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Contents

Monthly Volume 7 Number 8 August 15, 2015

## EDITORIAL



## MINIREVIEWS



## CASE REPORT

**Contents**

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*EDITORIAL*

# Anti program death-1/anti program death-ligand 1 in digestive cancers

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## Abstract

Human tumors tend to activate the immune system regulatory checkpoints as a means of escaping immunosurveillance. For instance, interaction between program death-1 (PD-1) and program death-ligand 1 (PD-L1) will lead the activated T cell to a state of anergy. PD-L1 is upregulated on a wide range of cancer cells. Anti-PD-1 and anti-PD-L1 monoclonal antibodies (mAbs), called immune checkpoint inhibitors (ICIs), have consequently been designed to restore T cell activity. Accumulating data are in favor of an association between PD-L1 expression in tumors and response to treatment. A PD-L1 expression is present in 30% to 50% of digestive cancers. Multiple anti-PD-1 (nivolumab, pembrolizumab) and anti-PD-L1 mAbs (MPDL3280A, Medi4736) are under evaluation in digestive cancers. Preliminary results in metastatic gastric cancer with pembrolizumab are highly promising and phase Ⅱ will start soon. In metastatic colorectal cancer (CRC), a phase Ⅲ trial of MPDL3280A as maintenance therapy will shortly be initiated. Trials are also ongoing in metastatic CRC with high immune T cell infiltration (*i.e.*, microsatellite instability). Major challenges are ahead in order to determine how, when and for which patients we should use these ICIs. New radiologic criteria to evaluate tumor response to ICIs are awaiting prospective validation. The optimal therapeutic sequence and association with cytotoxic chemotherapy needs to be established. Finally, biomarker identification will be crucial to selection of

patients likely to benefit from ICIs.

**Key words:** Program death-1; Program death-ligand 1; Antibody; Digestive cancer



**Core tip:** Anti-program death-1 and anti-program death-ligand 1 (PD-L1) monoclonal antibodies have been designed to restore T cell activity, since human tumors tend to activate this immune regulatory checkpoint as a means of escaping immunosurveillance. A PD-L1 expression is present in 30% to 50% of digestive cancers and accumulating data are in favor of an association between this PD-L1 expression and response to treatment, which make digestive cancers promising candidates for those breakthrough immunotherapies. We review the ongoing clinical trials and the major challenges ahead of us in order to learn how, when and for which patients we should use these therapeutics.

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## TUMOR IMMUNOLOGY

Up until recently, only melanoma and renal cell cancer (RCC) were considered as immunogenic tumors. But in 2012 the results of a phase I study with nivolumab, an anti program death-1 (PD-1) monoclonal antibody (mAb), showed clinical responses in non-small cell lung cancers (NSCLC), thereby introducing the notion that any tumor can respond to the immune checkpoint inhibition strategy[1]. To prevent autoimmunity, to allow peripheral tolerance (during a woman's pregnancy, for instance) or to permit negative feed-back on immune reactions and secure immune system homeostasis, multiple immune checkpoints must be crossed so that immune response can occur and last. Human tumors tend to activate these immune checkpoints as a means of escaping immunosurveillance. That is one reason why new therapeutics called immune checkpoints inhibitors (ICIs) have been designed.

### *Cancer immunoediting*

Cancer immunoediting is currently defined by three E's: elimination, equilibrium and escape[2]. The first phase reflects active immunosurveillance, which facilitates tumor eradication and is mostly mediated by tumor-associated antigen-specific lymphocytes. The second phase refers to the period during which tumor growth is still prevented by the host immune system even though the surviving tumor and its stroma are also shaped by the immune response, which they learn how to downsize. Lastly, the escape phase describes tumor growth notwithstanding an immunologically intact environment due to selection of tumor cell variants during the equilibrium phase.

### *T cell activation*

In order to be activated, a T lymphocyte needs an association of triggering signals. Antigen coupled with major histocompatibility complex recognition is the first step toward activation. A second signal arising from the interaction of co-stimulatory molecules of activation must occur, avoiding T cell anergy. CD28 is the most commonly cited example of co-stimulatory molecules, and it is constitutively expressed on the T cell surface. It binds to B7.1 (CD80) or B7.2 (CD86), which are primarily expressed on activated antigen-presenting cells. B7 molecules also interact with cytotoxic T lymphocyte associated antigen 4 (CTLA-4), which is expressed on T cells. CTLA-4 transmits an inhibitory signal to T cells to prevent early excessive T cell activation. The molecules involved are called immune checkpoint. PD-1 is more widely expressed than CTLA-4 and can be detected not only on T cells but also on B lymphocytes and natural killer cells. Program death-ligand 1 (PD-L1) expression is up-regulated by interferon-γ production, which follows T cell activation. PD-1/PD-L1 interaction allows for negative feedback on the immune response regulating effector T cell responses in peripheral tissues and leads to peripheral T cell tolerance[3,4] (Figure 1). PD-L1 expression is up-regulated on a wide range of cancer cells and tumor-infiltrating immune cells strongly involved in tumor immunosurveillance escape. Several ICIs have been developed so as to prevent those negative regulations of the host immune system.

## IMMUNE CHECKPOINT INHIBITORS

To boost immune responses, ipilimumab, an anti-CTLA-4 mAb has been designed and has produced good results in cases of melanoma. Its limiting toxicities are mostly autoimmunity since it seems to upregulate all immune reactions. The PD-1/PD-L1 axis can be targeted by either anti-PD-1 mAbs or anti-PD-L1 mAbs (Figure 2). Anti PD-1 mAbs target PD-1 interactions with both PD-L1 and program death-ligand 2 (PD-L2), while PD-L1 mAbs target interactions between PD-L1 and either PD-1 or B7.1. PD-1 mAbs have been approved for the treatment of unresectable melanoma and NSCLC and their development for bladder cancer and RCC is well-advanced. Targeting of the CTLA-4 pathway has changed the melanoma treatment landscape[5,6] but PD-1/PDL1 axis targeting is also highly promising in multiple tumors[1,7].

### *Association between PD-L1 expression and treatment response*

Several studies have demonstrated an association

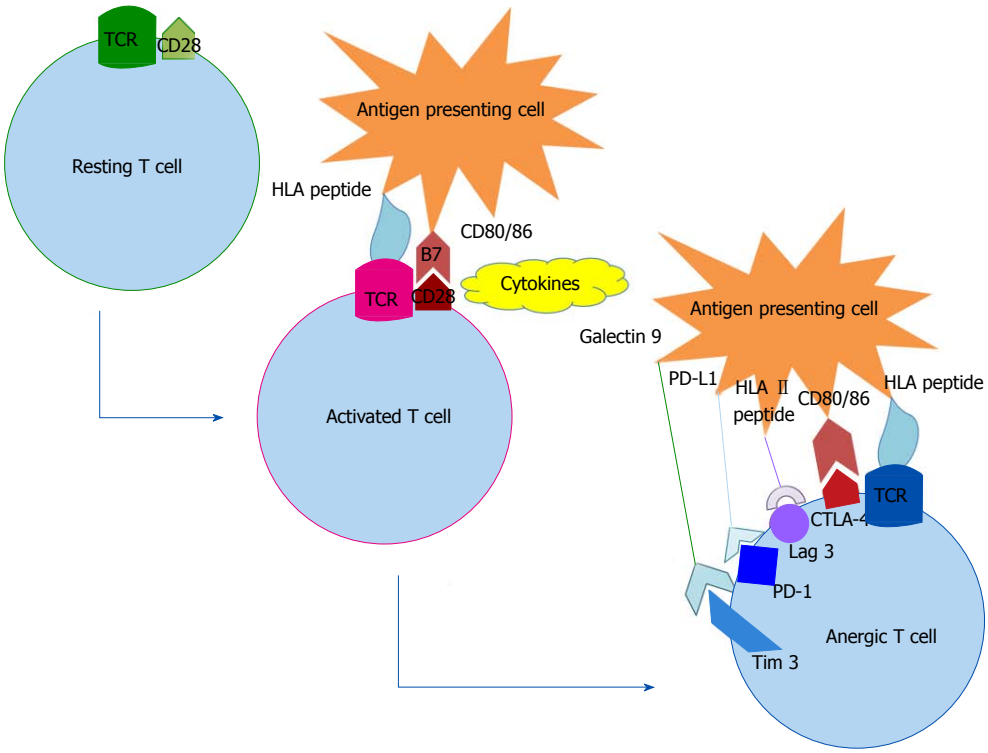


**Figure 1 From a resting T cell to an activated or an anergic T cell.** To be activated a T cell lymphocyte needs recognition of an antigen coupled with major histocompatibility complex by its specific TCR, adequate cytokines and activation of co-stimulatory molecules such as CD28. An inhibitory signal can instead be transmitted by co-inhibitory molecules (PD-1, CTLA-4, Lag 3, Tim 3…) and lead to T cell anergy. TCR: T cell receptor; CD28: Cluster of differenciation 28; HLA: Human leucocyte antigen; CD80/86: Cluster of differenciation CD80/86; PD-1: Program death-1; PD-L1: Program death-ligand 1; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4.

between pretreatment PD-L1 expression and tumor responses to anti-PD-1/PD-L1 therapies in melanoma, bladder cancer and NSCLC[1,8]. A PD-L1/PD-1 positive tumor should consequently be a good candidate for these treatments. For example, Dong *et al*[9] found 53% of PD-L1 positive colon carcinomas. Later, Droeser *et al*[10] studied PD-L1 expression in 1420 colorectal cancer (CRC). Strong PD-L1 positivity was found in 36% and 29%, respectively in mismatch repair (MMR)-proficient and deficient (dMMR) CRC. dMMR CRC has been associated with high level of tumor-infiltrating lymphocytes (TIL) and a good prognosis[11]. In other digestive cancers, especially in esophageal, gastric and pancreatic cancers, a PD-L1 expression was found in 30%-50% of cases[12-15].

### *Anti-PD-1 mAbs*

Preliminary results are available for two anti-PD-1 mAbs (nivolumab and pembrolizumab) in digestive cancers. Nineteen patients with CRC were enrolled in the phase Ⅰ study of nivolumab, but no efficacy was demonstrated[1]. However, nivolumab is currently being evaluated in multiple digestive cancers both alone and in combination with other ICIs (such as ipilumumab or anti-Lag 3) or with immune system stimulators. A phase Ⅱ clinical trial of nivolumab *vs* nivolumab plus ipilimumab in recurrent and metastatic colon cancer with a stratification between dMMR and pMMR status is ongoing. Pembrolizumab has been evaluated in gastric cancer and preliminary results were presented at the 2014 European Society for Medical Oncology meeting and updated at the 2015 American Society of Clinical Oncology Gastro Intestinal symposium[14]. In this trial, only PD-L1 positive tumors were eligible. Thirty-nine patients were enrolled and 67% had received at least two prior chemotherapy regimens. The overall response rate was 22%. The 6-mo progression-free survival and overall survival rates were 24% and 69%, respectively. Four patients experienced grade 3 to 4 adverse events and one patient died due to treatment-related hypoxia. A phase Ⅱ study will shortly be initiated with pembrolizumab monotherapy or in combination with cisplatin and 5 fluoro-uracil (5FU) in advanced gastric cancer treatment. Pembrolizumab is also currently under investigation in pancreatic cancer and in combination with aflibercept in CRC.

### *Anti-PD-L1 mAbs*

Now focusing on anti-PD-L1 mAbs (BMS936559, MPDL-3280A and MEDI4736) results in digestive cancers, the phase Ⅰ study with BMS936559 enrolled eighteen patients with CRC, fourteen with pancreatic cancer and seven with gastric cancer. None of the gastric cancer patients could be included in the efficacy analysis and no objective response was observed in either CRC or in pancreatic cancer[7]. MPDL3280A showed very promising

