*

# Multidisciplinary management of gastric and gastroesophageal cancers

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## Abstract

Carcinomas of the stomach and gastroesophageal junction are among the five top leading cancer types worldwide. In spite of radical surgical R0 resections being the basis of cure of gastric cancer, surgery alone provides long-term survival in only 30% of patients with advanced International Union Against Cancer (UICC) stages in Western countries because of the high risk of recurrence and metachronous metastases. However, recent large phase-Ⅲ studies improved the diagnostic and therapeutic options in gastric cancers, indicating a more multidisciplinary management of the disease. Multimodal strategies combining different neoadjuvant and/or adjuvant protocols have clearly improved the gastric cancer prognosis when combined with surgery with curative intention. In particular, the perioperative (neoadjuvant, adjuvant) chemotherapy is now a well-established new standard of care for advanced tumors. Adjuvant therapy alone should be carefully discussed after surgical resection, mainly in individual patients with large lymph node positive tumors when neoadjuvant therapy could not be done. The palliative treatment options have also been remarkably improved with new chemotherapeutic agents and will further be enhanced with targeted therapies such as different monoclonal antibodies. This article reviews the most relevant literature on the multidisciplinary management of gastric and gastroesophageal cancer, and discusses future strategies to improve locoregional failures.



**Key words:** Gastric cancer; Chemotherapy; Chemoradiation; Adjuvant; Neoadjuvant

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## INTRODUCTION

Gastric and esophageal cancers are among the leading causes of cancer-related death worldwide. Even if the incidence of distal gastric cancer has been decreasing over the past decades, the incidence of newly diagnosed proximal cancers (localized at cardia and gastro-esophageal junction), including Barrett's carcinoma, has dramatically increased[1]. Despite considerable progress in surgical resection as the primary curative treatment for gastric cancer in Japanese and Western countries, more than half of all patients with advanced UICC stage disease undergoing radical primary tumour resection relapse and die within five years[2]. The prognosis of these curatively resected cancer patients remains poor due to high rates of local recurrences as well as early lymph node and systemic metastases. Therefore, new perioperative, neoadjuvant, adjuvant and palliative chemotherapy strategies are of great importance in handling these patients.

## MULTISCIPLINARY STRATEGIES FOR DIAGNOSIS AND STAGING

Until recently, the standard diagnostic approach after endoscopic and histological diagnosis of localized advanced gastric adenocarcinoma was to perform only limited staging procedures with sonography and chest X-ray, followed nearly always by attempted surgical

resection. These limited diagnostic tools resulted in a non-optimal description of the local tumor extension and the detection of regional and distant metastases, often not allowing an optimal treatment selection.

It became accepted during the last decade that the lack of co-operation between different medical disciplines prevented an improvement in available therapies. Patient care often consisted of fragmented strategies and lacked long-term planning. The multidisciplinary management of gastric and gastroesophageal cancers, in diagnosis as well as in treatment strategies, gains now even more ground after results of recent randomised studies became available. The time has come for the launch of multimodal treatments to increase the chance of better outcome, longer survival or even cure[3]. By using this team approach, all diagnostic and therapeutic disciplines, such as the gastroenterologist, surgeon, oncologist, radiologist and radiotherapist, will be instrumental in planning the effective administration of their treatment modalities. The diagnostic arsenal, i.e. CT scan, endoscopic ultrasound (EUS), mini-laparoscopy, MRI and PET, allows improved pre- or postoperative staging[4,5]. For endoscopically large tumors and tumors of the gastro-esophageal junction in particular, CT scan of the abdomen/thorax and EUS are mandatory for an exact preoperative tumor and node metastases staging. EUS allows the differentiation between small and large tumours as well as staging or biopsies of mediastinal and celiac lymph nodes[6,7]. In addition, mini-laparoscopy is a valuable tool, as peritoneal carcinosis is found in about 20% to 30% of all gastric cancer patients at first diagnosis[8]. As PET scan has also been shown to effectively predict clinical response in esophageal and gastric cancer, it might potentially allow better allocations and adjustments for further individualized and optimized treatment strategies[9]. Staging with PET may best be used either in patients with locally advanced disease who may benefit from curative resection, if distant metastases are not found, or in patients with high grade stenosis, where EUS is not applicable.

