

# Follow-Up: The Evidence

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## Key Words

Gastric cancer · Postoperative follow-up · Surveillance

## Abstract

There is currently no consensus on the best strategy for the follow-up of patients who have undergone surgical treatment with curative intent for gastric cancer. The wide variation in recommendations for surveillance among international experts and hospital schedules clearly reflects a lack of an established body of evidence on this subject. Consequently, most of the international guidelines aimed at early detection of disease recurrence gloss over details concerning the mode, duration, and intensity of surveillance since they cannot be based on an acceptable grade of recommendation. Very few report anything other than the detection of recurrences or death as the primary endpoints, and, given the poor survival of patients with recurrent gastric cancer, the prognostic effect of early detection seems doubtful. In recent years, an increasing focus on evidence-based medicine, which has coincided with a growing concern about costs and efficiency in medicine, has caused a reevaluation of most surveillance practices. In this paper, we review and discuss the current body of evidence and follow-up practices after curative resection of gastric cancer.

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## Introduction

The potential value of a surveillance program in patients who have undergone cancer surgery is to detect recurrences in the early and asymptomatic period, to identify complications associated with surgery, and to collect outcome data. Early detection of cancer recurrence may be associated with improved survival because it may provide an opportunity for treatment to be initiated while the patient's condition is sufficiently stable to receive effective therapy.

A postoperative follow-up schedule is recommended for nearly all cancers in international guidelines even though the value of postoperative surveillance remains controversial [1, 2]. In colorectal and breast cancers, several randomized controlled trials and meta-analyses have demonstrated an overall survival advantage associated with detection of recurrences through intensive follow-up as compared with patients who present later with symptomatic recurrences [3, 4].

Gastric cancer is one of the most frequent malignancies and the second leading cause of cancer deaths worldwide, with 989,600 new cases and 738,000 deaths in 2008, accounting for 8% of the total cases and 10% of total deaths for cancer [5].

Recurrence is the most important factor associated with death even after potentially curative gastrectomy. Over two thirds of recurrences occur in the first 3 years following surgery and fewer than 10% occur after 5 years; given the poor survival of patients with recurrent gastric cancer, only palliative therapy is generally possible [6–8].

Most clinicians perform postoperative surveillance for their gastric cancer patients during the first 3 years after surgery. However, there is no consensus on the most appropriate regimen and frequency of follow-up after curative surgery [9]. It must also be said that patients could be possibly reassured from regular follow-up, although the psychological benefit of surveillance is debatable. There is a wide variation in recommendations for surveillance among experts. In recent years an increasing focus on evidence-based medicine that has coincided with growing concern about costs and efficiency in medicine has caused a reevaluation of surveillance practices.

To date, all of the recommendations on surveillance are based on low-level evidence or no evidence at all due to the complete lack of randomized controlled trials on this peculiar subject. Very few report anything other than the detection of recurrences or death as the primary endpoints, and the prognostic effect of early detection seems doubtful given the poor survival of patients with an ascertained recurrent gastric cancer [9].

The objective of this study is to review the literature about the efficacy of follow-up protocols and investigations after gastrectomy for cancer. Moreover, in this study we have tried to classify different follow-up policies after curative resection for gastric cancer using a questionnaire-based survey among high-volume centers for the treatment of gastric cancer worldwide.

### Reasons for Follow-Up

Surveillance after surgery in gastric cancer includes three main purposes: detecting local or distant recurrences and/or metachronous cancers in the remnant stomach, detecting long-term or late effects of surgical treatment, and collection of outcome data to evaluate the effectiveness of treatments and for research purposes.