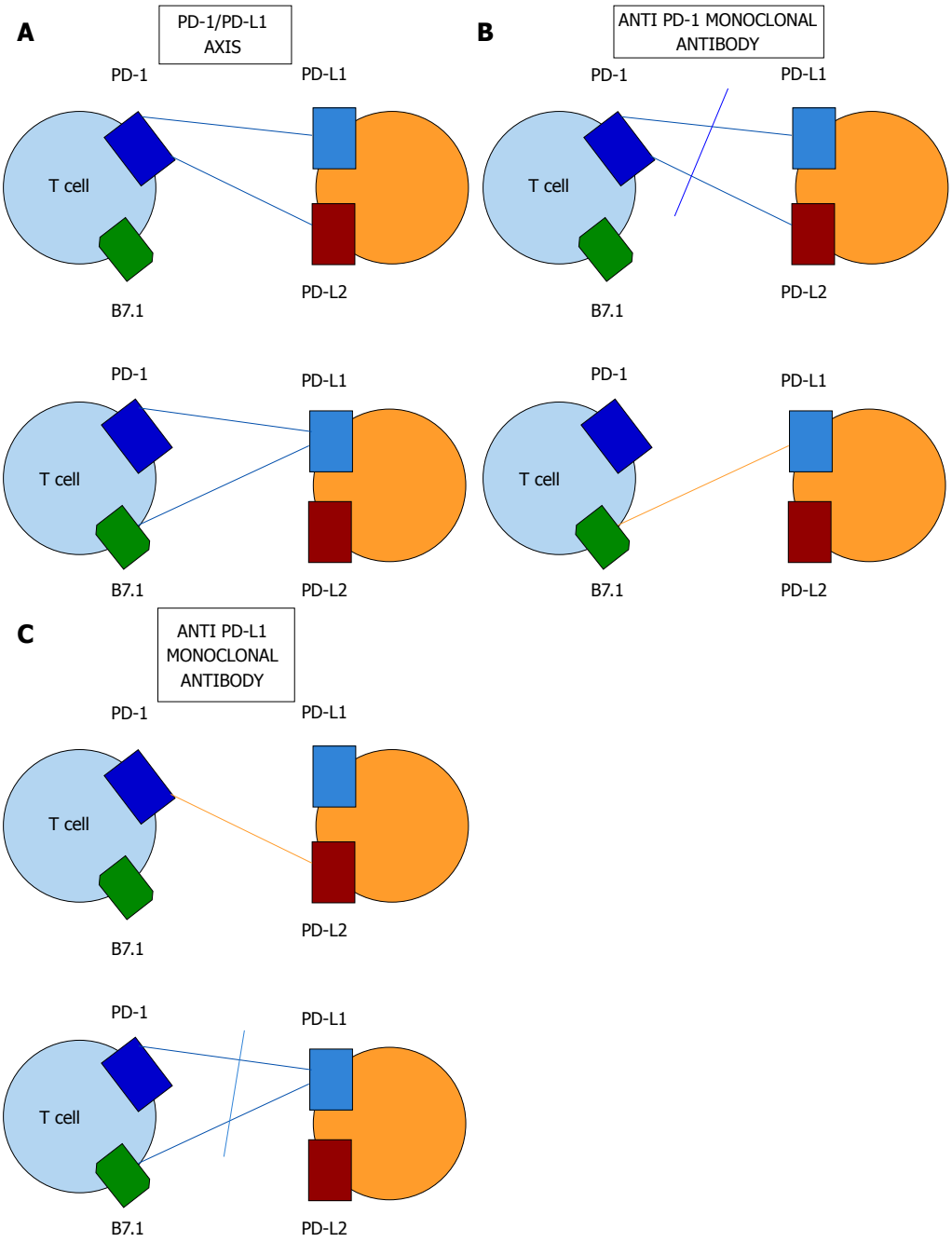


**Figure 2 The program death-1 and program death-ligand 1 axis blockade.** A: The PD-1 and PD-L1 interactions: PD1 has two ligands called PD-L1 and PD-L2. PD-L1 can interact either with PD-1 or B7.1; B: Anti PD-1 monoclonal antibody blockade prevents PD-L1 and PD-L2 ligation to PD-1 but not the B7.1 and PD-L1 interaction; C: Anti PD-L1 monoclonal antibody blockade prevents PD-1 and B7.1 ligation to PD-L1 but not the PD-1 and PD-L2 interaction. PD-1: Program death-1; PD-L1: Program death-ligand 1; PD-L2: Program death-ligand 2.

results in metastatic bladder cancer[8], NSCLC and RCC[16] but so far no result has been presented in digestive cancer. However, clinical trials are ongoing in combination with immune-modulating therapies (ipilumumab or interferon-$\alpha$) and in combination with bevacizumab, MEK inhibitor or CD40 agonist. Finally, the MODUL trial is a randomized phase Ⅲ multicenter trial with biomarker-driven maintenance therapy in metastatic CRC first-line treatment (Figure 3). After a four-month FOLFOX plus bevacizumab induction therapy, patients with disease control will be treated by maintenance therapy with 5FU, cetuximab and vemurafenib in *BRAF* mutated tumors or with 5FU, bevacizumab and MPDL3280A in *BRAF* wild-type tumors (the control arm will be 5FU and bevacizumab in both cohorts). MPDL3280A and MEDI4736 are both human IgG1 PD-L1 mAbs whose Fc domain has been engineered to prevent antibody-dependent cell-mediated cytotoxicity (ADCC). Indeed, PD-L1 can be expressed by the tumor-infiltrating immune cells, including T cells and if ADCC was induced, the latter would be killed, which would be counterproductive. The results of the MEDI4736

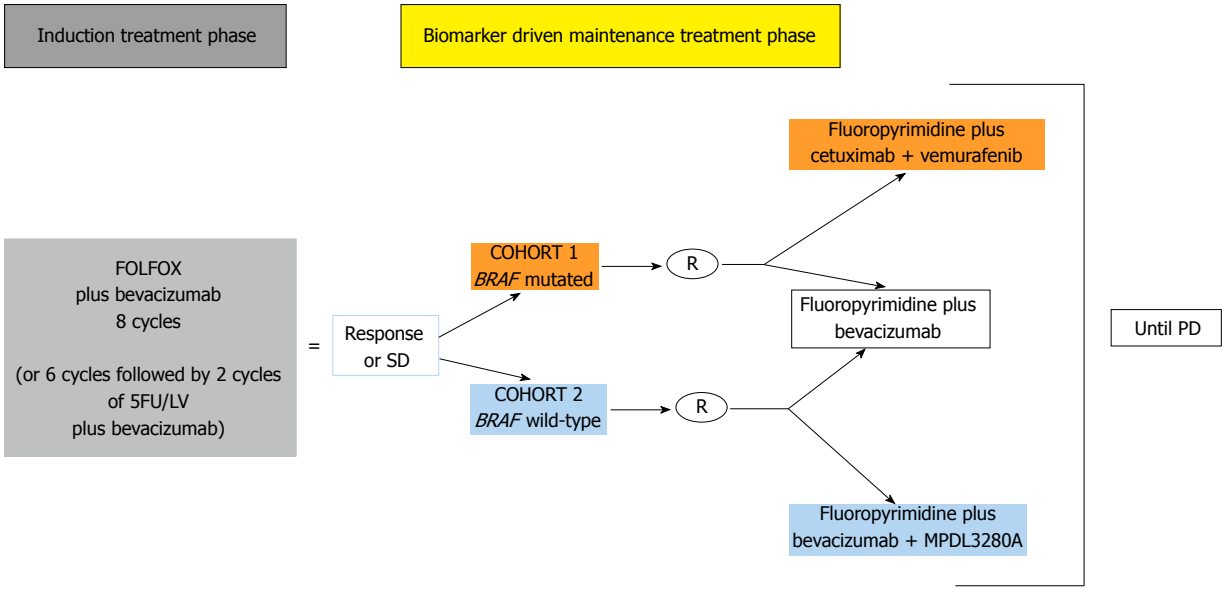


**Figure 3 MODUL Phase Ⅲ trial design.** 5FU: 5-Fluoro-Uracil; LV: Leucovorin; SD: Stable disease; R: Randomization; PD: Progressive disease.

**Table 1 Ongoing anti program death-1 or anti program death-ligand 1 monoclonal antibodies clinical trials in digestive cancers**

| Monoclonal antibody | Antibody description | Association | Tumors |
|---|---|---|---|
| MPDL3280A | Anti-PD-L1 Engineered Human IgG1[1] | MODUL trial: Phase Ⅲ biomarker driven maintenance therapy | Metastatic colorectal cancer |
| Medi 4736 | Anti-PD-L1 Engineered Human IgG1[1] | None | Immunological subsets of advanced colorectal cancer |
| Nivolumab | Anti-PD-1 Fully human IgG4[2] | Nab-paclitaxel +/- Gemcitabine | Pancreatic cancer |
| | | GVAX pancreas vaccine + CRS-207 | Pancreatic cancer |
| | | None | Squamous cell carcinoma of the anal canal |
| | | Ipilimumab | Recurrent and metastatic colon cancer |
| | | None | Hepatocellular carcinoma |
| | | None | Advanced or recurrent gastric cancer |
| Pembrolizumab | Anti-PD-1 Humanized IgG4[2] | None | Resectable or borderline resectable pancreas cancer |
| | | None | Advanced gastro-intestinal cancers |
| | | None | Metastatic colorectal cancer with and without microsatellite instability |

[1]Engineered Fc domain prevent antibody dependent cell mediated cytotoxicity (ADCC); [2]IgG4 antibody do not induce ADCC. PD-1: Program death-1; PD-L1: Program death-ligand 1; Ig: Immunoglobulin; GVAX: Granulocyte-macrophage colony-stimulating factor–secreting allogeneic pancreatic tumor cells, induces T-cell immunity to cancer antigens, including mesothelin; CRS-207: Live-attenuated L monocytogenes-expressing mesothelin.

multi-arm dose expansion study were presented at the 2014 ASCO meeting and updated at the 2014 ESMO meeting. A disease control rate of approximately 20% was observed across all relevant histology (10 mg/kg every two weeks), especially in hepatocellular carcinoma (19 patients), gastro-esophageal cancer (28 patients) and pancreatic cancer (29 patients)[15]. Tolerance was acceptable with 5.6% grade 3-4 adverse events, and no autoimmunity was reported. A study with MEDI4736 in dMMR CRC and pMMR CRC presenting with high TIL infiltration is scheduled to start.

## UPCOMING THERAPEUTIC CHALLENGES

Since ICIs seem as promising in digestive cancer as in other tumors, the same major challenges will be faced. Firstly, since initial progression is not rare, there arises the need for novel criteria to evaluate tumor response to immunotherapeutic agents. As with anti-angiogenic therapies, a tumor burden increase or appearance of new lesions can precede objective response and caution should be used before drawing any conclusion on disease progression[1,6,8,16]. Immune cell

infiltration can explain these features. Recently, immune-related response criteria have been defined and await prospective validation[17]. In any case, progression should be confirmed by a new radiological evaluation four weeks later. Secondly, optimal therapeutic sequences need to be established since most studies have included patients with advanced tumors. As of now no data are available in first-line therapy or in the adjuvant setting, but promising results with ipilimumab in melanoma have been reported[18]. Thirdly, in solid tumors, ICIs will probably need to be combined with chemotherapy, which could cause some problems, given the detrimental effects that chemotherapy can exert on the immune system. Combination with an immunogenic chemotherapy such as oxaliplatin should nonetheless be a good option. Finally, biomarkers are eagerly awaited to enable selection of the patients most likely to benefit from these ICIs. Only 20% to 30% of patients show objective response and in addition to inefficacy, patients are exposed to unnecessary toxicity. PD-L1 expression seems to correlate with clinical outcome but objective responses have been observed in PD-L1 negative tumors. Moreover, definition of a PD-L1 positive tumor needs standardization, given that the threshold of positivity varies between 1% and 5% across different studies and also given that PD-L1 expression can be analyzed either on tumor cells or on tumor-infiltrating cells[16,19]. In melanoma, a predictive model using CD8, PD-1 and PD-L1 positive cells at invasive margins and the tumor center has been correlated with a treatment response but requires prospective validation[20]. In addition, the expression of PD-L1 could be different in primary tumors at the beginning of the disease compared to metachronous metastasis several months later.

## CONCLUSION

Many digestive cancers are candidates for the anti-PD-1/PD-L1 axis blockade (Table 1) but we have still got to elucidate for whom, when and how to use them. dMMR CRCs are good candidates due to their high TIL infiltration associated with their high load of frameshift mutations[21]. dMMR CRCs are associated with high-CD8 cytotoxic T cells but also with up-regulation of at least five negative regulatory immune checkpoint molecules (PD-1, PD-L1, CTLA-4, LAG-3, IDO)[22]. One limit to use of ICIs in dMMR CRC could be that it represents only 5% of stage Ⅳ CRCs. Nevertheless, both nivolumab and pembrolizumab are currently being tested in this particular subset.

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MINIREVIEWS

# Neoadjuvant or adjuvant therapy for gastric cancer

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Author contributions: Quéro L designed, researched and analyzed the literature, and helped write the paper; Guillerm S and Hennequin C analyzed the literature, and helped write the paper.

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## Abstract

Currently, there is no international consensus on the best treatment regimen for patients with advanced resectable gastric carcinoma. In the United States, where a limited lymph-node dissection is frequently performed, adjuvant chemoradiotherapy after surgery is the standard treatment. In Europe, intensified perioperative chemotherapy is commonly administered. In Japan and South Korea, postoperative S-1-based adjuvant chemotherapy after surgery with D2 lymph-node dissection is the standard treatment. Several ongoing trials are currently evaluating the optimal sequence of chemotherapy, radiotherapy, and surgery, as well as the place of targeted therapeutic agents in the treatment of advanced gastric carcinoma.

**Key words:** Radiotherapy; Chemotherapy; Review; Gastric cancer



**Core tip:** Gastric cancer (GC) treatment is controversy, particularly between Asia and Western countries. In this paper, we have performed a systematic and up-to-date review of resectable GC treatment strategies and discussed different treatment options. We have also discribed ongoing clinical randomized phase 3 trials and future directions in GC treatment.

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## INTRODUCTION

Gastric cancer (GC) is one of the most common cancers worldwide, with a total of 989600 new cases diagnosed and 738000 deaths estimated for 2008, which accounted for 8% of total cancer cases and 10% of total deaths from cancer. Over 70% of new cases and deaths occur in developing countries, with the highest incidence rates in Eastern Asia, Eastern Europe, and South America[1]. In the United States, the incidence of GC is

**Table 1 Neoadjuvant chemotherapy in gastric carcinoma: Randomized meta-analysis**

| Studies | Country | Years | Randomization arms | Surgery | Protocol | Patients (*n*) | Overall survival | *P* value | Disease free survival | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Neoadjuvant chemotherapy | | | | | | | |
| Xiong *et al*[16] meta-analysis | - | 2014 | Chemotherapy | - | - | 753 | 46.6% at 53 mo[1] | 0.01 | 41.1% at 3 yr[1] | < 0.0001 |
| | | | Surgery alone | | - | 813 | 43.7% at 53 mo | | 27.5% at 3 yr | |

[1]Statistically significant result.

approximately 22000 per year and the mortality rate is nearly 11000 per year[2]. The worldwide incidence of GC has declined rapidly over the last three decades in Western countries.