## CURATIVE INTENT-THE OPTIMAL RESECTION

To date, the mainstay of curative treatment of gastric cancer has been radical surgical dissection (ESMO clinical recommendations 2007). However, high rates of local recurrences, early lymph node and systemic metastases highlight the need of further efforts to standardize and optimize the surgical treatment. Thus, the type of resection (subtotal *vs* total gastrectomy) and the role of extensive lymphadenectomy have been subjects of international debates. For distal gastric cancers, subtotal gastrectomy has been shown to have an equivalent oncologic result with significantly fewer complications when compared with total gastrectomy[10]. Even if the surgical procedure of choice for proximal gastric cancers is more controversial, because both proximal gastrectomy and total gastrectomy are associated with postoperative nutritional impairments, the oncologic outcome of patients with proximal gastric cancer is independent of the type of gastric resection performed[11]. Currently, total gastrectomy for proximal (cardia) tumors is recommended in Europe.

The extent of regional lymphadenectomy required for optimal results is still debated. Several prospective randomised trials examining the role of more extended lymph node dissections (D1 *vs* D2) did not find clinically relevant improvements in overall survival. However, the interest in extended lymphatic dissections (D2 and greater) has not waned. A retrospective multicentre observation study in Germany found a significant survival advantage in patients undergoing extended lymphadenectomy[1]. In contrast, however, at least two prospective European trials compared D1 with D2 dissection: one in the Netherlands, by the Dutch Gastric Cancer Group (DGCG), and one in the UK, by the Medical Research Council (MRC)[12,13]. Even though the results have been debated differently, both trials found that extended lymphadenectomy associated with significantly higher morbidity and mortality rates compared with limited lymphadenectomy. Likewise, splenectomy and pancreatectomy were associated with a significantly increased risk of operative mortality. Interestingly, no significant survival difference was found for either group in the final results of the DGCG study after 11 years of follow-up[14]. As defined in this study, for patients with N2 disease an extended lymph node dissection may offer cure, but it remains difficult to identify patients who have N2 disease. Morbidity and mortality are greatly influenced by the extent of lymph node dissection, pancreatectomy, splenectomy and age. Extended lymph node dissections may thus be of benefit if morbidity and mortality can be avoided. Recently, the Japan Clinical Oncology Group (JCOG) presented an ambitious trial comparing D2 lymph node dissection with more extensive lymphadenectomy[15]. Here, the mortality rate was remarkably low (1%). Thus, a surgical option that may decrease postoperative morbidity and mortality is an "over –D1" lymphadenectomy with preservation of the pancreatic tail without splenectomy[16].

With improvements in endoscopic techniques (endoscopic mucosal resection) and minimal access surgery, there has been interest in applying these modalities to early gastric cancer. Node-negative T1 tumors are associated with a 5-year survival of more than 90%[17]. As such, there is interest in performing more limited resection for these tumors. Endoscopic resection should be accepted as the treatment of choice in most patients with high-grade intraepithelial neoplasia and mucosal carcinoma in the esophagus. Low morbidity (1%-3%) and mortality (0%) and better quality of life, due to organ preservation, are points in favor of endoscopic resection and against surgical in cases of early oesophageal carcinoma (Barrett's)[18]. Here proper patient selection is paramount. The probability of lymph node metastasis in early gastric cancer is influenced by tumor factors and is correlated with increasing tumor size, submucosal, lymphatic and vascular invasion and poorly differentiated tumors[19].

To improve the acceptance of endoscopic treatment, further prospective trials with long-term data are necessary. Regardless of the technique used for resecting early gastric cancer, complete excision with negative margins is required.

## ADJUVANT STRATEGIES

Because of the high rates of local recurrences and distant metastases, different adjuvant chemotherapy protocols have been compared with surgery alone in advanced gastric cancer in Europe, Asia and the United States. In a recent review of these studies the 5-year survival results suggested only a moderate improvement following adjuvant treatment[20]. However, the majority of the chemotherapeutic regimens used in these studies are regarded as suboptimal today.

