

# Application of Regional Arterial Infusion Chemotherapy in Advanced Gastric Cancer

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**How to cite this paper:** Xu, H., Wang, W.C., Zhang, X.M., Zhou, Y., Zheng, J., Yang, C. and Yang, L. (2018) Application of Regional Arterial Infusion Chemotherapy in Advanced Gastric Cancer. *Journal of Cancer Therapy*, 9, 118-129.  
<https://doi.org/10.4236/jct.2018.92013>

**Received:** December 31, 2017

**Accepted:** February 8, 2018

**Published:** February 11, 2018

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## Abstract

Gastric cancer ranks as the fifth most common malignant tumor worldwide and is the third most common cause of cancer-related death. For advanced gastric cancer (AGC), neoadjuvant chemotherapy (NAC) can reduce its stage, increase the rate of radical resection, improve response to treatment, reduce the risk of local recurrence and improve survival rate. Regional arterial infusion chemotherapy (RAIC) is a form of NAC that involves directly injecting chemotherapeutic drugs into the tumor site through the tumor-feeding artery. RAIC increases the local drug concentration around the tumor, thereby improving the therapeutic responses and reducing the adverse effects of the drugs. In recent years, RAIC has attracted increasing attention. This article summarizes the basic principles, procedure, chemotherapy regimens, adverse drug reactions and complications, clinical applications and response evaluation of RAIC in the treatment of AGC.

## Keywords

Gastric Cancer, Neoadjuvant Chemotherapy, Regional Arterial Infusion Chemotherapy

## 1. Introduction

Gastric cancer ranks as the fifth most common malignant tumor worldwide and is the third most common cause of cancer-related death [1]. Currently, surgical resection is still considered the only cure for gastric cancer. However, the symptoms of gastric cancer are not obvious. Most gastric cancers are diagnosed in the late-stage, when surgical treatments are not available options. Neoadjuvant chemotherapy (NAC) improves the rate of radical resection and long-term survival

by reducing tumor stage [2]. Regional arterial infusion chemotherapy (RAIC) is a method of injecting chemotherapeutic drugs directly into the tumor tissue through a tumor-feeding artery to increase the concentration of the chemotherapy drug at the tumor lesion. RAIC improves the curative effect and reduces the adverse effects of chemotherapy drugs. In recent years, RAIC has attracted increasing attention [3]-[9]. This article summarizes the basic principles, procedure, chemotherapy regimens, adverse drug reactions and complications, clinical applications and response evaluation of RAIC in the treatment of AGC.

## 2. Basic Principles of RAIC

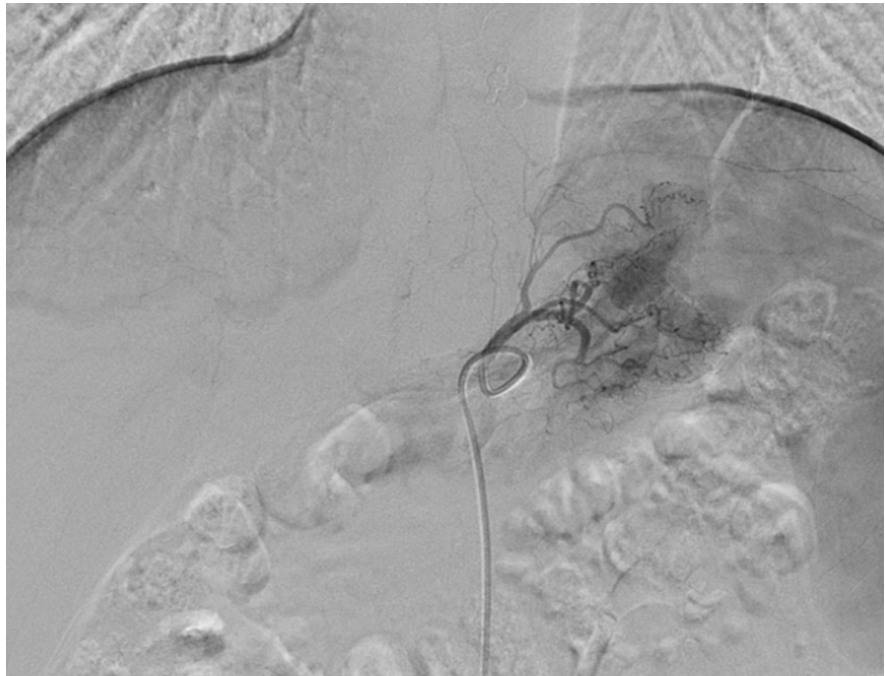
The efficacy of chemotherapy drugs is not only related to their pharmacological effects and the sensitivity of the lesion to the drugs but also drug concentration and the time of drug contact with the lesion at a suitable concentration. In conventional systemic chemotherapy, a drug flows through the superior vena cava or inferior vena cava and refluxes to the right side of the heart. After pulmonary circulation, the drug is pumped out from the left heart and distributed to the body (including lesions of the target organ). In this process, the drug is diluted in the blood. The drug concentration at the target organ is the same as the drug concentration in the peripheral plasma. Distribution of the drug to the target organ drug mainly depends on the amount of blood flow passing through the target organ. A method to increase drug concentration at the target organ is to increase the drug dose. Drug dose and peripheral plasma concentrations are associated with toxic adverse effects of the drug.