Patients with resectable gastric carcinoma have a poor prognosis with a 5-year overall survival of approximately 20%-30% worldwide, but, in Japan, patients with gastric carcinoma have a better prognosis with a 70% 5-year overall survival rate. This difference is probably because of screening programs for GC in Japan, where the higher incidence of GC results in detection of disease at an earlier stage in approximately 50% of cases. In contrast, gastric carcinoma is usually diagnosed at a later stage in Western countries where there is no such screening program[3]. Moreover, patients with GC in Western countries have more frequently lesions in the upper third of the stomach, whereas patients from Asia have more frequently lesions in the middle or lower third of the stomach; a lesion in the upper third of the stomach has a worse prognosis than a lesion in the lower third[4,5].

Surgical resection remains the cornerstone treatment for non-metastatic GC. In Asia, particularly in Japan and South Korea, gastrectomy with a D2 lymph-node dissection is the standard surgical treatment. In Europe, two randomized trials, performed in the United Kingdom and the Netherlands, have reported little initial benefit from gastrectomy with a D2 dissection compared to gastrectomy with a D1 dissection[6,7]. However, after a 15-year follow-up, the benefit of a gastrectomy with a D2 dissection was confirmed in the Dutch trial in terms of both locoregional recurrence and GC-related death[8]. Gastrectomy with a D2 dissection is now recommended by the National Comprehensive Cancer Network in the United States[9] and the European Society for Medical Oncology in Europe[10].

Resected GC recurs in multiple patterns: locoregional, peritoneal, and distant sites are common modes of recurrence[11,12].

To improve outcomes in patients with locally advanced GC, several strategies in association with surgical resection have been evaluated, such as neoadjuvant chemotherapy, perioperative chemotherapy, adjuvant chemotherapy, and adjuvant chemoradiotherapy.

## NEOADJUVANT CHEMOTHERAPY

Several randomized trials have evaluated neoadjuvant chemotherapy before surgery, but have reported conflicting results. To date, four meta-analyses have been published on neoadjuvant chemotherapy for GC[13-16]. The first two meta-analyses were underpowered with only four and five randomized trials analyzed, respectively[13,15]. The third meta-analysis was biased because it included both neoadjuvant chemotherapy and chemoradiotherapy trials[14] (Table 1).

In 2014, Xiong *et al*[16] published a meta-analysis based on results extracted from published trial reports on 1820 patients from 12 different studies. Among these 12 studies, six were from Asia and six were from Western countries. The median follow-up period was 53 mo. The meta-analysis showed that patients treated with neoadjuvant chemotherapy plus surgery had only a marginally improved survival benefit over patients treated with surgery alone, with an odds ratio of 1.32 ($P$ = 0.001). However, the 3-year progression-free survival rate, the tumor down-staging rate, and the R0-resection rate were better in patients treated with neoadjuvant chemotherapy plus surgery, with odds ratios of 1.85 ($P$ < 0.0001), 1.71 ($P$ = 0.0006), and 1.38 ($P$ = 0.01), respectively. Subgroup analyses showed that patients treated with polychemotherapy or *via* an Ⅳ route had better survival, with odds ratios of 1.14 and 1.42, respectively. Subgroup analyses also showed that 5-year overall survival rates of patients treated with neoadjuvant chemotherapy plus surgery were statistically improved in studies conducted in Western countries, with an odds ratio of 1.39 ($P$ < 0.01), whereas similar trials in Asian countries found no significant differences ($P$ = 0.32).

## PERIOPERATIVE CHEMOTHERAPY

In locally advanced disease, preoperative chemotherapy may result in tumor downstaging and eradicate micrometastases. Two randomized trials in Western countries have evaluated perioperative chemotherapy in advanced gastroesophageal junction or GC. The United Kingdom Medical Research Council Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC) randomized trial compared surgery with or without perioperative ECF chemotherapy (epirubicin, cisplatin, infused fluorouracil). A total of 503 patients were enrolled in this trial; most patients had GC (74%), and approximately 50% of patients had a (y)pT3-T4 and 70% had a (y)pN+ tumor[17]. In this study, about 25% and 50% of patients were treated for GC, and received D1 or D2 surgery, respectively. Of the 86% of patients assigned

**Table 2 Perioperative chemotherapy in gastric carcinoma: Randomized trials**

| Studies | Country | Years | Randomization arms | Surgery | Protocol | Patients (*n*) | Overall survival | *P* value | Disease free survival | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| MRC MAGIC trial[17] | United Kingdom | 2006 | Chemotherapy and surgery | 42.5% D2 surgery | ECF chemotherapy | 250 | 36.3% at 5 yr[1] | 0.009 | 34.8% at 5 yr[1] | < 0.001 |
| | | | Surgery alone | | | 253 | 23% at 5 yr | | 24.9% at 5 yr | |
| ACCORD07/FFCD 9703 trial[18] | France | 2011 | Chemotherapy and surgery | D2 recommended | 5FU-CDDP chemotherapy | 113 | 38% at 5 yr[1] | 0.02 | 34% at 5 yr[1] | 0.003 |
| | | | Surgery alone | | | 111 | 24% at 5 yr | | 19% at 5 yr | |

[1]Statistically significant result. ECF: Epirubicin, cisplatin, and 5-fluorouracil; 5FU: 5-fluorouracil; RT: Radiotherapy; CDDP: Cisplatin.

to perioperative-chemotherapy and who received preoperative chemotherapy, only 55% also received postoperative chemotherapy. In this study, perioperative chemotherapy improved overall survival, and local + distant control, when compared with surgery alone. Five-year overall survival rates were 36% for patients treated with perioperative-chemotherapy *vs* 23% for those treated with surgery alone ($P$ = 0.009). In the perioperative-chemotherapy group, 14% had local recurrence *vs* 21% in the surgery group. Metastatic progression was also less frequent in the perioperative-chemotherapy group compared to the surgery-only group, at 24% and 37%, respectively (Table 2).

In the French ACCORD07/FFCD 9703 multicenter phase-Ⅲ trial[18], 224 patients with resectable adenocarcinoma of the lower esophagus, the gastroesophageal junction, or the stomach were randomly assigned to receive surgery with or without infused fluorouracil–cisplatin perioperative chemotherapy. In this study, only approximately 25% of the patients had gastric carcinoma; most patients had lower esophageal or gastroesophageal-junction carcinoma (75%). Patients treated with surgery alone had a more advanced tumor than patients treated with surgery plus perioperative chemotherapy. Sixty-eight percent and 80% of patients treated with surgery alone had a (y)pT3-T4 or a (y)pN+ tumor, respectively, compared with 58% and 67% of patients treated with perioperative chemotherapy. Moreover, fewer patients had a R0 resection in the surgery arm compared to the perioperative-chemotherapy arm (74% *vs* 87%, $P$ = 0.004). Of the total, 87% of patients received preoperative chemotherapy as planned but only approximately 50% of patients were able to receive postoperative chemotherapy. Patients treated with surgery and perioperative chemotherapy had significantly better 5-year overall survival and disease-free survival rates than patients treated with surgery alone (38% *vs* 24%, $P$ = 0.02; 34% *vs* 19%, $P$ = 0.003), respectively. In both groups, of the approximately 80% of patients that had a relapse, this was a distant relapse. In multivariable analyses, perioperative chemotherapy was only significantly effective in patients with cancer within the esophagogastric junction, but not for those with GC; however, the gastric subgroup was too small (*i.e.*, 25% of the population) to distinguish between no effect or a small effect.

## ADJUVANT CHEMOTHERAPY

Several studies have evaluated adjuvant chemotherapy in GC, but the results are conflicting. Over the past two decades, six meta-analyses have been published regarding the role of adjuvant chemotherapy in GC[19-24]. Five of these six meta-analyses observed improved survival after adjuvant chemotherapy compared to surgery alone[20-24] (Table 3).

In 2010, the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration group published the largest meta-analysis to date, based on individual data from 3838 patients in 17 different studies. Among these studies, four were conducted in Asia and 13 in Western countries. The median follow-up period was approximately 7 years. This meta-analysis reported a small but significant absolute 5.8% benefit to 5-year overall survival (49.6% *vs* 55.3%, $P$ < 0.001) and a 7.4% benefit to 10-year overall survival (37.5% *vs* 44.9%). Adjuvant chemotherapy also improved disease-free survival compared with surgery alone, with an absolute 5.3% benefit at 5 years (48.7% *vs* 54.0%, $P$ < 0.001)[24].

The greatest benefit from adjuvant chemotherapy occurred in the Asian studies. Indeed, the Japanese Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer trial compared surgery with a D2 dissection and either with or without S-1 oral adjuvant chemotherapy in patients with stage-Ⅱ or -Ⅲ gastric carcinoma. This trial enrolled 1059 patients between October 2001 and December 2004[25]. Patients treated with surgery plus adjuvant S-1 chemotherapy had significantly better 5-year overall and disease-free survival rates than those treated with surgery alone (71.7% *vs* 61.1% and 65.4% *vs* 53.1%, respectively). Peritoneum and hematogenous metastases represented approximately 80% of the relapses. All tumor subgroups benefited from adjuvant chemotherapy. However, poor outcomes were observed in patients with stage-ⅢB gastric carcinoma, with a 5-year overall-survival rate of 50.2% in the S-1 group and 44.1% in the surgery-alone group[26]. This observation suggests the need for therapeutic improvement in advanced gastric carcinoma. Because of these results, adjuvant chemotherapy without radiation for GC has now become the standard-of-care in Japan.

The Asian CLASSIC trial compared surgery with a

**Table 3 Adjuvant chemotherapy in gastric carcinoma: Randomized trials/meta-analysis**

| Studies | Country | Years | Randomization arms | Surgery | Protocol | Patients (*n*) | Overall survival | *P* value | Disease free survival | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| ACTS-GC trial[25,26] | Japan | 2007 | Chemotherapy and surgery | D2 surgery | Oral S1 chemotherapy | 529 | 71.7% at 5 yr[1] | - | 65.4% at 5 yr[1] | - |
| | | | Surgery alone | | | 530 | 61.1% at 5 yr | | 53.1% at 5 yr | |
| GASTRIC metaanalysis[24] | - | 2010 | Chemotherapy | - | - | 1924 | 55.3% at 5 yr[1] | < 0.001 | 54% at 5 yr[1] | < 0.001 |
| | | | Surgery alone | | - | 1857 | 49.6% at 5 yr | | 48.7% at 5 yr | |
| CLASSIC trial[27] | South Korea | 2012 | Chemotherapy and surgery | D2 surgery | XELOX chemotherapy | 520 | 83% at 3 yr[1] | 0.049 | 74% at 3 yr[1] | < 0.0001 |
| | | | Surgery alone | | | 515 | 78% at 3 yr | | 59% at 3 yr | |

[1]Statistically significant result. XELOX: Xeloda and oxaliplatin.

D2 dissection either with or without adjuvant combined capecitabine/oxaliplatin (XELOX) chemotherapy in 1035 patients with stage Ⅱ–ⅢB gastric carcinoma[27]. After a median follow-up of 34 mo, 3-year disease-free and overall-survival rates were significantly better in the XELOX plus surgery group than with surgery alone (74% *vs* 59%, $P < 0.0001$; 83% *vs* 78%, $P = 0.0493$, respectively). The most common sites of disease progression were the peritoneum and distant sites (*i.e.*, > 80%).

## ADJUVANT CHEMORADIOTHERAPY

In the United States, the SWOG 9008/ Intergroup 0116 trial reported a benefit after postoperative chemoradiotherapy. In this trial, 556 patients with locally advanced gastric adenocarcinoma or cancer within the gastroesophageal junction were randomized to receive surgery alone or surgery plus postoperative radiotherapy associated with 5-fluorouracil/leucovorin chemotherapy[28]. Three-year overall survival was 50% in the chemoradiotherapy group *vs* 41% in the surgery-only group ($P = 0.005$). The 3-year relapse-free survival rate was 48% in the chemoradiotherapy group *vs* 31% in the surgery-only group ($P < 0.001$). This benefit from postoperative chemoradiotherapy was confirmed in an update, published by Smalley *et al*[29] in 2012, with 10-year overall survival of 25.9% *vs* 17.3% for surgery only ($P = 0.0046$) and a 10-year relapse-free survival rate of 21.6% *vs* 14.4% ($P < 0.001$).

Local and regional relapses were significantly less frequent in the chemoradiotherapy group, at 2% and 22% *vs* 5% and 31% in the surgery-alone group, respectively ($P = 0.012$). There were no differences in terms of distant relapses between the two groups (16% and 17%, respectively) (Table 4).

However, several criticisms have been raised regarding this study. Most patients had limited lymph-node dissection and only 10% of patients received a formal D2 dissection (36% had a D1 and 54% had a D0 dissection) and many patients experienced high rates of acute toxicity (54% and 33% of patients had ⩾ grade 3 hematological and gastrointestinal toxicities, respectively). Only 64% of patients completed the protocol treatment in the chemoradiotherapy group: 17% of patients interrupted treatment because of its toxic side-effects and 8% declined further treatment. These high rates of toxicity may be explained by the use of the older 2D radiotherapy technique associated with the 5-fluorouracil Mayo Clinic chemotherapy regimen.