Two recent phase Ⅲ trials again support adjuvant chemotherapy. Sasako *et al* examined the adjuvant efficacy of single-agent S-1 compared with surgery alone in a study with 1059 patients with Stage Ⅱ/Ⅲ disease, after potentially curative D2 gastrectomy (ACTS-GC study). After 3-year follow-up and rare grade 3/4 toxicities, overall survival and relapse-free survival favored the S-1 arm, with 81.1% *vs* 70.1% ($P = 0.0015$) and 72.2% *vs* 60.1% ($P = 0.0001$), respectively[21] (Figure 1). The Italian Gruppo Oncologico dell'Italia Meridionale (GOIM) study found also in trend some positive results for epirubicin/etoposide/5-FU/folinic acid (FA) in > D1 resected patients[22].

Adjuvant radiotherapy alone has failed over the last decades to improve treatment results and patient outcome. In the British Stomach Cancer Group trial, no survival advantage has been shown for 436 patients randomized between surgery only and surgery with 45 Gy-50 Gy radiotherapy or surgery with FAM chemotherapy[23]. This debate was further stimulated by the presentation of the SWOG 9008 group study, with combined radiochemotherapy in resected stage IB-IV gastric cancers[24]. After randomisation to either observation or to 2 cycles of FA/5-FU (Mayo-clinic regimen) followed by radiation + FA/5-FU and another 2 cycles FA/5-FU, a statistical significant difference in disease-free and overall survival in favor of the chemoradiation was shown. The absolute increase in median survival of 9 mo was hampered by suboptimal surgery (less than D1 in majority of patients) and radiotherapy; 35% protocol deviations. Additionally, in the multimodality arm, the local relapse rate was reduced from 90% to 29%. However, there was no difference in the risk of distant metastasis for either group. Despite positive data, several concerns have been raised concerning that in both arms the patients had high risk for relapse (more than 2/3 had T3 or T4 tumors and 85% positive lymph node metastases), the suboptimal surgery (54% of below D1) was counterbalanced by adjuvant chemoradiation and the number of patients (only 64%) who received the full schedule of chemotherapy and radiation.

In addition, Park and colleagues investigated a similar protocol in 290 patients, all of whom were curatively resected with extensive D2 lymph node dissection[25]. After a median follow up of 49 mo, 43% of patients relapsed, with 67% local relapses and 36% distant metastases. The five-year overall and relapse free survival rates were 60% and 57%, better than in the SWOG trail, respectively[25]. Therefore, it is still questionable whether Japanese or European patients undergoing D2 resection may benefit of postoperative chemoradiation.

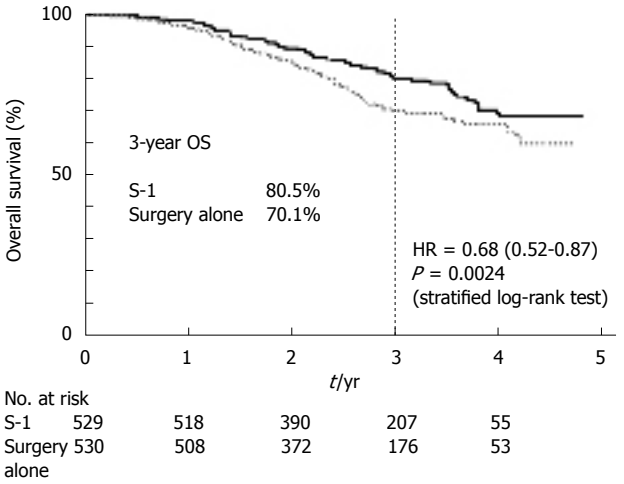


**Figure 1** Survival of S-1 monotherapy *versus* surgery alone for stage Ⅱ/Ⅲ gastric cancer patients after curative D2 gastrectomy (ACTS-GC study)[22].

## PERIOPERATIVE MULTISCIPLINARY APPROACHES

### *Neoadjuvant chemotherapy*

Many reasonable rationales justify the application of neoadjuvant chemotherapy, which is particularly interesting as a short-term therapy (i.e. two cycles of 6-8 wk) given simultaneously and/or sequentially with radio-chemotherapy. Possible advantages of neoadjuvant therapy +/- adjuvant strategies are: (1) Tumour vascularisation results in higher therapeutic efficacy and downstaging. (2) Excision of chemoradiated areas can result in lower long-term toxicity. (3) Early systemic therapy allows better control of tumour micrometastases. (4) Operation may not be compromised with higher morbidity and mortality.