RAIC involves directly delivering chemotherapy drug to the tumor through a tumor-feeding artery. The method not only increases the local concentration of the chemotherapy drug in the tumor but also extends the time of the drug contact with the lesions by various means. Therefore, compared with systemic chemotherapy through the peripheral vein, RAIC can improve the curative effect and can reduce the adverse effects of drugs [6] [10].

## 3. RAIC Procedure

The Seldinger technique is commonly used to puncture the right femoral artery. An angiographic catheter is placed in the celiac artery for digital subtraction angiography. A tumor-feeding artery (left gastric artery, right gastric artery, left gastroepiploic artery, right gastroepiploic artery, or gastroduodenal artery) is identified. Then, the tumor-feeding artery is subject to ultra-selective intubation and angiography. Once a clear range of lesions, blood supply, and other conditions are determined, chemotherapy drugs are slowly injected (**Figure 1**).

Puncturing the femoral artery is a convenient operation with a high success rate. The method is mainly used for short-term RAIC. Puncturing the axillary and subclavian arteries requires a relatively more complex technique. Because these types of punctures affect the activities of the patients, they are mainly used for long-term, intermittent chemotherapy (implantable port system) to avoid repeated punctures [11] [12].



**Figure 1.** Thirty-year-old female patient with advanced gastric cancer. Digital subtraction angiography via the left gastric artery reveals the tumor vasculature.

#### 4. Chemotherapy Regimens

When performing RAIC, physicians should choose concentration-dependent and tumor-sensitive drugs, use drugs of different mechanisms of action in combination, and avoid drugs with similar toxicity or cumulative toxicity to a same organ. Common clinical chemotherapy drugs include cisplatin, oxaliplatin, mitomycin, adriamycin, epirubicin, docetaxel, raltitrexed, and fluorouracil. There is currently no standard RAIC chemotherapy regimen, and physicians generally use drugs employed for systemic intravenous NAC. Commonly used chemotherapy regimens are shown in the following table (**Table 1**).

Treatment regimens vary from region to region. Among these regimens, those based on fluorouracil and platinum are very important [13] [14]. The dose of chemotherapeutic drug for RAIC is generally decided based on that of systemic chemotherapy and is adjusted according to the patient's body surface area and disease condition.

#### 5. Adverse Drug Reactions and Complications

With the administration of RAIC, chemotherapy drugs will also reach the entire body through the blood circulation and act as systemic chemotherapy [3] [7] [9] [15]. The adverse drug reactions of RAIC are similar to those of systemic chemotherapy but to a lesser extent [7]. The major toxicity was bone marrow suppression; other side effects included appetite loss, nausea and vomiting [9]. Most bone marrow toxicities, appetite loss, nausea and vomiting were acceptable. Complications related to arterial puncture and intubation include hematoma at

**Table 1.** Commonly used chemotherapy regimens.

Regimen	Drug composition
FAM regimen	Fluorouracil, adriamycin, mitomycin
DCF regimen	Docetaxel, cisplatin, fluorouracil
ECF regimen	Epirubicin, cisplatin, fluorouracil
FCA regimen	Fluorouracil, cisplatin, adriamycin
FCM regimen	Fluorouracil, cisplatin, mitomycin
EOX regimen	Epirubicin, oxaliplatin, capecitabine
FOLFOX regimen	Folinic acid, fluorouracil, oxaliplatin
SOX regimen	S-1, oxaliplatin

the puncture site, arterial thrombosis, artery dissection, pseudoaneurysm, and arteriovenous fistula [16] [17] [18] [19]. Methods to avoid these complications include mastering the puncture technique, avoiding repeated punctures, choosing fine and soft guide wires and catheters, standardizing the intubation operation, and paying postoperative attention to oppression hemostasis. Hematoma at the site of femoral artery puncture represents the most common complication. Most of these hematomas can be self-absorbed. Pelvic hematoma caused by an overly high puncture point or retroperitoneal hematoma often results in a large amount of blood loss. Once diagnosed, the patient should immediately receive transfusion and anti-bleeding treatments, and if necessary, surgical repair. Femoral artery thrombosis is also a common complication of femoral artery puncture. Once diagnosed, the patient should immediately receive anticoagulation and thrombolytic treatments. Patients who have femoral artery pseudoaneurysm and arteriovenous fistula and do not effectively respond to compression method should receive prompt surgical repair.