The United States CALGB80101 phase-Ⅲ trial compared 546 patients with resected gastric or gastroesophageal-junction adenocarcinoma who had adjuvant chemoradiotherapy with the 5-fluorouracil Mayo Clinic chemotherapy regimen (SWOG 9008/Intergroup 0116 protocol) *vs* adjuvant chemotherapy with ECF (epirubicin, cisplatin, 5-fluorouracil) followed by chemoradiotherapy with fluorouracil[30]. Seventy-five percent and 69% of patients completed the planned treatments in the ECF and Mayo 5-fluorouracil arms, respectively. Patients receiving adjuvant ECF chemotherapy had lower rates of grade ⩾ 3 diarrhea/mucositis (15% *vs* 7%) and also less grade-4 neutropenia compared to patients receiving the adjuvant fluorouracil Mayo-Clinic chemotherapy regimen (33% *vs* 19%). However, the 3- and 5-year overall survival rates were not significantly improved with ECF compared to fluorouracil (52% *vs* 50% and 44% *vs* 41%, respectively; $P = 0.8$). These results suggest that the intensified chemotherapy in association with adjuvant radiotherapy was better tolerated but was not associated with better outcomes compared to the fluorouracil-based chemoradiotherapy used in the SWOG 9008/Intergroup 0116 protocol. However, a longer follow-up period is needed to confirm these results.

The Korean phase-3 Adjuvant chemoRadiation Therapy In STomach cancer (ARTIST) trial randomized 458 patients with locally advanced gastric carcinoma and who had been initially treated with D2 lymph-node dissection. The trial compared postoperative capecitabine–cisplatin chemotherapy *vs* capecitabine–cisplatin chemotherapy plus chemoradiotherapy with capecitabine. In this trial, it is important to note that 60% of patients had early stages of gastric carcinoma (IB and Ⅱ) and, therefore, had a spontaneously better prognosis than patients with locally advanced-stage carcinoma. Treatment was completed as planned in 75.4% of patients in the chemotherapy arm *vs* 81.7% in the chemoradiotherapy arm.

After a median follow-up of 53.2 mo, there was no difference in 3-year disease-free survival (78.2% in the

**Table 4 Adjuvant chemoradiotherapy in gastric carcinoma: Randomized trials**

| Studies | Country | Years | Randomization arms | Surgery | Protocol | Patients (*n*) | Overall survival | *P* value | Disease free survival | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| INT 0116 trial[28,29] | United States | 2001 | Chemoradiotherapy and surgery | 10% D2 surgery | 5FU Mayo clinic/5FU RT | 281 | 50% at 3 yr[1] | 0.005 | 48% at 3 yr[1] | < 0.001 |
| | | | Surgery alone | | | 275 | 41% at 3 yr | | 31% at 3 yr | |
| Chinese multicentre trial[33] | China | 2012 | Chemoradiotherapy and surgery | D2 surgery | 5FU RT | 186 | 48.4% at 5 yr | 0.122 | 45.2% at 5 yr[1] | 0.029 |
| | | | Chemotherapy and surgery | | 5FU chemotherapy | 165 | 41.8% at 5 yr | | 35.8% at 5 yr | |
| ARTIST trial[31] | South Korea | 2012 | Chemoradiotherapy and surgery | D2 surgery | Xeloda CDDP/Xeloda RT | 230 | - | - | 74.2% at 3 yr | 0.086 |
| | | | Chemotherapy and surgery | | Xeloda CDDP | 228 | - | | 78.2% at 3 yr | |
| CALGB 80101 trial[30] | United States | 2011 | Chemoradiotherapy and surgery | Not available | ECF/5FU RT | 266 | 52% at 3 yr | 0.8 | 47% at 3 yr | 0.99 |
| | | | Chemoradiotherapy and surgery | | 5FU Mayo/ 5FU RT | 280 | 50% at 3 yr | | 46% at 3 yr | |

[1]Statistically significant result. 5FU: 5-fluorouracil; RT: Radiotherapy; CDDP: Cisplatin.

chemotherapy arm *vs* 74.2% in the chemoradiotherapy arm; $P = 0.0862$)[31]. However, in a subgroup analysis of 396 patients with positive pathological lymph nodes, there was statistically better 3-year disease-free survival in patients treated with chemoradiotherapy compared to those treated with chemotherapy (77.5% *vs* 72.3%, $P = 0.0365$). There were no significant differences between the two arms in terms of locoregional recurrence or distant metastases (8.3% *vs* 4.8%; $P = 0.353$ and 24.6% *vs* 20.4%; $P = 0.557$, respectively). Due to the lack of events at the time of analysis, the secondary end point for overall survival was not analyzed.

In a Korean observational study, Kim *et al*[32] compared 544 patients who had received postoperative chemoradiotherapy after a curative D2 dissection with 446 patients who had received surgery without any further treatment. In this study, it is important to note that the proportion of patients with advanced-stage carcinoma was significantly greater in the chemoradiotherapy group than in the surgery-only group (stage ⅢA: 34.1% *vs* 26.0%, and stage Ⅳ: 21.9% *vs* 13.9%).

Twenty-five percent of patients treated with chemoradiotherapy did not complete the planed protocol: the main reasons for this were its toxic side-effects (40%) and the patient's refusal to continue (35%). Thirty percent of patients experienced ≥ grade 3 hematological toxicity and 15% experienced ≥ grade 3 gastrointestinal toxicity. After a median follow-up of 66 mo, the 5-year overall survival and relapse-free survival rates were better in patients treated with chemoradiotherapy compared to those treated with surgery only (57.1% *vs* 51%; $P = 0.0198$, and 54.5% *vs* 47.9%; $P = 0.0161$, respectively). Locoregional recurrence rate was significantly lower in patients treated with chemoradiotherapy compared to those treated with surgery alone (14.9% *vs* 21.7%, $P = 0.005$). The occurrence of distant metastases did not differ between the treatment groups (37.7%).

A Chinese randomized trial compared postoperative fluorouracil–leucovorin chemotherapy *vs* intensity modulated radiation therapy plus fluorouracil–leucovorin chemotherapy in 380 patients initially treated with a D2 dissection for locally advanced gastric carcinoma (70% had stage Ⅲ or Ⅳ disease). Five-year overall survival in those that received postoperative radiotherapy was better than for those treated with chemotherapy only, but this difference was not statistically significant (48.4% *vs* 41.8%, $P = 0.122$). The 5-year recurrence-free survival rate in patients receiving chemoradiotherapy was also better (45.2% *vs* 35.8%, $P = 0.029$)[33]. Patients treated with chemoradiotherapy also had less local relapses than those treated with chemotherapy only (15.6% *vs* 24.2%; $P = 0.042$). However, the occurrence of distant metastases did not differ between the treatment arms (24.2% *vs* 26.7%, $P = 0.595$). In this study, multivariate analyses showed that pathological lymph node involvement and TNM stage were both independent prognostic factors.

## ONGOING TRIALS AND FUTURE DIRECTIONS

The ongoing CRITICS phase-Ⅲ study (ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach) (NCT00407186) is comparing patients undergoing preoperative epirubicin, cisplatin, capecitabine (ECC ) chemotherapy followed by a D1 dissection, with patients receiving postoperative ECC chemotherapy alone, with patients receiving radiotherapy plus concurrent capecitabine + cisplatin[34]. The study plans to accrue 788 patients with gastric carcinoma. The primary endpoint of the study is overall survival; secondary endpoints are disease-free survival, toxicity, health-related quality of life, prediction of response, and recurrence risk, assessed by genomic and expression profiling (Table 5).

**Table 5 Ongoing phase-Ⅲ randomized trials**

| Study | Country | No. registration | Standard arm | Experimental arm | Patients (*n*) |
|---|---|---|---|---|---|
| | | Neoadjuvant chemoradiotherapy | | | |
| EORTC 22114 - 40111 TOP GEAR study | Europe | NCT01924819 | ECC/ECF preoperative CT | ECC/ECF preoperative CT and RTCT preoperative | 752 |
| | | Perioperative chemotherapy | | | |
| MAGIC-B/ST03 study | United Kingdom | NCT00450203 | ECC perioperative CT | ECC + bevacizumab perioperative CT | 1100 |
| PRODIGY trial | South Korea | NCT01515748 | S-1 adjuvant CT | Neoadjuvant DOS CT and S-1 postoperative CT | 640 |
| | | Adjuvant chemotherapy | | | |
| ARTIST II Trial | South Korea | NCT01761461 | S-1 adjuvant CT (arm 1) | SOX adjuvant CT (arm 2), S-1 and RT adjuvant (arm 3) | 1000 |
| | | Adjuvant chemoradiotherapy | | | |
| CRITICS Trial | The Netherlands | NCT00407186 | ECC perioperative CT | ECC preoperative CT and RTCT postoperative | 788 |

CT: Chemotherapy; RTCT: Radiochemotherapy; ECC: Epirubicin, cisplatin and capecitabine; ECF: Epirubicin, cisplatin, and fluorouracil; DOS: Docetaxel, oxaliplatin, and S-1; SOX: S-1 and oxaliplatin.

The international ongoing phase-Ⅱ/Ⅲ European Organisation for Research and Treatment of Cancer (EORTC) 22114–40111 TOP GEAR study (Trial Of Preoperative therapy for Gastric and Esophagogastric junction AdenocaRcinoma) (NCT01924819) is currently testing whether adding chemoradiotherapy to ECF or ECC chemotherapy is superior to ECF or ECC chemotherapy alone for the preoperative treatment of resectable esophagogastric-junction or gastric carcinoma when treated with at least a D1 dissection (D2 dissection recommended). The phase-Ⅱ part of this study is being conducted in 35 medical centers in nine countries: Belgium, France, Germany, Israel, Czech Republic, Slovenia, Spain, Turkey, and Italy, and is planning to accrue 120 patients. The study is designed to demonstrate the efficacy of chemoradiotherapy. The phase-Ⅲ trial plans to accrue 752 patients and will determine whether chemoradiotherapy is superior to chemotherapy in these patients.

The Korean ARTIST Ⅱ phase-Ⅲ trial (Adjuvant chemoRadiation Therapy In STomach cancer Ⅱ) (NCT01761461) plans to accrue 1000 patients with stage-Ⅱ or -Ⅲ gastric or gastroesophageal carcinoma with positive lymph nodes (AJCC 2010), and who are being treated with curative gastrectomy and more than a D2 lymph-node dissection. This three-arm trial is currently comparing surgery + adjuvant S-1 chemotherapy for 1 year, *vs* surgery + adjuvant SOX (S-1 and oxaliplatin) chemotherapy, *vs* surgery + adjuvant SOX (S-1 and oxaliplatin) chemotherapy + radiotherapy. The primary endpoint of the study is disease-free survival.

The United Kingdom MRC MAGIC-B/ST03 study (NCT00450203) is an ongoing phase-Ⅱ/Ⅲ study being conducted in 106 United Kingdom centers, which plans to accrue 1100 patients with histological stage Ib (T1 N1, T2a/b N0), Ⅱ, Ⅲ or stage Ⅳ (T4 N1 or N2) gastric or gastroesophageal-junction carcinoma. This randomized trial is currently comparing standard surgery + ECC (epirubicin, cisplatin, capecitabine) perioperative chemotherapy *vs* standard surgery + ECC perioperative chemotherapy + bevacizumab. Primary endpoints are the safety and efficacy of the phase-Ⅱ trial and overall survival in the phase-Ⅲ trial. Secondary endpoints are response rates to preoperative treatment, surgical-resection rates, disease-free survival, quality of life, and cost-effectiveness. A pilot study within ST03, which is randomizing *HER2*-positive patients to standard ECX with modified ECX plus Lapatinib (Tyverb), will assess the safety and *HER2* positivity rate in 40 patients.

The Japanese JCOG 0501 phase-Ⅲ trial (NCT00252161) plans to accrue 316 patients, from 35 institutions, with type-4 and large type-3 gastric carcinoma and who have undergone a gastrectomy + more than a D2 dissection. The primary endpoint will be overall survival; secondary endpoints will be progression-free survival, response rate, proportion completing treatment, proportion having a curative resection, and adverse events.

The ongoing Korean PRODIGY phase-Ⅲ randomized trial (NCT01515748) plans to accrue 640 patients with resectable advanced GC (T2–3, N+, or T4 tumors). This study is currently testing neoadjuvant DOS (docetaxel, oxaliplatin, S-1) chemotherapy + surgery + adjuvant S-1 chemotherapy for 1 year *vs* surgery + adjuvant S-1 chemotherapy for 1 year. The primary endpoint is progression-free survival; the secondary endpoints are overall survival, stage distribution between the groups assessed after surgery, and R0 resection rate.

### *Targeted therapy in GO*

Several molecular pathways are known to be involved in gastric carcinogenesis, such as HER2, HER3, EGFR, HGFR/c-MET, E-Cadherin, MMP, VEGF/VEGFR, WNT/β-catenin, FGFR and Akt/PI3K/mTOR[35]. Targeted and biological therapies are promising treatments in advanced GC. Combining chemotherapy with a targeted therapy may improve the complete pathological response (pCR) and survival, but also individualize

therapies and reduce toxicities.

HER2 is a transmembrane growth-factor receptor encoded by the proto-oncogene *ERBB2*, which is located on chromosome 17q21. The frequency of HER2-positive GC varies considerably between studies, ranging from 6.0%-36.6%[36].

HER2 overexpression has been shown to predict the response to trastuzumab, a humanized recombinant monoclonal antibody that selectively binds to the extracellular domain of HER2, thereby blocking its downstream signaling. In the randomized ToGA trial, the addition of trastuzumab to cisplatin + capecitabine–fluorouracil significantly improved the objective response rate from 35% to 47% ($P$ = 0.0017), progression-free survival from 5.5 to 6.7 mo ($P$ = 0.0002), and overall survival from 11.1 to 13.8 mo ($P$ = 0.0046)[37].