#### *Recurrence*

The recurrence patterns of gastric cancer are classified as locoregional, peritoneal, and hematogenous. Locoregional recurrence is defined as cancer recurrence at the resection margin, within the lymph nodes (including regional, retropancreatic, retrocrural, and para-aortic

nodes), or in the operation bed within the region of the resection (below the diaphragm and liver and above the pancreas and abdominal wound). In addition, the resection margin is divided into the proximal margin (including the lower third of the esophagus, remnant stomach, and gastrointestinal anastomosis) and the distal margin (duodenal stump). Peritoneal recurrence is defined as cancer recurrence in the abdominal cavity because of intraperitoneal distribution including visceral metastasis and rectal shelf, pericholedochal, and periureteral infiltration. Hematogenous recurrence has been defined as any metastatic lesion detected in distant organs [10, 11].

The timing of recurrence has been investigated by many researchers and data are not uniform as reported. More than 90% of patients relapse within 5 years after surgery and 70% relapse within 2–3 years [6, 7]. In early gastric cancer, the rate of recurrence after gastrectomy is reported to vary from 1.3 to 12.2%. Median time to recurrence is 16 months, and hematogenous spread is probably the most common pattern of recurrence [12].

Many investigators have analyzed recurrence patterns, but the data have shown variable incidences of these patterns. This disagreement is attributed to differences in patient population, stage of the disease at the time of diagnosis, surgical treatment, and the mode and timing of recurrence detection. Based on a review of the literature, the pattern of recurrence tends to be local in the West, whereas the pattern is different in the East, with more peritoneal and hematogenous recurrences [9].

Occasionally, after partial gastrectomy a second primary tumor can arise in the remnant stomach. Much of the literature relates to gastrectomies for peptic ulcer disease, which estimates a risk that is not so different from the general population [13, 14].

As regards gastric cancer, second primaries are more common after surgery for early gastric cancer because these patients have a good prognosis after curative surgery. The reported incidence of metachronous gastric cancer after partial gastrectomy for early gastric cancer is 0.6–3% [15]. In clinical oncology practice, the detection of the recurrence in the early stage may provide an opportunity for effective treatment when patients are still fit enough to receive surgical or medical therapy.

Patients with gastric cancer recurrence are more often managed similarly to nonresectable patients because early detection of recurrence is quite difficult and peritoneal recurrence, one of the main patterns of recurrence, is usually diagnosed at an advanced stage.

With the possible exception of a few locoregional (anastomotic and lymph nodal) and hepatic metastases suitable for radical resection, the vast majority of recurrences are not surgically curable, and any resection is likely to be palliative or futile. Most patients with liver metastases are not candidates for resection and the survival rate after liver resection is very low and treatments for peritoneal metastases are still investigational [16, 17].

Chemotherapy is considered the mainstay in the treatment of recurrent gastric cancer and is offered with the aim of improving survival and quality of life. Several randomized trials have indicated that patients with recurrent gastric cancer generally live longer when treated with chemotherapy than with optimal supportive care [18–20]. Recent advances in chemotherapy have achieved considerable tumor regression with the median overall survival time reported to be between 6 and 13 months [21].

To date, these results notwithstanding, there is no clear evidence that treatment of a recurrence detected at an earlier stage improves outcome.

#### *Quality of Life Issues*

Follow-up is also important to evaluate the side effects of gastric surgery. Gastric resection leads to radical changes in the anatomy and physiology of the gastrointestinal tract and can cause severe nutritional complications.

Feeding problems occur in approximately 30% of patients, but severe symptoms are present only in 1–2%. The main symptoms are early postprandial satiety, loss of appetite, alteration of taste, reflux, dyspepsia, nausea and/or vomiting, and diarrhea. There are various ‘postgastrectomy syndromes’ depending on the type of surgery (total or subtotal gastrectomy) and reconstruction technique (BI, BII, or Roux-en-Y). Gastric reservoir dysfunction (dumping syndromes), afferent and efferent loop syndromes, Roux-en-Y stasis syndrome, and bile reflux can lead to a reduction of food intake and occasionally to severe malnutrition [22].

Along with feeding concerns after gastric resection, regardless of the reconstruction technique, three metabolic and nutritional disorders may occur: anemia, bone disease, and weight loss due to malabsorption.