As for any drug, iodine-based contrast agents can cause adverse events [20] [21] [22] [23]. Mild adverse effects of the contrasting agent include vomiting and rash. If necessary, the patient should receive injection of antihistamines or dexamethasone. Short-term symptoms are often reduced or disappear. Severe reactions manifest as dyspnea, tracheal spasm and shock. Patients should immediately receive adrenaline, oxygen inhalation and other treatments [20] [21] [22] [23]. For patients with impaired renal function, the physician should pay attention to contrast agent selection, dose control, and preoperative and postoperative hydration.

Vasovagal reflexes [24] manifest as a sudden drop in blood pressure, reduced heart rate, paleness, sweating, slow breathing, and disturbance of consciousness when the arterial sheath is removed. Once these symptoms occurred, emergency measures should be initiated, including maintaining the patient in the supine position, rapidly replenishing isotonic saline, and intravenous injection of atropine and dopamine.

## 6. Clinical Applications

### 6.1. Preoperative Chemotherapy

The concept of NAC was proposed in 1982 [25]. Wilke *et al.* [15] reported the use of NAC in gastric cancer in 1989. In their study, when NAC was administered to 34 patients with unresectable AGCs, 33 patients exhibited reduced AGC stages and successfully underwent radical gastrectomy and lymph node clearance. The median survival time for all patients was 18 months, and the median disease-free survival time for all patients was 24 months. Subsequent studies have obtained similar results [4] [26] [27].

Given that neoadjuvant RAIC can improve the curative effect and reduce the adverse effects of chemotherapy drugs, it has received increasing attention in recent years. Studies have demonstrated that treating well defined AGCs with neoadjuvant RAIC can effectively reduce the AGC stage, improve the rate of radical resection, increase treatment response, and prolong survival [4] [28] [29] [30]. Tao *et al.* [29] studied the effects of preoperative RAIC in inducing apoptosis and inhibiting the growth of gastric cancer cells. A total of 110 cases of GC and 68 cases of metastatic lymph nodes with or without RAIC were adopted. The apoptotic index in the RAIC treatment group was significantly increased compared with the untreated group, whereas the proliferation index in the RAIC treatment group was significantly reduced compared with the untreated group. A postoperative survey demonstrated that the 5-year survival rate of GC patients in the RAIC group was significantly increased compared with the untreated group. Wu *et al.* [7] analyzed 178 AGCs receiving short-term neoadjuvant EOX chemotherapy. The postoperative pathological response rate was 46.1%, and the complete remission rate was 2.2%. Pathological response and tumor differentiation are significantly correlated with the modes of chemotherapy administration (intravenous and arterial regional perfusion chemotherapy). The 3-year overall survival (OS) and recurrence-free survival (RFS) rates were 67% and 53%, respectively. Compared with the intravenous chemotherapy group, the RAIC group exhibited a better median RFS. In a study by He *et al.* [31], 47 AGC patients with para-aortic lymph node metastasis (PALM) received NAC. Forty-six patients completed 2 cycles of NAC. The total effective rate of NAC on primary tumors was 80.4% (37/46). The response rate of the para-aortic lymph node (PAL) was 76.1% (35/46). Thirty-two patients completed D2 radical surgery. Six patients achieved complete remission. The toxicity profile was well tolerable. No treatment-related deaths were noted. The median survival time of all patients was 23 months. The median survival time of patients in the nonsurgical and surgical groups were 12 months and 29 months, respectively. The 1-, 2-, and 3-year survival rates were 70.96%, 43.27%, and 35.48%, respectively, for all patients and 96.87%, 68.75%, and 40.63%, respectively, for patients in the surgical group.