The ongoing German Herceptin in combination with Fluorouracil, Leucovorin, Oxaliplatin, and Taxotere AIO-STO-0310 multicenter phase-Ⅱ study is currently testing perioperative chemotherapy with 5-FU, leucovorin, docetaxel, and oxaliplatin (FLOT) in combination with trastuzumab in patients with HER2-positive, locally advanced, resectable adenocarcinoma of the gastroesophageal junction or stomach (NCT01472029). The primary endpoint is the rate of pCR. Hofheinz *et al*[38] reported the preliminary results from the first 25 patients at the 2014 ASCO meeting: A pCR was found in 22% of patients and near complete regression (< 10% residual tumor cells) was observed in 24% of patients. The complete resection rate was 90%.

The Spanish NEOHX multicenter phase-Ⅱ study evaluated the efficacy and toxicity profile for perioperative XELOX-T (capecitabine, oxaliplatin, trastuzumab) followed by adjuvant trastuzumab as a monotherapy in patients with advanced resectable stomach or esophagogastric-junction adenocarcinoma that was HER-2+. The primary endpoint was 18-mo disease-free survival. By the end of the study, 36 patients had been included. Preliminary results were reported at the 2013 ASCO meeting: pCR was observed in 19% and complete-resection rate (R0) was observed in 78% of patients. However, the follow-up period was too short for disease-free survival or overall survival to be assessed[39].

The future EORTC randomized phase-Ⅱ trial (INNOVATION) will test neoadjuvant chemotherapy with cisplatin–capecitabine plus trastuzumab *vs* cisplatin–capecitabine plus trastuzumab plus pertuzumab in HER2-positive resectable gastric or gastroesophageal-junction adenocarcinoma (NCT02205047). Pertuzumab is a humanized monoclonal antibody that binds to extracellular dimerization domain Ⅱ of HER2, and inhibits heterodimerization of HER2 with other HER family members, especially HER2–HER3, which is the most potent signaling HER heterodimer. The primary endpoint will be the rate of major pathological response (*i.e.*, < 10% vital tumor cells).

## CONCLUSION

Currently, the treatment for locally advanced gastric carcinoma is based on R0 surgical resection with D2 lymph-node dissection. A D1 lymph-node dissection, with at least 15 lymph nodes resected, could also be performed in less experienced centers. Complementary treatment after curative surgical resection in T3 and/or N+ gastric carcinoma should be discussed. Perioperative chemotherapy and adjuvant chemoradiotherapy have significantly improved overall survival compared to surgery alone in Europe and the United States. In Asia, adjuvant chemotherapy, with S-1 or XELOX delivered after surgery + a D2 lymph-node dissection has shown significantly improved survival compared to surgery alone. Ongoing randomized trials are currently testing the efficacy of adjuvant chemoradiotherapy after neoadjuvant chemotherapy; intensified chemotherapy, and targeted therapy plus chemotherapy.

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# Inflammation-based factors and prognosis in patients with colorectal cancer

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## Abstract

Several parameters for predicting survival in patients with colorectal cancer have been identified, including the performance status, age, gender and tumor-node-metastasis (TNM) stage. Although the TNM stage is important and useful for predicting the prognosis and determining the appropriate treatment, it is well known that the survival time varies widely, even in patients with the same stage of disease. Therefore, the identification of new parameters capable of more precisely predicting patient survival is needed to help select the optimal treatment, especially in patients in the advanced stage of disease. Although the TNM stage reflects the tumor characteristics, cancer progression and survival are not determined solely based on the local characteristics of the tumor, but also the host systemic immune/inflammatory response. Therefore, using a combination of parameters that reflect both tumor characteristics and the host systemic inflammatory status is thought to be important for accurately predicting patient survival.

**Key words:** Colorectal cancer; Platelet-to-lymphocyte ratio; Prognosis; Glasgow Prognostic Score; C-reactive protein; Neutrophil-to-lymphocyte ratio; Inflammation-based factor; Nutritional Prognostic Index



**Core tip:** Recently, it has become clear that an elevated systemic inflammatory response is consistently associated with a poor outcome, independent of the tumor stage. The inflammatory response is represented by the levels of serum neutrophils, lymphocytes and platelet s as well as acute-phase proteins and their combinations. These parameters are simple and easy to measure using widely available standardized assays. In this review, we discuss the prognostic value of various inflammation-based factors in patients with colorectal cancer.

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## INTRODUCTION

Colorectal cancer (CRC) is one of the most common causes of cancer-related death worldwide[1]. Approximately 20% of patients with CRC present with distant metastasis at the time of diagnosis[1], and the survival of patients with unresectable stage Ⅳ CRC is very poor, with a median survival time (MST) of approximately six to eight months among those who receive the best supportive care without chemotherapy[2]. However, due to the development of chemotherapeutic and molecular targeting agents, the survival time has improved dramatically within the last decade, with an MST of 24-30 mo[3-6].

Several parameters for predicting survival in patients with CRC have been identified, including patient characteristics, such as the performance status (PS), age and gender, and tumor characteristics, such as clinicopathological factors and the TNM stage. Although the stage determined according to the Union for International Cancer Control (UICC) TNM classification[7] is important and useful for predicting the prognosis and determining the appropriate treatment, it is well known that the survival time varies widely, even in patients with the same stage of disease. Therefore, the development of a new parameter able to more precisely predict the patient survival required to help select the optimal treatment, especially in patients with advanced disease. It has been reported that many molecular parameters (such as proteins involved in cell cycle regulation, apoptosis and angiogenesis or RAS/RAF mutations) are associated with survival[8-14]. However, measuring these molecular parameters requires sophisticated and expensive laboratory techniques.

It is now recognized that disease progression in cancer patients is determined not only by tumor characteristics, but also the host inflammatory response[15]. Moreover, it has become clear that an elevated systemic inflammatory response is consistently associated with a poor outcome independent of the tumor stage[16-18]. The inflammatory response is represented by the levels of serum white blood cells, neutrophils, lymphocytes and platelets and acute-phase proteins, such as C-reactive protein (CRP) and albumin. These parameters are simple and easy to measure using widely available standardized assays.

Recently, several combinations of these factors, including Glasgow Prognostic Score (GPS), neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and prognostic nutritional index (PNI), have also been reported to be useful prognostic factors in various malignant solid tumors, including CRC (Table 1)[19-32].

The aim of this review was to examine the value of various inflammation-based factors as useful prognostic factors in patients with CRC.

## CRP LEVEL

CRP is an acute-phase protein synthesized in hepatocytes whose serum level increases in response to inflammatory disease[33,34]. Cancer growth also induces a tissue inflammatory response, and thus increases the serum CRP level. Elevation of the serum CRP concentration reflects a state of hyper-cytokinemia, as the CRP level is upregulated by proinflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)[33,34]. These cytokines have the ability to promote tumor growth and metastasis and play a role in tumor progression.

Many investigators have reported that a high level of serum CRP significantly correlates with poor survival in patients with CRC treated with curative surgery[19-21]. Nozoe *et al*[19] reported that the preoperative elevation of CRP was related to recurrence after curative resection for CRC. Toiyama *et al*[20] reported a correlation between elevated CRP and recurrence in patients with rectal cancer undergoing chemoradiotherapy followed by surgery. We investigated the correlation between serum CRP levels and the prognosis of patients with stage Ⅳ CRC who underwent the palliative resection of their primary tumor[20]. We found that a high preoperative serum CRP level was a convenient marker for identifying the stage Ⅳ CRC patients with a poor prognosis.

### *GPS*

GPS, which is also an inflammation-based factor, is defined according to the presence of an elevated serum CRP level and hypoalbuminemia. Briefly, patients with both an elevated CRP level (> 1.0 mg/dL) and hypoalbuminemia (< 3.5 g/dL) are allocated a score of 2. Patients in whom only one of these biochemical abnormalities is present are allocated a score of 1 and those in whom neither of these abnormalities are present are allocated a score of 0[17,18]. This score has been shown to be a prognostic indicator, independent of the tumor stage, in a variety of gastrointestinal cancers[22-24,35,36]. Sugimoto *et al*[22] examined patients with stage Ⅱ CRC who underwent a curative resection and reported that the cancer specific survival was significantly worse in the patients with a GPS of 2 than in those with a GPS of 1 or 0. Proctor *et al*[35] also reported that a raised GPS was associated with reduced overall survival and cancer specific survival in CRC patients, independent of age, gender and Dukes' stage. Moreover, GPS of 2 has been reported to be an independent significant prognostic factor, even in patients with unresectable stage Ⅳ CRC[23,24]. Ishizuka *et al*[24] reported a correlation between GPS and chemotherapy tolerance and noted that it would be useful for deciding

**Table 1 Previously reported correlations between various inflammation-based factors and the prognosis**

| Inflammation-based factors | Ref. | Year | Timing of measurement | *n* | TNM staging | Treatment | Survival analysis | Summary results |
|---|---|---|---|---|---|---|---|---|
| CRP | Nozoe *et al*[19] | 1998 | Preoperation | 120 | Ⅰ-Ⅳ | Resection | OS | Positive |
| | Toiyama *et al*[20] | 2013 | Preoperation | 84 | Ⅰ-Ⅲ | Resection and CRT | DFS, OS | Positive |
| | Shibutani *et al*[21] | 2014 | Preoperation | 144 | Ⅳ | Resection and CT | PFS, OS | Positive |
| GPS | Sugimoto *et al*[22] | 2012 | Preoperation | 166 | Ⅱ | Resection | OS | Positive |
| | Kishiki *et al*[23] | 2013 | Pretreatment | 79 | Ⅳ | CT | OS | Positive |
| | Ishizuka *et al*[24] | 2013 | Preoperation | 108 | Ⅳ | Resection | OS | Positive |
| NLR | Chua *et al*[26] | 2011 | Pre and post treatment | 171 | Ⅳ | CT | OS | Positive |
| | Chua *et al*[26] | 2011 | Preoperation | 674 | Ⅰ-Ⅳ | Resection | OS | Positive |
| | Li *et al*[27] | 2014 | - | - | Meta-analysis | - | DFS, OS | Positive |
| OPNI | Nozoe *et al*[28] | 2012 | Preoperation | 219 | Ⅰ-Ⅳ | Resection | OS | Positive |
| | Maeda *et al*[29] | 2014 | Preoperation | 100 | Ⅳ | Resection and CT | OS | Positive |
| | Ikeya *et al*[30] | 2014 | Pre and post treatment | 80 | Ⅳ | CT | OS | Positive |
| PLR, NLR | Kwon *et al*[31] | 2012 | Preoperation | 200 | Ⅰ-Ⅲ | Resection | OS | Positive |
| GPS, NLR | Maeda *et al*[32] | 2013 | Preoperation | 94 | Ⅳ | resection and CT | OS | Positive |

CRP: C-reactive protein; GPS: Glasgow Prognostic Score; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; CT: Chemotherapy; CRT: Chemoradiotherapy; OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival.

the indications for palliative surgery or preoperative chemotherapy.

### *Neutrophil-to-lymphocyte ratio*

The neutrophil-to-lymphocyte ratio (NLR), calculated as the neutrophil count divided by the lymphocyte count, is suggested to be a marker of general immune response to various stress stimuli. Initially, the NLR was described to be correlated with the severity of the clinical course of severely ill patients in the intensive care unit by Zahorec *et al*[37].

Neutrophils play a key role in tumor proliferation, producing a number of ligands that induce tumor cell proliferation and invasion and promoting tumor vascularization by releasing proangiogenic chemokines and other factors[38,39]. Therefore, increased neutrophils may promote tumor growth and metastasis. On the other hand, lymphocytes play a key role in tumor suppression[40]. The function of lymphocytes is to induce cytotoxic cell death and the production of cytokines in cancer cells[40]. A decrease in the number of lymphocytes impairs the host's antitumor immune response and confers a poor prognosis[25]. NLR can therefore be considered as a balance between the pro-tumor inflammation status and the anti-tumor immune status. Although the cut-off values varied between 2.5 to 5 in the previous reports[25-27], emerging evidence shows that an elevated NLR is significantly associated with poor prognosis in patients with CRC. We analyzed 674 CRC patients who underwent surgery and used a receiver operating characteristic curve to determine an appropriate cut-off value[25]. As a result, an NLR > 2.5 was a significant independent predictive factor for cancer-specific survival. With respect to patients with unresectable stage Ⅳ CRC, Chua *et al*[26] examined 349 patients with unresectable CRC who received first-line palliative chemotherapy and reported that the prognosis of patients with an NLR of > 5 was significantly worse than the prognosis of the patients with an NLR of < 5. They also reported that a high NLR resulted in a reduced response to chemotherapy and that the reduction of NLR after one cycle of chemotherapy in a subset of patients resulted in improved survival. Li *et al*[27] performed a meta-analysis of CRC patients and concluded that the NLR is an inexpensive, widely available and reproducible index that is closely associated with survival. Because a peripheral blood cell count is a quick and easy assay to perform, NLR is a useful marker for identifying patients with a poor prognosis and allows for the planning of more frequent surveillance and intensive therapy in patients with unresectable stage Ⅳ CRC.

### *Platelet-to-lymphocyte ratio*

Malignant solid tumors commonly induce a hypercoagulable state, resulting in a predisposition to thromboembolic events[41,42]. Reactive thrombocytosis is induced against a background of hypercytokinemia *via* tumor *vs* host interactions[43]. Among several inflammatory cytokines, IL-6 has an important role in the onset of reactive thrombocytosis, as it is a multifunctional cytokine with a number of physiological actions, stimulating not only CRP up-regulation but also albumin down-regulation in the liver, as well as protein synthesis[44]. Similarly, IL-6 has a cell-proliferative effect, triggering the differentiation of megakaryocytes to platelets in the bone marrow[44]. Hence, it is reasonable that reactive thrombocytosis would be associated with the survival of patients with malignant tumors.