Neoadjuvant chemotherapy aims at downstaging patients, improving curative resectability of locally advanced disease, and eventually increasing patient survival. It can also provide important information for the postoperative use of chemotherapeutic agents, by evaluating the response of the resected primary tumor, and it is also considered effective in reducing occult micrometastases. Theoretically, introducing chemotherapy at an early phase of the disease may facilitate delivery of drugs towards the primary lesion without impairing vascularization. In addition, major surgery such as total gastrectomy delays the start of postoperative systemic chemotherapy by a month or more, potentially giving microscopic residual diseases an opportunity to proliferate. On the other hand, it has been suggested that patho-

**Table 1 Ongoing important phase Ⅲ clinical trials, including monoclonal antibodies and signal transduction/tyrosine kinase inhibitors**

| Name | Design | Indication |
|---|---|---|
| TOGA | XP or FP +/- trastuzumab | Advanced gastric cancer HER2-positive |
| AVAGAST | XP +/- bevacizumab | Metastatic gastric cancer |
| REAL-3 | EOX +/- panitumumab | Advanced esophagogastric cancer |
| FFCD 03-07 | ECX followed by FOLFIRI *vs* FOLFIRI followed by ECX | Advanced esophagogastric cancer |
| EXPAND | XP +/- Cetuximab | Advanced/Metastatic gastric cancer |
| MAGIC-B | Perioperative ECX +/- bevacizumab | Neo-adjuvant gastric cancer |
| CLASSIC | XELOX *vs* observation | Adjuvant gastric cancer |

logical non-staging of the tumor could be the major disadvantage of neoadjuvant strategies. However, since modern imaging technologies such as CT, MRI and EUS plus fine-needle biopsies allow preoperative clinical staging for locoregional lymph node spread, overtreatment of patients with gastric cancer is less likely compared with earlier trials.

Patients responding to neoadjuvant treatment presented with a better performance status during their remission without compromising the subsequent operation with higher morbidity and mortality[26]. Although a number of randomised (mainly phase Ⅱ) studies for neoadjuvant chemotherapy alone have suggested improved survival compared with historical controls, evidence from a randomised phase Ⅲ trial were still missing[27,28].

Apart from the newly updated version of the neoadjuvant MRC trial[29,30], two large phase Ⅲ studies have now clearly proved the preoperative concept to be beneficial for patients with gastric and gastro-oesophageal cancers[31,32]. The recently published MAGIC trial was the first large randomised study of perioperative chemotherapy to be conducted with an adequate follow-up period. It was initiated to compare surgery alone *versus* surgery with perioperative chemotherapy in which patients received three preoperative and three postoperative cycles of ECF[31]. After enrolment of 503 patients with resectable gastric (74%) or lower oesophageal cancer (26%), the proportion of patients with curative resection was larger in the chemotherapy plus surgery arm (79% *vs* 69%, $P = 0.018$). After 5 years, the overall survival rate clearly favored the chemotherapy plus surgery arm over the surgery alone arm (hazard ratio for death, 0.75; 95% CI, 0.60-0.93; $P = 0.009$; 5-year survival rate, 36% *vs* 23%), as did the progression-free survival rate (hazard ratio for progression, 0.66; 95% CI, 0.53-0.81; $P < 0.001$).

The French FFCD (Federation Française de Cancerologie Digestive) Group trial confirmed these important data with their phase Ⅲ study in which they randomized 224 patients to perioperative FUP (5-FU/cisplatin; surgery; 5-FU/cisplatin) or surgery alone. With the same postoperative mortality rates for both arms, the perioperative group presented with significantly higher R0 resection rates. In addition, 3-year disease-free survival increased by 15% (40% *vs* 25%) and 5-year survival improved (38% *vs* 24%)[32].

To generate additional neoadjuvant data on tumors of the gastro-oesophageal junction, three randomised studies for oesophageal cancer included high percentages of adenocarcinomas of the lower oesophagus or the cardia region[33]. In contrast to one large negative phase Ⅲ trial with chemotherapy/surgery *vs* surgery alone[34], one study showed a significant survival benefit and one study found a trend for improved 3-year survival for radiochemotherapy[35,36]. Additionally, the recently updated MRC trial with 802 patients demonstrated a long lasting benefit in median survival (16.8 mo *vs* 13.3 mo) and the increase in 2-year survival of 9% for the chemotherapy group, with no difference in the rate of perioperative death or postoperative complications[29,30].