However, reports with inconsistent findings are also noted in the literature [32] [33]. These findings suggest that NAC could reduce tumor stage and increase the rate of surgical R0 resections but has no clear advantage in improving

long-term survival. Schuhmacher *et al.* [32] randomly divided 144 patients with AGC into two groups. Patients in one group received surgery after NAC, and patients in the other group exclusively underwent surgical resection. The R0 resection rate of the group that received surgery after NAC was 81.9%, which was significantly increased compared with the 66.7% rate ( $P = 0.036$ ) in the simple surgical resection group. No significant difference in postoperative complications was noted between the two groups (27.1% and 16.2%, respectively) % ( $P = 0.09$ ). After a median follow-up of 4.4 years and 67 deaths, a survival benefit was not demonstrated (hazard ratio, 0.84; 95% CI, 0.52 to 1.35;  $P = 0.466$ ). A study by Basi *et al.* [33] reported similar conclusions.

Currently, the duration of NAC in patients with AGC is inconclusive. In a study of resected AGCs after NAC, physicians established 2 - 4 courses of chemotherapy. If progressive disease (PD) developed after 2 cycles, the patient underwent surgery as soon as possible. If complete remission (CR), partial remission (PR), or stable disease (SD) was achieved, the patient received two additional courses [34].

## 6.2. Postoperative Chemotherapy

Studies have demonstrated that postoperative chemotherapy can reduce the risk of local recurrence and metastasis and improve survival rates [35] [36] [37]. You *et al.* [35] assessed 126 cases of AGC with R0 resection and D2 lymphadenectomy. Patients were divided into an infusion chemotherapy group (65 cases) and a control group (61 cases) according to postoperative regional infusion of chemotherapy (1000 mg fluorine and 60 mg cisplatin). No significant differences in the recovery time of intestinal function and the incidence of early and late complications were noted. The 3-year survival and 3-year relapse-free survival rates of patients in the infusion chemotherapy group were significantly increased compared with the control group. Wang *et al.* [38] observed the effect of RAIC on liver metastasis after gastric cancer resection. They surgically removed T2, N2, and M0 gastric adenocarcinoma without metastasis, and patients were administered RAIC or systemic chemotherapy 30 days after surgery. Both regimens comprised 100 mg/m<sup>2</sup> oxaliplatin and 500 mg/m<sup>2</sup> fluorodeoxy uridine. Patients who developed liver metastasis during the 3-year follow-up period were offered transarterial chemoembolization. The times to liver metastasis in patients of the RAIC group ( $n = 13$ ) and the systemic chemotherapy group ( $n = 29$ ) were  $944 \pm 231$  days and  $506 \pm 77$  days after treatment, respectively. The former was significantly longer than the latter. Their results demonstrated that RAIC is more effective compared with systemic chemotherapy in controlling postoperative liver metastases of gastric cancer.

## 7. Response Evaluation

A therapeutic response evaluation of RAIC is crucial for selecting the next treatment regimen. Medical imaging still plays an important role in response

evaluation of tumor therapy. The application of functional imaging in the diagnosis and treatment of tumors is becoming increasingly significant [39]-[50].

Survival status is relatively ideal to reflect the efficacy of NAC for gastric cancer [3] [7] [15] [30] [51] [52] [53] [54]. OS was a reliable end-point indicator. Disease-free survival, time to progression, and progression-free survival are main indicators to evaluate efficacy. However, the survival time is recorded after the end of treatment. Its role together with other prognostic indicators of efficacy in the adjustment of the current treatment options and the prediction long-term survival cannot be ignored.

The pathological residue rate of surgically resected specimens after chemotherapy is a relatively objective method to determine the curative effect of NAC. However, in the actual practice of pathological evaluation, it is still difficult to accurately determine the tumor range before chemotherapy and the residual tumor rate.

In addition, biomarkers can also be used as indicators of efficacy [54]-[60].

In short, standards for clinical evaluation of NAC for gastric cancer are lacking. Combining various evaluation indicators may help to improve the accuracy of the evaluation.

## 8. Conclusion

In conclusion, RAIC involves directly delivering chemotherapy drugs to tumor lesions, thereby improving the therapeutic responses and reducing the adverse effects of the drugs. RAIC can effectively reduce the AGC stage and improve the rate of radical resection. Postoperative chemotherapy can reduce the risk of local recurrence and metastasis. Although the number of reports on the use of RAIC for the treatment of AGC is increasing yearly, uniform standards are lacking. In addition, our understanding of important areas about RAIC is limited. These areas include the chemotherapy regimen and doses of chemotherapeutic drugs; the number of courses of preoperative RAIC treatment and the timing of surgical resection; and an evaluation system of treatment response. With the extensive application of RAIC and the development of evidence-based medical research, RAIC, as a treatment method of AGC, will be gradually standardized, and more AGC patients will benefit.

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