

New prospects for the control of peritoneal surface dissemination of gastric cancer using perioperative intraperitoneal chemotherapy

Review Article

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Key Words: Gastrectomy, carcinomatosis, induction chemotherapy, mitomycin C, cisplatin, doxorubicin

Received: 5 April 2004; Accepted: 15 April 2004; electronically published: May 2004

Summary

Background: Gastric cancer is a disease whose sites of surgical treatment failure have been well defined. Recurrence at the resection site and peritoneal dissemination is a prominent cause of patient demise. **Methods:** The natural history of surgically treated gastric cancer was reviewed and the mechanisms for local-regional treatment failure studied. The publications regarding perioperative intraperitoneal chemotherapy to reduce the incidence of local-regional treatment failure were reviewed and the results summarized. **Results:** Eight clinical trials that used chemotherapy as part of the surgical intervention showed a statistically significant or a trend towards improved survival. Two trials that used multiple cycles of intraperitoneal chemotherapy initiated weeks after the gastric cancer surgery showed no benefit. Morbidity and mortality are acceptable. **Conclusions:** Lymph node positive and serosal invasive gastric cancer have a high incidence of microscopic residual disease following gastrectomy. This results in local and peritoneal surface recurrence. This failure of surgical treatment can be reduced by perioperative intraperitoneal chemotherapy.

I. Introduction

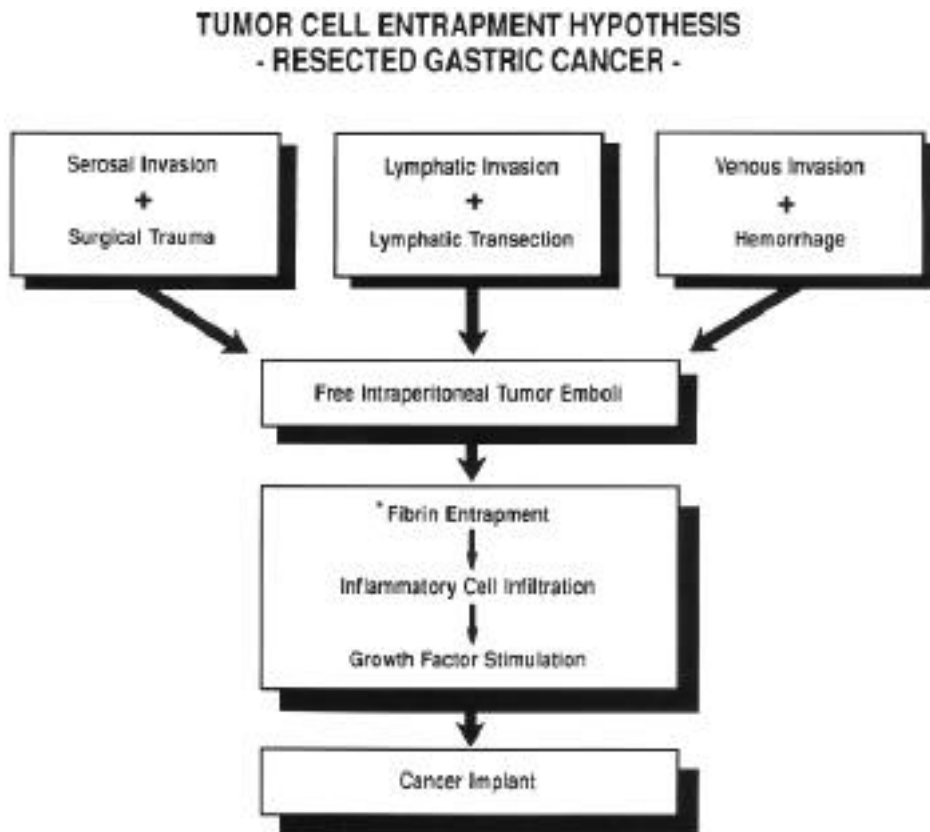
Gastric cancers that extend to the serosal surface or that involve lymph nodes are at high risk for resection site recurrence and for peritoneal carcinomatosis. The incidence varies from 20-50% (Gunderson and Sosin, 1982; Wisbek et al, 1986; Landry et al, 1990; Yoo et al, 2000). Systemic chemotherapy has not been found to be effective as an adjuvant treatment to reduce the incidence of local-regional recurrence for patients with peritoneal carcinomatosis. Intraperitoneal chemotherapy in the perioperative period has shown benefit in clinical trials. In this review the theoretical basis for local-regional recurrence.