The identification of an effective chemotherapy regimen and optimal treatment schedule for locally advanced disease has been another important issue in neoadjuvant treatment for gastric cancer. There is optimism that the use of multiple targeted therapies in gastric cancer will produce further improved results. Thus, various phase Ⅰ/Ⅱ clinical trials, including monoclonal antibodies and signal transduction/tyrosine kinase inhibitors for EGFR, monoclonal antibodies to the HER-2/*neu* receptor and VEGF-ligand, and other novel drugs acting on intracellular signaling pathways, are under way, like bevacizumab[37] or cetuximab or panitumumab (Table 1).

### Neoadjuvant radiation

With regard to optimizing locoregional tumour control, radiotherapy in the neoadjuvant setting recently came into focus. Preoperative radio-chemotherapy has the advantage that the location of the primary cancer is known more precisely, which facilitates the planning of more accurate and effective radiation fields. In addition, the preoperative approach may allow significant time to observe high-risk patients for future growth of advanced cancers or metastases.

The German Oesophageal Cancer Study Group recently analysed the additional contribution of preoperative radiotherapy to neoadjuvant chemotherapy (POET study)[38] (Figure 2). Patients with locally advanced oesophagogastric adenocarcinomas (Stage T3-T4 NX M0 according to EUS, CT and laparoscopy) were randomised to 2.5 courses of chemotherapy (cisplatin/FA/5-FU weekly) *versus* two courses of the same chemotherapy followed by 3 wk of chemoradiotherapy (30 Gy/cisplatin/etoposide). Despite some increased postoperative mortality after chemoradiotherapy (five *vs* two patients), the median survival (32.8 mo) and the 3-year survival rate (43%) were

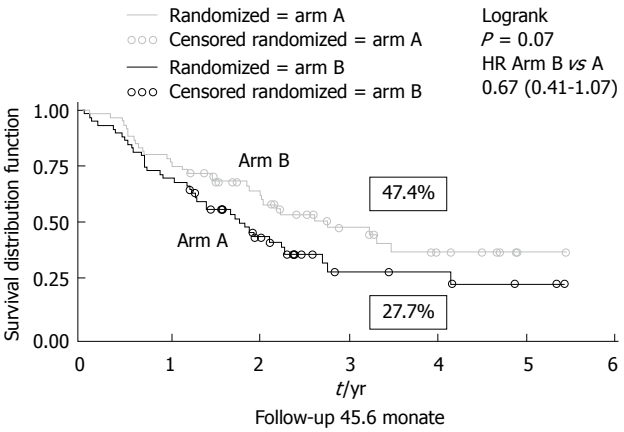


**Figure 2** Overall survival of patients with locally advanced oesophagogastric cancers with preoperative neoadjuvant chemoradiation (Arm B) *vs* neoadjuvant chemotherapy alone (Arm A, POET study)[38].

significantly improved in this group compared with patients who received chemotherapy alone (21.1 mo and 27%, respectively).

Pathological responses of oesophageal cancers strongly correlated with disease-free survival after preoperative radio-chemotherapy[39,40]. Ajani *et al* investigated the effects of induction chemotherapy combined with preoperative radio-chemotherapy. Taxanes, cisplatin and 5-FU were followed by radiation with 45 Gy (25 fractions in 5 wk) plus 5-FU infusions[41]. Interestingly, pCR/pPR response rates were 64% in all operated patients, with a significantly longer median survival (64 mo *vs* 30 mo) in patients with pathological remissions. In a second multicentre study of Ajani and colleagues, the pCR and R0 resection rates were 26% and 77%, respectively. At 1 year, more patients with pCR (82%) were alive compared with those with < pCR (69%). Again, these parameters were closely associated with better progression-free and overall survival[42]. Furthermore, it has still to be determined whether any radiation escalation by hyperfractionation (more than one fraction of radiotherapy per day) or acceleration (shortening of treatment duration) may improve local control whilst maintaining a similar risk of late normal tissue damage[43].