Nearly 30% of patients present microcytic anemia (iron deficiency anemia) or megaloblastic anemia (vitamin B<sub>12</sub> deficiency). Iron deficiency is the most common anemia following gastric resection. After gastric resection, both acid and pepsin, which are needed for iron absorption, are reduced. Moreover, owing to a lack of intrinsic factor secretion, vitamin B<sub>12</sub> deficiency is common after gastric resection (mostly after total gastrectomy). In-

tramuscular injection of vitamin B<sub>12</sub> every 3–4 months is recommended as a standard treatment for patients with vitamin B<sub>12</sub> deficiency after total gastrectomy even if daily oral replacement therapy provides a safe and effective alternative treatment [23].

Bone disease, such as osteoporosis, osteopenia, and osteomalacia, is commonly reported in gastrectomy patients. Its etiology appears to be a combination of decreased intake of calcium, vitamin D, and lactose-containing foods, coupled with altered absorption and metabolism. Symptoms of osteoporosis may develop 10 or more years after gastric surgery because of the large amount of calcium that is normally stored in bone [24].

Weight loss is a frequent finding after gastric surgery and is often temporary. Malabsorption is related to the accelerated passage of a large bolus in the jejunum, vagal denervation which increases the rapidity of the orocecal transit, and bacterial overgrowth due to the decrease in gastric acid secretion, and pancreatic insufficiency [25, 26].

#### **Components of Surveillance**

The main components of a surveillance strategy are office visits for postoperative history and physical examination, blood tests (especially tumor markers), imaging, and endoscopic studies.

There is no consensus regarding the follow-up plan after gastrectomy for cancer, and the optimum modality for the diagnosis of early recurrence is indeed unclear. Although there are many tools to detect recurrent disease in addition to clinical examination (laboratory tests, imaging, and endoscopy), none has high tumor specificity.

#### *Laboratory Tests*

The dosage of serum tumor markers is commonly used during postoperative follow-up because their positivity is easily measured with a simple blood test, but it is well known that they are not specific and cannot localize the recurrence site. CEA and CA19-9 are known to be elevated in the serum of patients with advanced gastric cancer, and the monitoring of CEA and CA19-9 monitoring has been used for the early detection of recurrence after operation for advanced gastric cancer.

In prospective studies, both tumor markers were useful indicators of recurrence, especially in almost all the patients who showed high preoperative levels of these markers [27, 28]. CA19-9 may be especially useful as a marker for peritoneal recurrence of gastric cancer, and

CEA for recurrence in the liver [29]. Other tumor markers, such as CA 72-4 and CA125, have been investigated, but their sensitivity is significantly lower than that of CEA and CA19-9 [30].

### *Imaging*

Reports on the use of imaging in detecting recurrent gastric cancer are few and often limited to descriptions of typical findings. Contrast-enhanced abdominal computed tomography (CT) is used most frequently and is regarded as the most reliable method for assessing cancer recurrence, with a reported accuracy of 60–70% [31]. To date, however, only few reports have been published on CT findings after gastrectomy. A CT scan has limited value in the distinction of postoperative morphologic changes from tumor recurrence and has a low positive predictive value to detect peritoneal and distant lymph node metastasis [32].

Positron emission tomography (PET) is often useful for detecting different patterns of recurrence, such as local recurrence involving the stomach remnant, regional lymph nodes, peritoneal dissemination, liver metastases, and remote metastases. PET is an advantageous imaging tool because it enables the evaluation of the entire body at once, although PET has limitations such as frequent false-negative cases in early cancer and signet-ring cell tumors and poorly differentiated histotypes. PET is useful when conventional imaging is equivocal, as it can confirm the presence of true recurrence [33].

PET represents the most useful noninvasive imaging modality for the detection of hepatic metastases from gastric cancer with a sensitivity of 90% compared with a sensitivity of 76, 72, and 55% reported for magnetic resonance imaging, CT, and ultrasonography, respectively [34–36].