II. Analysis of failure of gastrectomy alone as a treatment for gastric cancer

Yoo et al, (2000) reviewed 2328 patients with gastric cancer who underwent curative resection between 1987-1995. In 508 patients there was documented evidence of recurrence. A single anatomic site for recurrence was

observed in 403 patients and 83 had recurrence at two or more sites. Isolated peritoneal recurrence was noted in 172 patients and was the most frequent single pattern (33.9%). Hematogenous recurrence, the second pattern observed, was seen in 133 cases (26%) of which 75 cases had hepatic metastases. Local-regional recurrence involving the gastric stump, anastomoses, lymph nodes or an adjacent organ, the third observed pattern, was seen in 19.3% of cases. The length of time to recurrence was 27.3 months for local-regional recurrence, 18.1 months for peritoneal recurrence and 14.6 months for haematogenous recurrence. Serosal invasion and lymph node metastases were common risk factors for all patterns of recurrence. These data demonstrate the need for achieving better local-regional control and for prevention of peritoneal seeding.

The rationale for integrating perioperative intraperitoneal chemotherapy into the surgical treatment of gastric cancer was presented by Sugarbaker and coworkers (Sugarbaker et al, 1989). They suggested that three sources of microscopic residual disease could occur after gastrectomy (**Figure 1**). The first and most obvious cause



*Occurs at resection site, on abraded bowel surfaces and beneath abdominal incision.

Figure 1. The tumor cell entrapment hypothesis suggests three mechanisms for microscopic residual cancer cells in patients having an R-0 gastrectomy.

of contamination of the peritoneal cavity by the cancer cells is serosal invasion by T3 or T4 malignancy. The surgical trauma of cancer resection combined with the natural tendency of the cells to exfoliate result in a positive cytology in these patients (Boku et al, 1990; Bando et al, 1999; Kodera et al, 1999).

A second prominent cause of cancer cell spillage with surgery occurs as a result of transection of lymphatic channels in patients with positive lymph nodes. This is more an issue with multiple nodes involved rather than a few positive perigastric lymph nodes. Fujimura and colleagues, (1997) documented the ability of the reverse transcriptase polymerase chain reaction to identify free gastric cancer cells in the peritoneal cavity. Marutsuka and coworkers established that lymph node positive patients have a high likelihood of cancer cells in the peritoneal cavity after gastrectomy. They concluded that lymph node dissection opened lymphatic channels and spread viable cancer cells into the free peritoneal cavity (Koga et al, 1988).

A third source of cancer cell contamination is blood lost from the cancer specimen into the peritoneal space. Perhaps this is a contributor to the poor prognosis seen when cancer patients require large blood transfusion.

III. Rationale for perioperative intraperitoneal chemotherapy

Tumor cells are dislodged at the time of surgery as a

result of surgical trauma and are then implanted onto traumatized peritoneal surfaces. Here the implants are entrapped by blood clots and enmeshed in fibrin deposits. They are presumably nourished by the growth factors released during the inflammatory phase of healing. To prevent this sequence of events chemotherapy is given intraoperatively and in the early postoperative phase.

In the operating room the chemotherapy solution is heated to a temperature of 41°C at the point of delivery. The effects of hyperthermia are:

- 1) Heat greater than 43°C affects cancerous tissues more than the normal tissues.
- 2) Heat softens the tissues and decreases the interstitial pressure thereby facilitating drug penetration into the tumour.
- 3) Heat increases the cytotoxicity of selected chemotherapeutic agents.

A temperature profile observed in the operating room with hyperthermic intraoperative intraperitoneal chemotherapy is shown in **Figure 2**.

The pharmacology of intraperitoneal drug delivery provides strong theoretical support for these treatments. The local exposure of tissues to chemotherapy solution fare greater and the systemic toxicities lower if the drug delivery is intraperitoneal (**Figure 3**).