As previously described, lymphocytopenia has shown to be associated with poor survival. Therefore, the platelet-to-lymphocyte ratio (PLR) is also thought to be a powerful prognostic factor in patients with malignant tumors. Indeed, PLR is an independent prognostic factor, in addition to other inflammation-based factors, for pancreatic ductal adenocarcinoma according to Smith *et al*[45], ovarian cancer according to Raungkaewmanee *et al*[46], and CRC accrding to Kwon *et al*[31].

### *Nutritional Prognostic Index*

The inflammatory response has been proposed to be pathogenic with respect to the development of cancer-associated malnutrition[47]. Several studies have reported that patients with advanced gastrointestinal malignancies are often malnourished, and that the preoperative nutritional status is associated with postoperative complications, tumor progression and a poor clinical outcome[48,49]. There are several assessment tools for evaluating the nutritional status, including the malnutrition universal screening tool (MUST), nutritional risk scoring 2002 (NRS2002) and mini nutritional assessment[50,51]. These tools are simple, well-validated and cost-effective and are widely utilized to assess the nutritional status of cancer patients. Onodera's Prognostic Nutritional Index (OPNI) is another such tool and a simple index that can be calculated using only two parameters, the serum albumin level and total lymphocyte count (TLC)[52]. The OPNI is calculated using the following formula: 10 × serum albumin concentration (g/dL) + 0.005 × lymphocyte count (number/mm$^2$) in the peripheral blood. Albumin is a main component of plasma proteins that preserves the colloid osmotic pressure, and its level reflects the nutritional status. The TLC has also been proposed to be a useful indicator of the nutritional, as well as host inflammatory status. Both albumin and TLC levels are routinely examined in daily clinical practice. Therefore, the OPNI, which reflects the immunonutritional status, is thought to be a useful and convenient index for predicting tumor progression and survival in patients with malignancy.

Regarding the prognosis, Nozoe *et al*[28] reported that the OPNI is significantly correlated with the prognosis of patients with CRC. The above study examined patients who underwent curative surgery. Therefore, we thought to clarify the prognostic value of the OPNI in patients with unresectable stage Ⅳ CRC[29]. Initially, we examined patients who underwent palliative resection of the primary tumor. The result revealed that a low-OPNI is an independent predictor of a worse prognosis, even in patients limited to stage Ⅳ CRC disease. In particular, the MST of the patients with a low-OPNI was 9.5 mo, which was shorter than that reported for patients with stage Ⅳ CRC treated with chemotherapy alone. Therefore, although the necessity of palliative resection in patients with asymptomatic primary tumors and unresectable stage Ⅳ CRC remains controversial, measuring the OPNI may be useful for selecting patients expected to receive a survival benefit associated with palliative resection.

It has been reported that malnutrition results in the loss of lean body mass, an impaired immune function, a reduced rate of response to chemotherapy and poor survival[53]. Therefore, we evaluated the clinical significance of the OPNI among patients with unresectable stage Ⅳ CRC treated with chemotherapy[30]. We collected data from blood tests conducted within one week prior to the start of the first-line chemotherapy and at eight weeks after the first day of chemotherapy. As a result, the overall survival of the patients with a high pretreatment OPNI was significantly ($P$ = 0.005) better than that of the patients with a low pretreatment OPNI; the MST was 37 and 22.8 mo, respectively. Moreover, when we categorized the patients into four groups according to the combination of the pre- and post-treatment OPNI values, only the group who maintained a high OPNI had a better prognosis than the other groups, and a decrease in the OPNI after chemotherapy was associated with a worse survival, even in the patients with a high pretreatment OPNI value. Therefore, it is important to maintain a good nutritional and immune status before and during treatment in patients receiving chemotherapy. It has also been reported that nutritional interventions may improve the immunonutritional system, response to chemotherapy and patient survival[54-56]. Such nutritional interventions should be implemented in order to improve the survival of patients with a low-OPNI.

## COMBINATION OF CLINICOPATHOLOGICAL AND INFLAMMATION-BASED FACTORS

The current report of inflammation-based factors is by no means exhaustive, although we wish to provide an overview of the topic in order to help guide the management of CRC patients. Both clinicopathological and inflammation-based parameters are independent powerful prognostic factors; therefore, the user of a combination of these factors may have more precise clinical, prognostic and therapeutic value compared to a single factor.

From the above point of view, Laird *et al*[17] reported that the GPS is similar to the PS in terms of prognostic power and that the combination of these factors may have a potential role in effectively predicting survival.

We investigated the correlation between clinicopathological factors, the GPS, NLR and prognosis in order to identify parameters useful for selecting stage Ⅳ CRC patients with a poor prognosis. As a result, the GPS, NLR, performance status (PS) and extent of distant metastasis were found to be independent predictors of survival[32]. We classified the patients, using a combination of four prognostic factors, into three risk groups: patients without any prognostic factors (the low-risk group), patients with one or two prognostic factors (the intermediate-risk group) and patients with three or four prognostic factors (the high-risk group). There were significant ($P$ < 0.0001) differences in the postoperative cancer specific survival rates among the three groups. The median survival time (MST) was only five months in the high-risk group, compared to 21.5 mo in the intermediate-risk group and 37 mo in the low-risk group. The MST of the high-risk group was five months, which was very short and similar

to that reported for patients with stage Ⅳ CRC who received the best supportive care without surgery or chemotherapy. Therefore, there may be no survival benefit associated with palliative resection in the high-risk group. On the other hand, relatively better survival is expected in the low-risk group. This risk classification is simple and easy to use and may be helpful for determining the optimal treatment for patients with stage Ⅳ CRC.

## CONCLUSION

Conventional clinicopathological factors are currently widely- used and important prognostic factors for patients with CRC. However, these factors are not universally helpful for predicting the prognosis in patients within the same stage of disease. Inflammation-based factors are determined based on laboratory data that are routinely recorded in the clinical setting and can be easily estimated prior to treatment.

Although clinicopathological factors reflect the tumor characteristics, cancer progression and survival are not determined solely according to the local characteristics of the tumor, but also the host systemic immune/inflammatory response. Therefore, the application of a combination of these parameters reflecting both the tumor characteristics and host systemic inflammatory status is important for predicting patient survival more precisely and selecting the optimal treatment in patients with CRC.

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CASE REPORT

# Gastric carcinoma originating from the heterotopic submucosal gastric gland treated by laparoscopy and endoscopy cooperative surgery

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## Abstract

Gastric carcinoma is derived from epithelial cells in the gastric mucosa. We reported an extremely rare case of submucosal gastric carcinoma originating from the heterotopic submucosal gastric gland (HSG) that was safely diagnosed by laparoscopy and endoscopy cooperative surgery (LECS). A 66-year-old man underwent gastrointestinal endoscopy, which detected a submucosal tumor (SMT) of 1.5 cm in diameter on the lesser-anterior wall of the upper gastric body. The tumor could not be diagnosed histologically, even by endoscopic ultrasound-guided fine-needle aspiration biopsy. Local resection by LECS was performed to confirm a diagnosis. Pathologically, the tumor was an intra-submucosal well differentiated adenocarcinoma invading 5000 μm into

the submucosal layer. The resected tumor had negative lateral and vertical margins. Based on the Japanese treatment guidelines, additional laparoscopic proximal gastrectomy was curatively performed. LECS is a less invasive and safer approach for the diagnosis of SMT, even in submucosal gastric carcinoma originating from the HSG.

**Key words:** Heterotopic submucosal gland; Laparoscopy and endoscopy cooperative surgery; Gastric carcinoma; Gastric submucosal tumor; Less invasive treatment



**Core tip:** This report describes the rare case of a submucosal gastric carcinoma originating from the heterotopic submucosal gastric gland (HSG) that was safely diagnosed by laparoscopy and endoscopy cooperative surgery (LECS). LECS is a less invasive and safer approach for the diagnosis of submucosal tumor, even in submucosal gastric carcinoma originating from the HSG.

Imamura T, Komatsu S, Ichikawa D, Kobayashi H, Miyamae M, Hirajima S, Kawaguchi T, Kubota T, Kosuga T, Okamoto K, Konishi H, Shiozaki A, Fujiwara H, Ogiso K, Yagi N, Yanagisawa A, Ando T, Otsuji E. Gastric carcinoma originating from the heterotopic submucosal gastric gland treated by laparoscopy and endoscopy cooperative surgery. *World J Gastrointest Oncol* 2015; 7(8): 118-122 Available from: URL: http://www.wjgnet.com/1948-5204/full/v7/i8/118.htm DOI: http://dx.doi.org/10.4251/wjgo.v7.i8.118

## INTRODUCTION

Gastric carcinoma is commonly derived from epithelial cells in the gastric mucosa and is very rarely initially diagnosed as a submucosal tumor (SMT). We herein presented a case of submucosal gastric carcinoma originating from the heterotopic submucosal gastric gland (HSG) that was safely diagnosed by laparoscopy and endoscopy cooperative surgery (LECS) and treated by subsequent laparoscopic gastrectomy with D1+ lymphadenectomy. We reviewed the clinical features of this rare tumor and selected successful decision-making using the LECS technique.

## CASE REPORT

### *Patient*

The patient was a 66-year-old man who underwent upper endoscopy in a medical checkup, which showed a SMT on the upper gastric body. The patient was referred to the hospital for diagnosis and treatment. Endoscopic re-examination detected a SMT of 15 mm in diameter on the anterior wall of the upper gastric body. The tumor did not have a depression or ulceration (Figure 1A). The results of endoscopic biopsy from the gastric mucosa on the tumor were chronic gastritis with no evidence of malignancy. Barium gastrography showed a smooth elevated lesion of 2 cm in diameter on the anterior wall of the upper gastric body near the esophago-gastric junction (Figure 1B). Computed tomography revealed a 15-mm low density area with calcification in the anterior wall of the upper gastric body and no lymph node or distant metastasis (Figure 1C). Endoscopic ultrasound (EUS) showed an 11.2 mm × 13.5 mm SMT that was derived from the third layer of the gastric wall as a heterogeneous lesion with a mixture of a high echoic lesion, low echoic lesion, and calcification (Figure 1D). The tumor could not be diagnosed histologically, even by EUS-guided fine-needle aspiration biopsy at multiple sites. LECS for gastric local resection was selected as decision-making for a pathological diagnosis and safe removal.

### *LECS for the SMT*

Observations in the abdominal cavity by laparoscopy confirmed no distant or nodal metastasis. The SMT was endoscopically detected on the anterior wall of the lesser curvature of the upper gastric body, but not by laparoscopy. To avoid bleeding, the peripheral branches of the left gastric artery near the tumor were coagulated using a laparoscopic ultrasonically activated device. Endoscopic submucosal resection around the tumor was performed using the endoscopic submucosal dissection technique and seromuscular dissection was performed around the tumor along the line of submucosal resection. The incisional line in the stomach was closed using a laparoscopic stapling device. The resected tumor had negative lateral and vertical margins with normal mucosa (Figure 2A). A pathological examination confirmed that the tumor was a SMT that invaded 5000 μm into the submucosal layer, measured 20 mm × 11 mm × 6 mm, and was a well differentiated adenocarcinoma (Figure 2B). Dilated gastric glands were detected in the submucosal layer (Figure 2C). There was no lymphovascular invasion. Immunohistochemical staining revealed the positive expression of MUC5AC and MUC6, indicating differentiation into the pyloric glands (Figure 2D).

Eighty-four days after LECS, additional laparoscopic proximal gastrectomy with D1+ lymphadenectomy was performed based on the Japanese Gastric Cancer Treatment Guidelines[1]. A pathological examination confirmed no residual tumor cells or lymph node metastasis. The postoperative course was uneventful and the patient is alive without recurrence 1 year after surgery.

## DISCUSSION

HSG shows that cystic dilated gastric glands exist in the gastric submucosal layer and has been recognized as a benign condition occurring as a result of repeated mucosal damage[2,3]. HSG was previously described

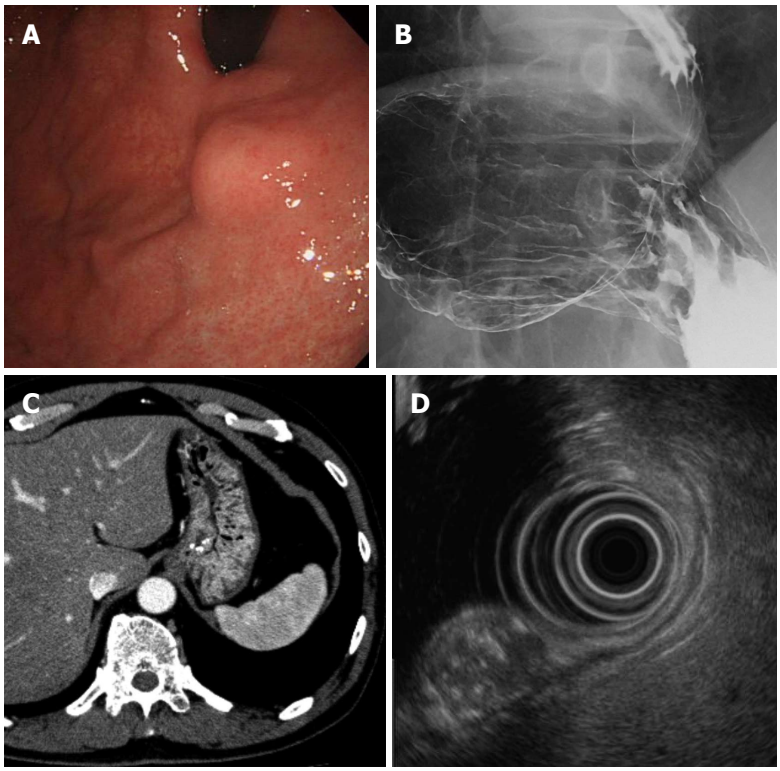


**Figure 1 Results of pre-operative examinations.** A: Endoscopic findings showing a submucosal lesion of 15 mm in diameter on the anterior wall of the upper gastric body near the esophago-gastric junction. The surface was covered with normal gastric mucosa; B: Barium gastrography showed a smooth elevated lesion of 2 cm in diameter on the anterior wall of the upper gastric body near the esophago-gastric junction; C: Computed tomography revealed a 15-mm submucosal low density area with calcification in the anterior wall of the upper gastric body. No lymph node or distant metastasis was detected; D: Endoscopic ultrasound showed an 11.2 mm × 13.5 mm submucosal tumor derived from the third layer of the gastric wall as a heterogeneous lesion with a mixture of a high echoic lesion, low echoic lesion, and calcification.