An integrated PET/CT scan provides fusion images, combining functional and anatomic imaging together. This modality has a diagnostic accuracy ranging from 75 to 97%. A PET/CT scan has the greatest utility in patients with a suspicion of recurrences based on tumor marker tests and findings of other imaging modalities [37–39].

All imaging studies have a low accuracy in detecting peritoneal disease, which represents one of the most frequent and feared patterns of recurrence. Barium enema has been used in the diagnosis of peritoneal carcinomatosis in colorectal cancer [40], and this imaging has been used in Japanese institutions to confirm the presence of peritoneal disease when clinically suspected [9].

A recent study by Inoue et al. [41] evaluated the feasibility and accuracy of second-look laparoscopy for pa-

tients with gastric cancer at high risk of peritoneal recurrence after completion of 6 months of systemic adjuvant chemotherapy. In this study, second-look laparoscopy was a safe and effective approach for early reassessment of peritoneal disease for the selection of patients who needed further systemic chemotherapy.

### *Endoscopy*

The use of endoscopy during the follow-up period is recommended when there is a risk of recurrence in the stomach remnant in two cases: after a subtotal gastrectomy and after endoscopic treatment for early gastric cancer. After total gastrectomy endoscopy, it is mostly useful to detect surgical complications like a benign stricture [42].

Lifelong annual follow-up endoscopy is recommended after partial gastrectomy. Two thirds of the patients destined to develop a second primary gastric cancer will show signs of disease within 10 years after surgery. The risk is higher in patients with multiple lesions at initial surgery and in patients with undifferentiated-type carcinoma [43].

Careful endoscopic examination of the entire stump, particularly around the lesser curvature and posterior wall, is essential. Elevated and depressed mucosal changes should be examined histologically. Follow-up endoscopy seems important for the early diagnosis of the second primary. When detected at an early stage, treatment provides excellent disease-free survival. However, when a second primary is detected at a later stage ( $\geq T2$ ), the prognosis is poor even after curative resection [44–46].

After endoscopic treatment by submucosal dissection of early gastric cancer, patients are at high risk for synchronous or metachronous multiple gastric cancers. A large multicenter retrospective cohort study indicated that the incidence rate of synchronous cancer was 9%, that about 20% of synchronous cancers were missed, and that the annual incidence of metachronous cancer was 3.5%. With an annual follow-up examination, almost all multiple lesions could be treated by endoscopic resection [47].

### **Evidence from Follow-Up Studies**

All of the medical literature reviews to date have failed to show high-level evidence about any follow-up schedule for curatively resected gastric cancer patients. All data are retrospective and observational, thus preventing any definitive conclusion.

We selected six studies and one systematic review concerning follow-up after surgery for gastric cancer. All these studies focused on the possible survival benefit of early detection of recurrence by intensive postoperative surveillance. Three studies indicated that an intense postoperative follow-up protocol was successful in identifying asymptomatic recurrences earlier than symptomatic recurrences. Nevertheless, they could not achieve any evident advantage in overall survival [9, 48, 49].

With this purpose, a study from Memorial Sloan-Kettering Cancer Center [50] showed that follow-up did not detect asymptomatic recurrences earlier than symptomatic recurrences in patients with gastric cancer who underwent a curative gastrectomy. In that report, patients with asymptomatic recurrences showed better postrecurrence and disease-specific survival than those with symptomatic recurrences. In their conclusions, the authors indicated that symptomatic and asymptomatic recurrence patterns are biologically different and associated with different survival outcomes. Similarly in a paper by Kim et al. [31], median overall survival and postrecurrence survival were worse for patients with a symptomatic recurrence than for those with an asymptomatic recurrence. Moreover, in this study, multivariate analysis revealed that the presence of a symptomatic recurrence and disease-free interval were independent prognostic indicators for postrecurrence survival. Furthermore, asymptomatic patients had more benefit from re-resection and postrecurrence chemotherapy; at multivariate survival analysis the presence of symptoms was the only independent factor of poor survival, suggesting a more biologically aggressive disease in symptomatic patients. Bilici et al. [51], in a study on 173 patients with recurrent gastric cancer, found that symptomatic recurrence is an important prognostic factor for postrecurrence survival and that the presence of symptoms may be considered a marker of biologic tumor aggressiveness, which is an important determinant of survival at the time of recurrence diagnosis during follow-up for gastric cancer.