In addition to cisplatin/5-FU, new anticancer drugs such as taxanes, irinotecan and oxaliplatin have been reported to induce even higher objective response rates of up to 70% in recent years, and an improvement in overall median survival of up to 12 mo in palliative treatment[44]. The taxanes, docetaxel or paclitaxel promote microtubule stabilisation by increasing tubulin polymerization. As a result, they may also enhance radiosensitivity by causing cell cycle arrest in the G2/M phase[45]. These new chemotherapy regimens may be additional combinations to intensify localized multidisciplinary approaches in resectable or unresectable advanced diseases to further decrease incomplete resection rates as well as morbidity and mortality rates.

Additionally, results of other tumor entities, such as the JCOG 9907 study for esophageal squamous cell cancers, clearly favour a combined modality approach in the neoadjuvant setting[46]. Even more, some randomized trials of chemo-radiotherapy *vs* radiotherapy alone in head and neck, oesophageal or anal cancer showed better locoregional control and overall survival rates for the multimodal protocols. Thus, direct comparisons between neoadjuvant and postoperative adjuvant strategies will be worthwhile in the near future.

## TREATMENT OF METASTATIC DISEASE (STAGE IV)

Chemotherapy has increasingly justified its role in the treatment of metastatic disease, with the survival of treated patients being significantly better than that for patients receiving best supportive care. To date, 5-FU derivatives combined with cisplatin have been accepted as the most useful form of palliative chemotherapy, often additionally modulated by combinations with other anticancer drugs, such as epirubicin or leucovorin (FA)[44,47]. In a Cochrane review of randomised trials in advanced gastric cancer, the best survival rates were achieved with anthracyclines, cisplatin and 5-FU, both independently and in combination[48]. Within these combinations, ECF proved to be the best tolerated. Other trials have shown improved overall survival with palliative regimens, such as docetaxel/cisplatin/5-FU[49], oxaliplatin/FA/5-FU[50] and irinotecan/FA/5-FU[51,52]. However, continuous infusion of 5-FU is considered cumbersome because it requires the implantation of central venous catheter and the use of portable infusion pumps, which are associated with complications such as thromboses and wound infections. Capecitabine and S1, prodrugs and oral analogues of 5-FU, can mimic 5-FU continuous infusions and are at least equally effective in tumor control and less toxic than intravenous 5-FU in gastric cancer patients[53,54]. Remarkably, just recently Cunningham and colleagues evaluated capecitabine and oxaliplatin as alternatives to infused 5-FU and cisplatin for untreated advanced esophagogastric cancer and depicted at least similar effectiveness for both regimens[55].

Moreover, the use of multiple targeted therapies renewed hope for more effective and better tolerated chemotherapy regimes in the palliative setting to further improve efficacy and survival. Pinto *et al* combined Cetuximab + FOLFIRI (FOLCETUX) in a phase II study and they demonstrated an overall response rate (ORR) of 44.1%, with a median TTP of 8 mo and a median OS time of 16 mo[56]. The major toxicity appeared to be limited to neutropenia (42.1% of grade 3-4), together with the typical side effects associated with cetuximab (skin 21.1%/grade 3-4). Two additional German AIO trials recently support the efficacy of cetuximab, favouring the analysis of standard therapy with or without EGFR inhibitors in advanced cancers[57,58].

Additionally, response rate (65%), time to disease progression (8.3 mo), and overall survival (12.3 mo) were encouraging when bevacizumab was combined with

Irinotecan/Cisplatin in a multicenter phase Ⅱ study[37]. Ongoing studies testing novel agents will further assess the potential improvement in the treatment of patients with metastatic gastric or gastroesophageal junction adenocarcinoma advanced gastric cancer.

## CONCLUSION

With respect to the new perioperative and neoadjuvant achievements in improving the treatment options for advanced gastric cancer, multidisciplinary strategies should be integrated into the daily practice of a patient's work-up[54,59]. Clinical co-operative groups of local comprehensive cancer centers and international study groups, such as the JCOG, SWOG, EORTC, MRC, AIO, FFCD and others, have shown that complex preoperative strategies can be implemented. Thus, patients should be included into the aforementioned innovative studies whenever possible. However, if the local clinical setting does not allow participation in such trials, regionally organized treating physicians, e.g. general practitioner, gastroenterologist, surgeon, radiotherapist and oncologist, should meet regularly, ideally weekly, to decide the multimodal therapeutic concepts, integrating pre-operative and post-operative strategies. With all these clinical and scientific efforts, these treatment strategies will definitely continue to further improve the outcome of gastric cancer patients.

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