**Table 1 Previous case reports of gastric carcinoma originating from the heterotopic submucosal gastric gland**

| Total number of reported cases | | *n* 17 | (%) |
|---|---|---|---|
| Age | | 64.1 (45-81) | |
| Sex | Male | 11 | 65 |
| | Female | 6 | 35 |
| Location | Upper | 4 | 24 |
| | Middle | 8 | 47 |
| | Lower | 5 | 29 |
| Size (mm) | | 20.5 (8-50) | |
| Ulceration or depression | Present | 13 | 76 |
| | Absent | 4 | 24 |
| Histological type | Well differentiated | 16 | 94 |
| | Unknown | 1 | 6 |
| Depth of invasion | m | 1 | 6 |
| | sm | 14 | 82 |
| | T2 or more | 2 | 12 |
| Diagnosis by biopsy | Present | 6 | 35 |
| | Absent | 11 | 35 |
| EUS-FNA | Present | 2 | 12 |
| | Absent | 15 | 88 |
| Treatment | EMR | 1 | 6 |
| | EMR and surgical resection | 3 | 18 |
| | Surgical resection | 12 | 71 |
| | LECS + surgical resection | 1 | 6 |

EUS-FNA: Endoscopic ultrasound-guided fine-needle aspiration biopsy; EMR: Endoscopic mucosal resection; LECS: Laparoscopy and endoscopy cooperative surgery. Note: Ref. [2,6-18].

as a para-cancerous lesion found in 4% of resected specimen from the stomachs of patients with gastric carcinoma, and multiple cancers have been detected in 30% of specimens of gastric carcinoma associated with HSG[4]. However, little is known about the carcinogenesis of HSG itself. Kim *et al*[5] described two cases of early gastric carcinoma arising from HSG that were treated by laparoscopic gastric wedge resection. To the best of our knowledge, there have been no other studies in English concerning gastric carcinoma originating from HSG.

Table 1 shows a summary of 17 previously reported cases, including cases in Japan and our case. Gastric carcinoma originating from HSG occurred more frequently in males and in the middle area of the stomach. Regarding histological findings, the well differentiated type was more common. A study has not yet been conducted on lymph node metastasis from gastric carcinoma originating from HSG. This summary showed that more than 65% of patients could not be histologically diagnosed by biopsy and FNA using EUS before resection.

The recent development of endoscopic and laparoscopic techniques has allowed for less invasive diagnoses and treatments. LECS is a novel and excellent approach for local gastric resection, and was developed by Hiki *et al*[19] as an alternative strategy to laparoscopic wedge resection for gastric SMT. The feasibility and safety of this procedure for gastric SMT have been demonstrated

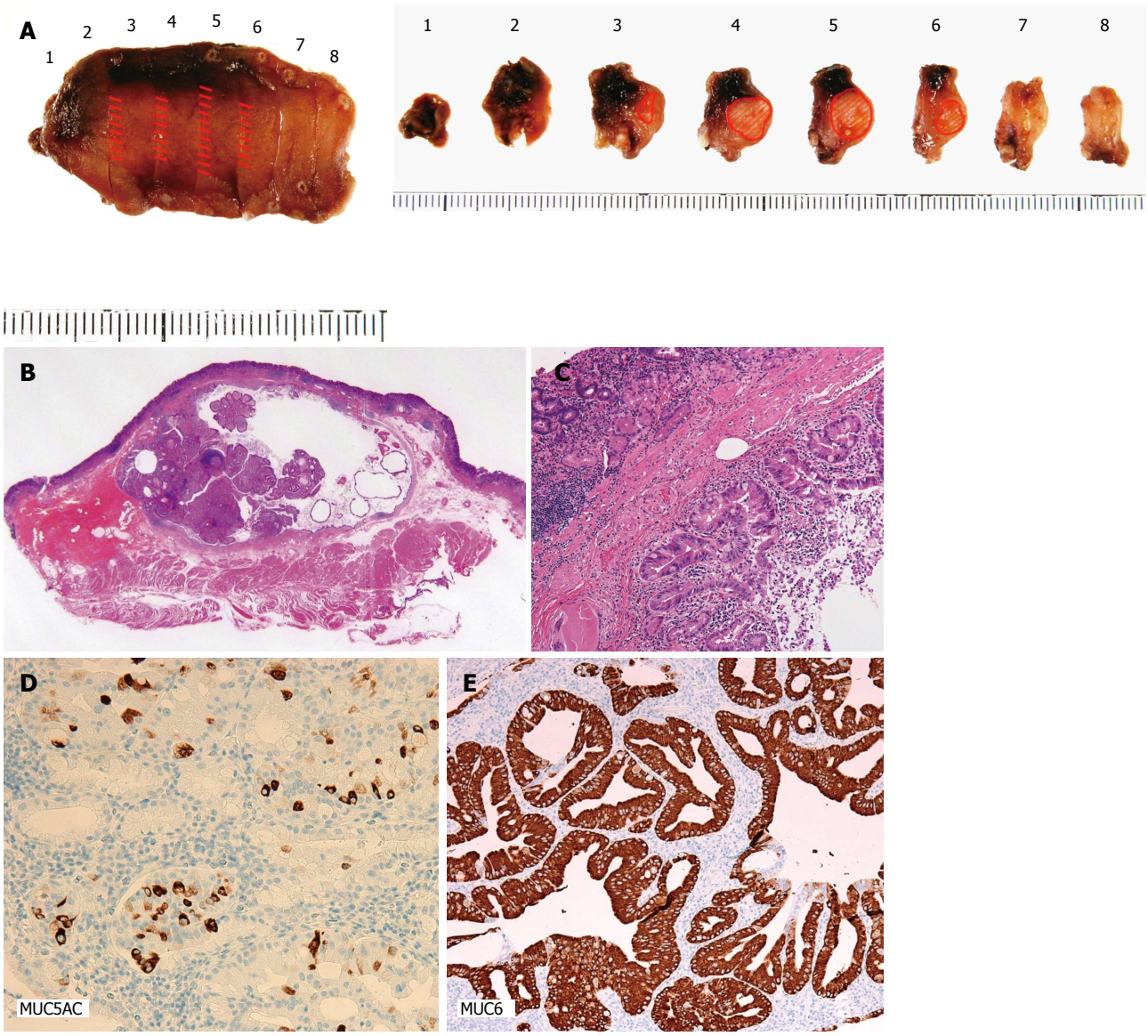


**Figure 2 Results of histopathological examinations.** A: The resected specimen had negative lateral and vertical margins with normal mucosa; B: A pathological examination confirmed that the tumor was intrasubmucosal (the depth of invasion into the submucosal layer was 5000 μm), measured 20 mm × 11 mm × 6 mm, and was a well differentiated adenocarcinoma; C: Dilated gastric glands were found in the submucosal layer. There was no lymphovascular invasion; D: An immunostaining method showed MUC5AC (+) and MUC6 (+), indicating differentiation into the pyloric glands.

in several studies[20-22]. LECS is now being applied to the treatment of early gastric cancer[23]. The most critical issue associated with its application to gastric cancer is the dissemination of cancer cells into the peritoneal cavity during surgery. Therefore, several methods have been investigated for LECS[24-26]. LECS is a promising approach for the diagnosis of SMT, even in gastric carcinoma originating from HSG.

## COMMENTS

### *Case characteristics*

A 66-year-old man who underwent upper endoscopy in a medical checkup, which showed a submucosal tumor (SMT) on the upper gastric body.

### *Clinical diagnosis*

The presented patients had submucosal gastric tumor that could not be diagnosed histologically by endoscopic biopsy.

### *Differential diagnosis*

**G**astrointestinal stromal tumor, early gastric tumor, smooth muscle tumor.

### *Laboratory diagnosis*

There were no abnormal findings in laboratory examinations including tumor markers.

### *Imaging diagnosis*

Endoscopic ultrasound and computed tomography showed that the tumor was derived from the third layer of the gastric wall.

### *Pathological diagnosis*

Pathological examination confirmed that the tumor was an intra submucosal tumor that was a well differentiated adenocarcinoma.

### *Treatment*

Laparoscopy and endoscopy cooperative surgery (LECS) for gastric local resection was selected as decision-making for a pathological diagnosis and safe removal.

### *Term explanation*

LECS: Laparoscopy and endoscopy cooperative surgery; HSG: Heterotopic submucosal gastric gland.

### *Experiences and lessons*

Gastric carcinoma originating from the HSG forms a submucosal gastric tumor and is often difficult to diagnose by endoscopic biopsy. If unable to deny malignant disease, resection of the tumor should be considered.

### *Peer-review*

This manuscript described a rare case of submucosal gastric carcinoma originating from the HSG and the authors also described the treatment of the carcinoma by LECS.

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CASE REPORT

# Esophageal granular cell tumors: Case report and literature review

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## Abstract

We reported 5 cases of granular cell tumors (GCTs) of esophagus and reviewed the literature. There were 4 females and 1 male with a median age of 43 years and an average age of 44 years. All of the cases had solitary tumors. Tumor size was 0.4-2.5 cm in diameter. Gastroscopy revealed that 2 cases were located in the middle esophagus, 1 case in the upper esophagus, and 2 cases in the distal one. Five cases displayed gray-white, pink, yellow mucosal uplifts of esophagus, 3 cases had smooth surface, 1 case was slightly concave, and the biggest tumor had erosion. Tumor cells were large and polygonal with rich granular and eosinophilic cytoplasm, and small oval nuclei. Cells were arranged in nest or aciniform. Immunohistochemistry and histochemistry staining showed S-100+, neuron specific enolase+, Vim+, CD68+, smooth muscle actin-, Des-, CK-, CD117-, CD34-, Ki67-or $\leqslant$ 5%+. Periodic acid-Schiff reaction and epithelial membrane antigen were both weakly positive. GCTs of esophagus are rare and most of the cases have good prognosis.

**Key words:** Immunohistochemistry; Granular cell tumors of esophagus; Gastroscope examination



**Core tip:** Granular cell tumors (GCTs) of esophagus are rare and most of the cases have good prognosis. We reported 5 cases of GCTs of esophagus and reviewed the literature. The report is helpful in comprehensively understanding the characteristics of GCTs and guiding the treatment of this disease.

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## INTRODUCTION

Granular cell tumors (GCTs) of the esophagus are rare and mostly isolated lesions, usually accidentally discovered by annual endoscopic examination[1,2]. Reports of esophageal GCTs have increased with socioeconomic development and improvement of medical technology in recent years. To explore the clinicopathological characteristics of esophageal GCTs, we reported five cases of esophageal GCTs, including four from the Third People's Hospital of Hefei and one from the Chinese People's Liberation Army General Hospital between 2012 and 2014. The study was approved by the Research Ethics Committee of the Third People's Hospital of Hefei and the Chinese People's Liberation Army General Hospital in China, and consent was obtained from all patients who were enrolled in the study.

## CASE REPORT

Some clinicopathological data are shown in Table 1. Case 1 had intermittent heartburn for 3 mo. The patient was diagnosed with superficial gastritis (active phase). She had hepatitis B for > 20 years. Case 2 was accidentally found through physical examination 3 mo ago. Case 3 had dysphagia for approximately 3 mo. Clinicians' first impression was stromal tumor. Case 4 had slight pain behind the sternum for 6 mo. Clinical diagnosis was chronic gastritis with erosion, gastric polyps, and xanthoma of the esophagus. Case 5 complained of acid reflux for 1 mo, with intermittent abdominal distension and belching. Endoscopic ultrasonography revealed a low-echo lesion in the submucosa of the distal esophagus, with integrity of the muscularis propria. Clinicians' first impression was GCT. The patient also had diabetes.

All cases underwent successful endoscopic mucosal resection without complications, using endoscopic electrosurgical snare resection. The lesions were found by gastroscopy and the size, color, topography and peripheral tissue were observed. The motion and position of the lesion were assessed with biopsy forceps. If the lesion was located in the mucosa and submucosa, and $\leqslant$ 3 cm in diameter, trap resection could be used. This involved fixing the position of the tumor by gastroscopy, focusing on the base of the tumor with a snare trap, tightening the snare, cutting the tumor with an electrotome, and stemming the bleeding. Finally the specimen was sent for pathological examination.