A recent systematic review by Cardoso et al. [52] reviewed five studies enrolling a total of 810 patients and assessing outcomes of follow-up after gastrectomy for gastric cancer. They did not find any evidence suggesting that postoperative surveillance has any survival benefit; it is also stressed that no studies addressed quality of life issues. Major limitations in the review were the study design and a lead-time bias in which the observed prolonged survival is due to earlier detection of recurrence, rather than to an effect on disease outcome.

## International Guidelines Review and Expert Interview

The lack of evidence of follow-up is revealed by the fact that most leading scientific societies and cooperative groups propose different schedules and that many centers apply a follow-up program dictated by past common practices in their medical center. Although guidelines are generally supposed to be based on strong evidence (therefore valid and unbiased), to date they have been based on low level evidence or no evidence at all.

### *International Guidelines Review*

The American Society of Clinical Oncology (ASCO) does not provide formal guidelines or recommendations for follow-up after gastrectomy for cancer. Similarly, the Japanese Gastric Cancer Association (JGCA) guidelines offer no guidelines on follow-up.

The National Cancer Comprehensive Network (NCCN) guidelines include for all patients a complete history and physical examination every 3–6 months for 1–2 years, every 6–12 months for 3–5 years, and annually thereafter. Other investigations should be made if clinically indicated. Patients who have undergone surgical resection should be monitored and treated as indicated for vitamin B<sub>12</sub> and iron deficiency [2].

The European Society of Medical Oncology (ESMO) recommends symptom-driven visits. When symptoms occur, a complete history with physical examination and blood tests should be performed. Other investigations are required only in patients who are candidates for treatment [1].

The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology, and the British Association of Surgical Oncology agree that regular review may identify early recurrence, but there is no evidence for specific investigations or that follow-up can affect overall survival. Endoscopy, cross-sectional imaging, and tumor markers have all been evaluated, but lack specificity or sensitivity [53].

The GIRCG (Italian Group for Research on Gastric Cancer) has proposed three different follow-up schedules (mild, moderate, or intensive) after gastrectomy for cancer in relation to a risk score calculated for an individual patient. A logistic regression model is used for the computation of the score; the coefficient Z is calculated as  $Z = -3.888 - 0.339$  (middle third) + 0.917 (upper third) + 6.266 (diffuse location) + 0.027 (age) + 1.075(pT2) + 2.013(pT3–T4) + 1.668(pN1) + 3.056(pN2) + 4.971(pN3) – 0.848(D2–D3 dissection). The value of parametric vari-

ables was 0 (negative) or 1 (positive), whereas age was considered as a continuous variable. For each patient, the value of the coefficient  $Z$  obtained was included in the formula:  $(e^Z/1 + e^Z) \times 100$ , which gives risk values ranging from 0 to 100% [54].

For patients with mild risk (<10% or patients over 80 years), they propose ultrasound of the abdomen and tumor marker assay every 6 months, endoscopy and chest X-ray annually, and a CT scan in case of clinical suspicion or increased levels of tumor markers. For patients with moderate risk (between 10 and 50%), they propose tumor markers be investigated every 3 months, abdominal ultrasound after 6, 18, and 30, and CT scan and endoscopy annually. For patients with high risk (>50%), they propose tumor markers every 3 months, CT scan every 6 months, and endoscopy annually. After 5 years of annual clinical monitoring, other exams if clinically indicated should be performed as well as any screening for a second cancer (occult blood test, mammography, PSA, etc.). It should be noted that no evaluation of nutritional or quality of life issues is considered in international guidelines.