These studies of the natural history of gastric cancer suggest that patients with primary disease could be specially selected for adjuvant intraperitoneal chemotherapy.

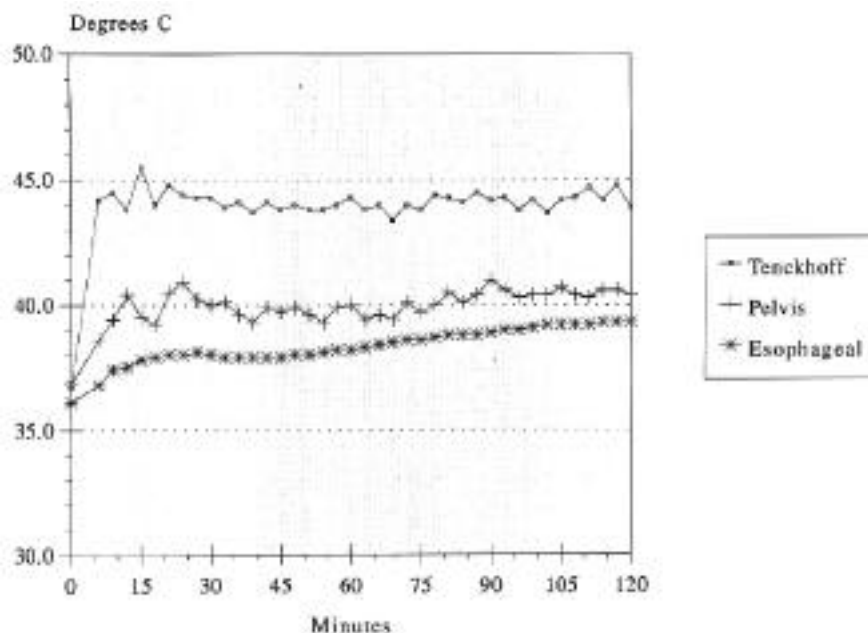


Figure 2. Temperature profile for heated intraoperative intraperitoneal chemotherapy drugs. Mitomycin C, cisplatin, doxorubicin have been used.

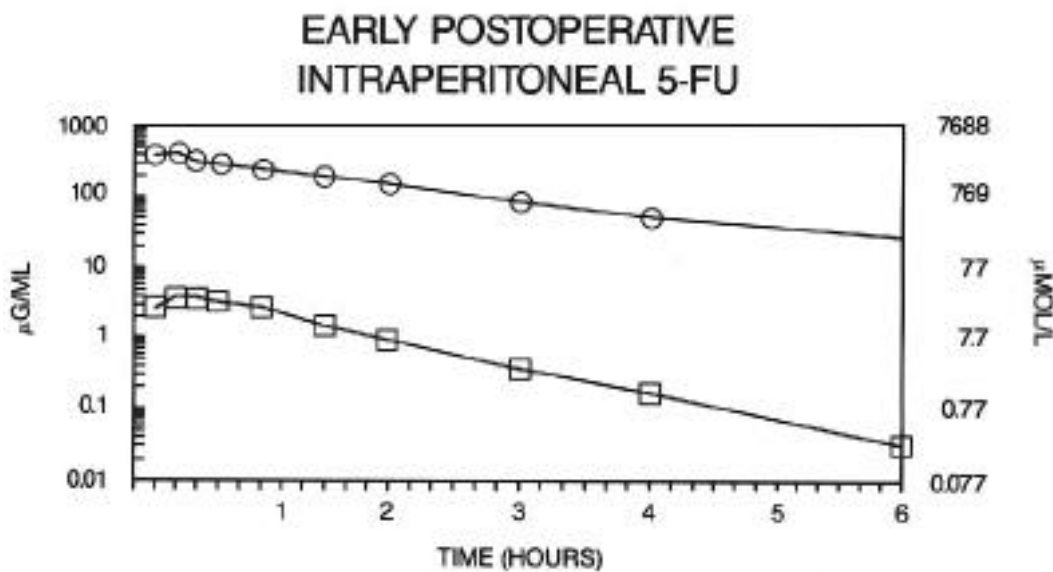


Figure 3. Pharmacokinetic study of intraperitoneal 5-fluorouracil 1000 mg in 2 liters 1.5% dextrose peritoneal dialysis solution. The intraperitoneal concentration is shown as circles and the plasma concentration as squares. The concentration difference over time peritoneal fluid to plasma is 250:1.