Under light microscopy, the tumor was located under the mucosal squamous epithelial basement membrane. The tumor cells were large and polygonal. The cytoplasm was granular and eosinophilic. The nuclei were small, ovoid or slightly irregular with fine chromatin, and some were deviated. Small nucleoli were visible in some cells (Figure 2). Small crack-like blood vessels were observed. In Case 3, a few lymphocytes infiltrated the stroma, and lymph follicles were formed around the tumor. In Case 4, the tumor was located between the mucosal squamous epithelial basement membrane and the submucosa. The polygonal cells were arranged in an aciniform manner. Immunohistochemical and histochemical staining are shown in Table 2 and Figure 3.

The above five cases were all diagnosed with esophageal GCT. Four patients had no recurrence during follow-up of 7-33 mo. One patient was lost to follow-up.

## DISCUSSION

GCTs in the esophagus are rare, however, the study of rare diseases has repeatedly led to breakthroughs in our understanding of more common diseases. GCTs in the esophagus mainly occur in the middle age. Most tumors are solitary and benign, and located in the middle and lower esophagus[1-7]. In the present study, There were four women and one man, with a median age of 43 years and average age of 44 years. All of our cases had solitary GCTs. Tumor diameter ranged from 0.4 to 2.5 cm. Two cases were located in the middle esophagus, one in the upper esophagus, and two in the lower esophagus.

The tumors were mostly located in the mucosa and submucosa, and only a few invaded into the muscular layer. The tumor cells were large and appeared polygonal. The cytoplasm was granular and eosinophilic. The cell nuclei were ovoid with fine chromatin and no mitotic figures. The cells were arranged in nest or acinar form[1-6].

GCTs are commonly identified as nonspecific painless masses. Patients with small tumors are often asymptomatic[1,2], and the emergence of clinical symptoms is related to tumor size. When the tumor diameter is > 1 cm, patients may experience dysphagia[1]. Esophageal lesions are often found by chance through gastroscopic examination[1,2,3,6]. Patient complaints are mostly abdominal distension, acid reflux, belching, and loss of appetite[3]. In our study, the patients complained of intermittent heartburn, dysphagia, acid reflux with intermittent abdominal distension and belching, and slight pain behind the sternum. GCT in Case 2 was accidentally found through physical examination.

The color of the tumor surface is usually white-gray, pink or yellow. The tumors show polypoid or nodular uplift without pedicles, and most have a smooth surface[2,6,8]. In the five cases described in this report, the tumors were gray-white, pink or yellow, with mucosal uplifts of the esophagus under gastroscopy. Three cases had a smooth mucous surface, one had slight concavity, and the largest tumor had erosion.

By EUS, GCTs are often located in the mucosal layer or submucosa, as round or circle-like masses, hypoechoic and homogeneous lesions, with clear borders. A few GCTs invade the muscular layer. In EUS images, average grayscale values of GCTs are greater than those of esophageal leiomyoma, which can help with differential diagnosis and improve the accuracy of EUS for the diagnosis of esophageal GCTs[2-4,9]. In the present Case 5, EUS showed a low-echo lesion in the submucosa, with

**Table 1 Clinicopathological data of five cases of granular cell tumor**

| Case | Gender | Age (yr) | Esophageal location | Diameter (cm) | Color and quality | Surface |
|---|---|---|---|---|---|---|
| 1 | Female | 43 | Middle | 0.5 | Gray-white | Smooth |
| 2 | Female | 32 | Middle | 0.4 | Gray-white | Smooth |
| 3 | Male | 47 | Distal | 2.5 | Gray-white and pink, fine quality | Erosion |
| 4 | Female | 42 | Upper | 0.6 | Grayish yellow (Figure 1) | Smooth |
| 5 | Female | 56 | Distal | 0.8 | Yellow | Slightly concave |

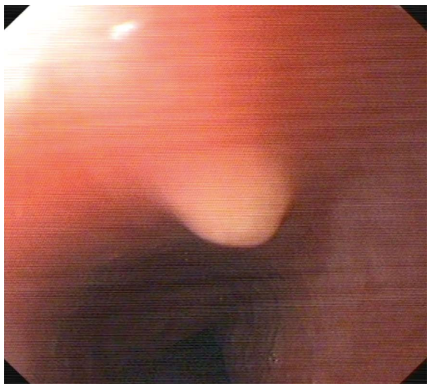

**Figure 1 A grayish-yellow uplift was seen in the esophagus 18 cm from the incisor with smooth surface under endoscope in Case 4.**

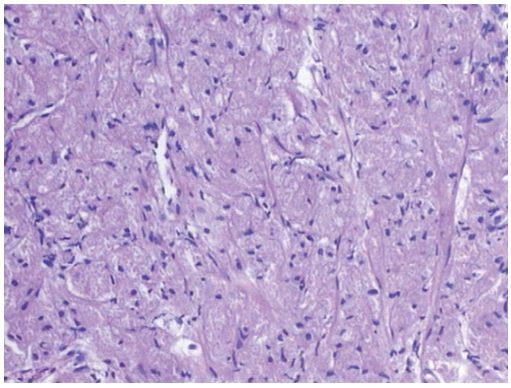

**Figure 2 The tumor cells were large and polygonal with granular and eosinophilic cytoplasm, and small oval nuclei.** Hematoxylin and eosin staining, × 100.

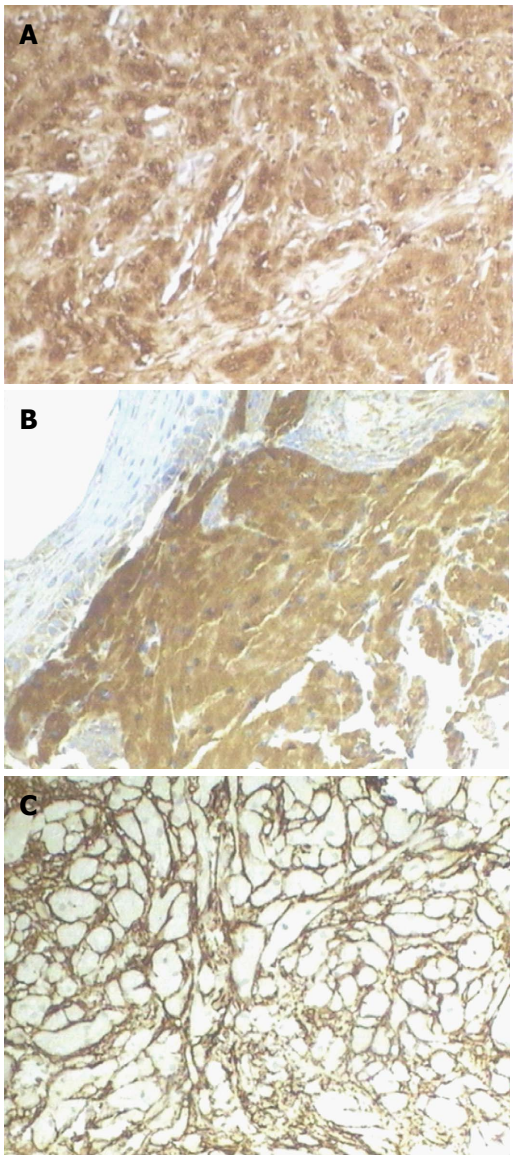


**Figure 3 Immunohistochemical and histochemical staining.** Envision method, × 100. A: S-100 was strongly positive in tumor cells; B: CD68 was strongly positive in tumor cells; C: CD34 was negative in tumor cells, but the surrounding mesenchymal cells were positive for CD34.

no violation of the muscularis propria layer, which was similar to previously described cases. Palazzo *et al*[10] found that GCTs had three characteristics: (1) tumor size < 2 cm in 95% of cases; (2) a hypoechoic solid pattern in all cases; and (3) a tumor arising in the inner layers in 95% of cases[10].

Immunohistochemical and histochemical staining was positive for S-100, CD68, neuron speoific enolase (NSE) and vimentin. Periodic acid-Schiff (PAS) and epithelial membrane antigen staining was weakly positive. Staining was negative for cytokeratin, desmin, smooth muscle actin (SMA) and CD34 (although surrounding mesenchymal cells were positive for CD34). This was most in accordance with the literature[2,3,6,11].

Differential diagnosis includes the following tumors: (1) Gastrointestinal stromal tumors (GISTs). GISTs are usually located in the submucosa, and are rare in the esophagus. The tumor cells are spindle-shaped or round and arranged in fasciculus, weave or whirlpool shape. Immunohistochemical staining is positive for CD117 and CD34[12]; (2) Leiomyoma. Leiomyoma is composed of moderate spindle cells with eosinophilic cytoplasm. The spindle cells are arranged in beam and/or weave

**Table 2 Immunohistochemical and histochemical staining of five cases of granular cell tumor**

| Case | S-100 | NSE | Vim | CD68 | Des | SMA | CK | Ki-67 | CD117 | CD34[a] | EMA | PAS | Dog-1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | + | + | + | + | - | - | - | - | None[b] | None | None | Weak+ | None |
| 2 | + | + | + | + | None | - | - | - | - | - | Weak+ | Weak+ | None |
| 3 | + | + | + | + | - | - | - | 2%+ | - | - | None | Weak+ | - |
| 4 | + | + | + | + | None | None | - | None | None | None | Weak+ | Weak+ | None |
| 5 | + | + | + | + | None | - | - | 5%+ | - | - | None | Weak+ | - |

[a]Surrounding mesenchymal cells were positive for CD34; [b]None means the tissue was too small, and immunohistochemical staining was not possible. CK: Cytokeratin; Des: Desmin; EMA: Epithelial membrane antigen; Vim: Vimentin; NSE: Neuron speoific enolase; SMA: Smooth muscle actin; PAS: Periodic acid-Schiff.

pattern. The nuclei are rod-shaped or cigar-shaped. Immunohistochemical staining is positive for SMA and desmin, and negative for CD34 and CD117. Average grayscale values of esophageal leiomyoma are lower than those of GCTs; (3) Schwannoma and neurofibroma. Schwannoma has a complete capsule. The tumor cells are spindle-shaped or stellate. Typical schwannoma has two kinds of histological structure under microscope: pyknotic Antoni type A and loose Antoni type B. Neurofibroma is composed of thin and long spindle cells with wavy shape and pale cytoplasm. Negative staining for CD68 helps with differential diagnosis; and (4) Xanthoma. Cells are round or polygonal with pale cytoplasm. The nuclei are round, small and moderate, and usually located in the center of the cells. Cells are located in the mucosal lamina propria. Xanthoma usually occurs in the stomach. Cells have a lack of granular cytoplasm, and stain positive for CD68 and negative for PAS.

Benign and malignant GCTs have similar histopathology, and there are no clear histological diagnostic criteria for benign and malignant tumors. The following are suggestive of malignant GCT: rapid tumor growth, > 5 cm in diameter and karyokinesis in > 2/10 high-power fields; tumor cells are spindle shaped, with vesicular nuclei and nucleoli; high ratio of nucleus to cytoplasm with cellular pleomorphism; and tumor tissue necrosis[13]. One study found that > 50% p53-positive cells and > 10% Ki-67 positive cells were significantly correlated with malignancy[13].

In recent years, most investigators have thought that GCT is related to peripheral nerve tissue. Some studies have found that tumor cells are surrounded by nerve bundles, and there is a transition phenomenon from Schwann cells to tumor cells. Immunohistochemistry and ultrastructural analysis show the differentiation of Schwann cells. All the present cases were strongly positive for S-100 and NSE, which suggested the neurogenic origin of GCTs.

Narra *et al*[8] showed that treatment options include endoscopic surveillance, endoscopic resection, and surgery. According to EUS, 11 cases with lesions ≤ 3 cm in diameter without muscular layer invasion underwent endoscopic resection without complications, and another three cases underwent surgical resection[9]. A new technique of submucosal tunnel endoscopic resection was performed in three submucosal cases with lesions ranging from 2 to 3 cm in diameter[9]. The chief complications of gastrointestinal submucosal endoscopic resection are bleeding and perforation[14].

The prognosis of esophageal GCT is good, and recurrence and metastasis are uncommon. Many studies have shown no recurrence and metastasis during follow-up[1,3,8].

## COMMENTS

### *Cases characteristics*

Case 1, a 43-year-old woman with intermittent heartburn for 3 mo. Case 2, a 32-year-old woman was accidentally found through physical examination 3 mo ago. Case 3, a 47-year-old man with dysphagia for about 3 mo. Case 4, a 42-year-old woman with slight pain behind the sternum for 6 mo. Case 5, a 56-year-old woman with acid reflux for 1 mo, with intermittent abdominal distension and belching.

### *Clinical diagnosis*

Case 1, superficial gastritis (active phase); Case 2, middle esophageal apophysis; Case 3, first impression was stromal tumor; Case 4, chronic gastritis with erosion, gastric polyps, and xanthoma of the esophagus; Case 5, first impression was esophageal granular cell tumor (GCT).

### *Differential diagnosis*

Gastrointestinal stromal tumor, leiomyoma, schwannoma and neurofibroma, xanthoma.

### *Laboratory diagnosis*

Case 1 had hepatitis B for > 20 years.

### *Imaging diagnosis*

In Case 5, endoscopic ultrasonography revealed a low-echo lesion in the submucosa of the distal esophagus, with integrity of the muscularis propria.

### *Pathological diagnosis*

Five cases were all diagnosed with esophageal GCTs.

### *Treatment*

All five cases underwent successful endoscopic mucosal resection without complications.

### *Term explanation*

GCTs of the esophagus are rare benign tumors.

### *Experiences and lessons*

The prognosis of esophageal GCTs is good, and recurrence and metastasis are rare.

### *Peer-review*

This is an interesting article on the rare tumor of esophagus. The experiments are well designed and described in detail.

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