Patients for treatment must have complete (R0) resection. If persistent disease exists at any site, the intraperitoneal chemotherapy treatment cannot confer a survival advantage. As a result of radical surgery there must be complete clearance of the primary tumor and involved lymph nodes for proper use of these treatments.

Incomplete containment of the cancer as a result of microscopic residual disease may be unavoidable as a result of the surgical event. Patients with this small volume of cancer recently seeded on peritoneal surfaces may be the ideal patients for perioperative intraperitoneal chemotherapy. However, the timing of the chemotherapy

(perioperative) and the route of administration (intraperitoneal) are absolute requirements for benefit in this group of patients. Multiple cycles of intraperitoneal chemotherapy initiated weeks after the gastric cancer surgery showed no benefit.

IV. Clinical studies to date

Clinical studies to support the use of perioperative intraperitoneal chemotherapy as an adjuvant to gastric cancer have steadily accumulated over a decade. The published information is shown in **Table 1**. Eight studies

show a significant advantage or an advantageous trend for patients treated with perioperative intraperitoneal chemotherapy (Figure 4). Most of these studies used hyperthermic intraperitoneal chemotherapy (Koga et al, 1988; Hamazoe et al, 1994; Yonemura et al, 1995; 2001; Ikeguchi et al, 1995; Fujimoto et al, 1999; Hirose et al, 1999). A single study used early postoperative intraperitoneal chemotherapy (Yu et al, 1998). Two studies of intraperitoneal chemotherapy for gastric cancer

did not show benefit as an adjuvant treatment. Schiessel and coworkers used adjuvant intraperitoneal cisplatin in a multicenter trial in 64 randomized patients. The treatment was initiated within 4 weeks of surgery; none of the patients had perioperative treatment. There were no survival advantages (Schiessel et al, 1989). Sautner and colleagues reported a similar negative study (Sautner et al, 1994).

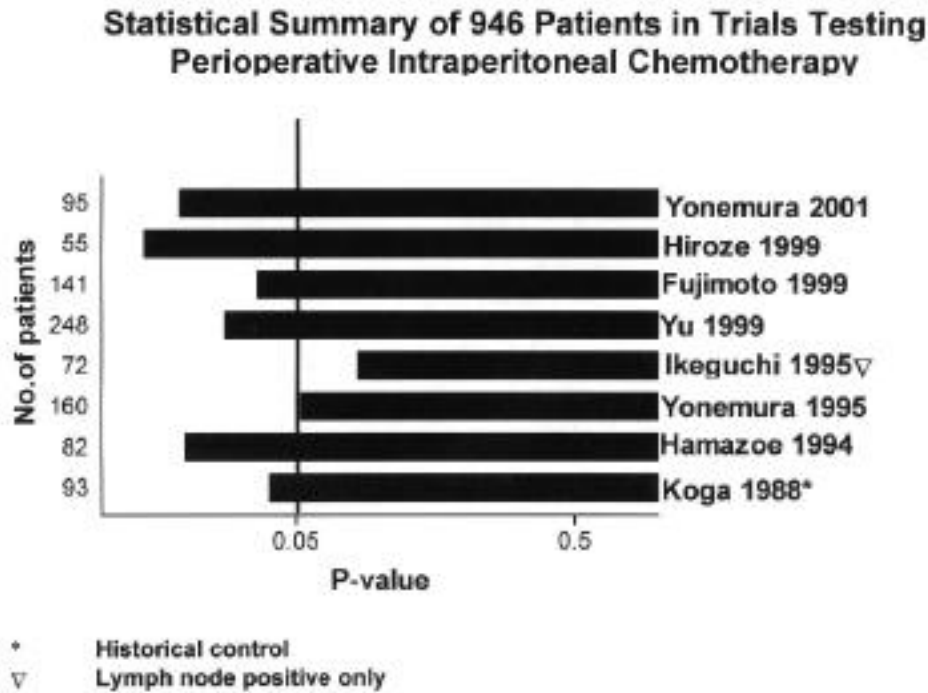


Figure 4. A statistical summary of 8 trials testing perioperative intraperitoneal chemotherapy.

Table 1. Eight reports of adjuvant treatment with perioperative intraperitoneal chemotherapy in gastric cancer patients having an R-0 resection (negative margins of excision and absence of disseminated disease).

Year	Authors	Location	Number of patients study/control	Survival rates % study/control	p	Study/control morbidity %	Study/control mortality %
1988	Koga et al.	Yonago	26/21	5-year 63/43	0.04	8.5/12	NA
1994	Hamazoe et al.	Yonago	42/40	5-year 61.3/52.5	0.02	4.8/7.7	0
1995	Yonemura et al.	Kanazawa	79/81	3-year 55/38	0.052	3/2.5	3/2.5
1995	Ikeguchi et al.	Yonago	78/96	5-year 51/46	NS	1.2/2.08	1.2/2.08
1999	Yu et al.	Taegu	125/123	5-year 54.1/38.1	0.0278	28.8/20.3	6.4/1.6
1999	Fujimoto et al.	Chiba	71/70	5-year 69/55	0.0362	2.81/2.85	0
1999	Hirose et al.	Fukui	15/40	5-year 39/17	0.0142	60/42.5	0/5
2001	Yonemura et al.	Kanazawa	48/47	5-year 61/42	0.019	19/19	4/4

NA = not available; NS = not significant.

V. Future prospects

Currently, there is a large theoretical basis and a moderate support from clinical studies to suggest that perioperative intraperitoneal chemotherapy is an important part of a program in management of gastric cancer. However, to date this innovation in patient management has only been adopted at a small number of institutions in the United States, Korea, and Japan. Certainly, it does not represent a standard of practice. It may emerge as a standard of practice if further clinical data can be obtained in the future that shows similar benefit to that presented in this manuscript.

The need is further phase III trials in patients with gastric cancer. Also, a trial must be performed in Western patients with gastric malignancy. Before this can occur as a multi-institutional effort with adequate number of randomized patients, standardization of these perioperative treatments must occur. The group conducting the trial will need to agree on the timing (between 30 and 120 minutes), the heat (between 39 and 43°C), the drugs (mitomycin C, cisplatin, doxorubicin, VP16), open versus closed technology, heated intraoperative chemotherapy versus early postoperative intraperitoneal chemotherapy versus both, and drugs for early postoperative intraperitoneal treatments if used (5-fluorouracil or taxol). A great deal of thought and some further pharmacokinetic and dose escalation studies may be necessary. Also, the patient eligibility requirements will be controversial. Should only stage III patients be entered? Should patients be entered prior to an exploration of the abdomen or would the randomization be intraoperatively after the completion of the gastrectomy? Should patients with early carcinomatosis such as P1 or P2 peritoneal seeding receive treatment? What about patients that have ovarian involvement; should these patients enter the trial? Should cytology, both before and after gastric cancer resection, be required? Should patients with positive cytology be included or excluded from the adjuvant study?

Not only should the perioperative chemotherapy treatments and eligibility treatments be definitely determined, the surgical procedure needs to be well defined too. Most likely, on the basis of the positive result of Yu and colleagues, a D2 gastrectomy should be recommended (Yu et al, 1998).

All these and many other questions will need to be resolved before a multi-institutional trial of perioperative intraperitoneal chemotherapy in patients with resectable gastric cancer can proceed. A workshop to define these parameters and to produce a workable protocol needs to be a high priority goal for the future.

VI. Conclusions

Lymph node positive and serosal invasive gastric cancer have a high incidence of microscopic residual disease following gastrectomy. This results in local and peritoneal surface recurrence. This surgical treatment failure can be reduced by perioperative intraperitoneal chemotherapy. Further studies are necessary to confirm these benefits.

References

- Bando E, Yonemura Y, Takeshita Y, Taniguchi K, Yasui T, Yoshimitsu Y, Fushida S, Fujimura T, Nishimura G, Miwa K (1999) Intraoperative lavage for cytological examination in 1,297 patients with gastric carcinoma. *Am J Surg* 178, 256-262.
- Boku T, Nakane Y, Minoura T, Takada H, Yamamura M, Hioki K, Yamamoto M (1990) Prognostic significance of serosal invasion and free intraperitoneal cancer cells in gastric cancer. *Br J Surg* 77, 436-439.
- Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T (1999) Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. *Cancer* 85, 529-534.
- Fujimura T, Yonemura Y, Ninomiya I, et al. (1997) Early detection of peritoneal dissemination of gastrointestinal cancers by reverse-transcriptase polymerase chain reaction. *Oncology Reports* 4, 1015-1019.
- Gunderson LL, Sosin H (1982) Adenocarcinoma of the stomach: Areas of failure in a reoperation series (second or symptomatic look), clinico-pathologic correlation and implications for adjuvant therapy. *Int J Radiat Biol Phys* 8, 1-11.
- Hamazoe R, Maeta M, Kaibara N (1994) Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study. *Cancer* 73, 2048-2052.
- Hirose K, Katayama K, Iida A, Yamaguchi A, Nakagawara G, Umeda S, Kusaka Y (1999) Efficacy of continuous hyperthermic peritoneal perfusion for the prophylaxis and treatment of peritoneal metastasis of advanced gastric cancer: evaluation by multivariate regression analysis. *Oncology* 57, 106-114.
- Ikeguchi M, Kondou A, Oka A, Tsujitani S, Maeta M, Kaibara N (1995) Effects of continuous hyperthermic peritoneal perfusion on prognosis of gastric cancer with serosal invasion. *Eur J Surg* 161, 581-586.
- Kodera Y, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K, Morimoto T, Kato T (1999) Peritoneal washing cytology: prognostic value of positive findings in patients with gastric carcinoma undergoing a potentially curative resection. *J Surg Oncol* 72, 60-65.
- Koga S, Hamazoe R, Maeta M, Shimizu N, Murakami A, Wakatsuki T (1988) Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. *Cancer* 61, 232-237.
- Landry J, Tepper JE, Wood WC, Moulton EO, Koerner F, Sullinger J (1990) Patterns of failure following curative resection of gastric carcinoma. *Int J Radiat Biol Phys* 19, 1357-1362.
- Sautner T, Hofbauer F, Depisch D, Schiessel R, Jakesz R (1994) Adjuvant intraperitoneal cisplatin chemotherapy does not improve long-term survival after surgery for advanced gastric cancer. *J Clin Oncol* 12, 970-974.
- Schiessel R, Funovics J, Schick B, Bohmig HJ, Depisch D, Hofbauer F, Jakesz R (1989) Adjuvant intraperitoneal cisplatin therapy in patients with operated gastric carcinoma: results of a randomized trial. *Acta Med Austriaca* 16, 68-69.
- Sugarbaker PH, Cunliffe WJ, Belliveau J, de Bruijn EA, Graves T, Mullins RD, Schlag P (1989) Rationale for integrating early postoperative intraperitoneal chemotherapy into the surgical treatment of gastrointestinal cancer. *Semin Oncol* 16 (Suppl 6), 83-97.
- Wisbeck WM, Beecher EM, Russell AH (1986) Adenocarcinoma of the stomach: Autopsy observations with therapeutic implications for the radiation oncologist. *Radiother Oncol* 7, 13-18.

- Yonemura Y, de Aretxabala X, Fujimura T, Fushida S, Katayama K, Bandou E, Sugiyama K, Kawamura T, Kinoshita K, Endou Y, Sasaki T (2001) Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: final results of a randomized controlled study. **Hepato-gastroenterology** 48, 1776-1782.
- Yonemura Y, Ninomiya I, Kaji M, Sugiyama K, Fujimura K, Sawa T, Katayama K, Tanaka S, Hirono Y, Miwa K, et al. (1995) Prophylaxis with intraoperative chemohyperthermia against peritoneal recurrence of serosal invasion-positive gastric cancer. **World J Surg** 19, 450-455.
- Yoo CH, Noh SH, Shin DW, Choi SH, Min JS (2000) Recurrence following curative resection for gastric carcinoma. **Br J Surg** 87, 236-242.
- Yu W, Whang I, Suh I, Averbach A, Chang D, Sugarbaker PH (1998) Prospective randomized trial of early postoperative intraperitoneal chemotherapy as an adjuvant to resectable gastric cancer. **Ann Surg** 228, 347-354.



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