#### *Expert Interviews*

A questionnaire was sent out to a selected group of world-renowned experts in the field of surgical oncology. From August to October 2012, the survey was performed via electronic mail. The questionnaire was composed of two sections. The first section was an introductory covering letter in which the purpose of the survey was indicated. The second section made up the main portion of the survey, and asked about follow-up schedules and methodologies. Most questions were yes/no or multiple choice, with several text boxes which allowed for comments from participants to provide additional information or clarification. Six out of 16 questionnaires were returned (table 1). All respondents reported having a strategy for surveillance after surgery for gastric cancer, but there was variance in strategy.

First of all, we asked about the main reason for follow-up. The primary aim of the follow-up schedule for almost all respondents (4/6) is the evaluation of complications associated with surgery and quality of life issues, and most of them perform nutritional assessment at visits. In one institution (University Hospital of Lille, France), the primary aim is the early detection of recurrence, and another institution's primary aim (Jagiellonian University, Krakow, Poland) is the collection of outcome data for treatment evaluation and/or research purposes.

In four of the six of responders, a follow-up schedule is carried out by a multidisciplinary team (surgeons with

medical oncologists) that perform follow-up in their hospitals. In two institutions the follow-up is performed by the surgical team.

No significant differences were reported in terms of follow-up frequency for different disease stages. On average, advanced gastric cancer patients are followed-up every 3 months in the first year postoperatively, as opposed to follow-up every 6 months for early gastric cancer during the first year postoperatively. From the second to fourth postoperative year, the patients were usually seen every 6 months. In all cases, follow-up ends at 5 years after surgery.

Table 1 summarizes the follow-up schedules as reported by respondents. Almost all respondents considered a CT scan as mandatory for detection of all types of recurrence and a PET scan as optional.

One respondent left the question blank because he did not have a systematic follow-up schedule and performs advanced imaging and/or endoscopy during follow-up when symptoms or clinical suspicion of recurrence arise.

#### **Conclusion**

The reported international variations in guidelines for surveillance among follow-up schedules reflects a complete lack of an established body of evidence. Consequently, most recommendations aiming to detect early recurrence of the disease often avoid details on the mode, duration, and intensity of surveillance since they cannot be based on studies with high levels of evidence. Moreover, quality of life issues are omitted in the current literature on surveillance, even though most experts underline the importance of this peculiar subject especially after total gastrectomy.

On the other hand, there is almost no doubt that from most patients' and physicians' perspectives, a good clinical practice should not disregard some kind of postoperative surveillance. However, based on a review of the literature and interviews of experts, we found that routine follow-up of gastric cancer patients is nothing more than a common behavior that is (at least) justified by data collection and outcome auditing in addition to ethical-psychological reasons concerning the anxiety of patients regarding full and prompt information about the evolution of their disease.

Although retrospective series have clearly demonstrated that early diagnosis of tumor recurrence in the asymptomatic phase has not resulted in any evident survival benefit compared to a later symptom-driven diagnosis,

**Table 1.** Follow-up schedules

		Months after resection													
		3	6	9	12	15	18	21	24	30	36	42	48	54	60
Memorial Sloan-Kettering Cancer Center, New York, N.Y., USA	HP exam														
	HP exam, chest and abdominal CT, endoscopy, B12				HP exam, abdominal CT, endoscopy, B12		HP exam, abdominal CT, endoscopy		HP exam, abdominal CT, endoscopy, B12		HP exam, abdominal CT, endoscopy, B12		HP exam, abdominal CT, endoscopy, B12		HP exam, abdominal CT, endoscopy, B12
University Hospital of Lille, Lille, France	HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, upper-GI X-ray				HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, endoscopy PET (optional)		HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, PET (optional)		HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, ET (optional)		HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, endoscopy PET (optional)		HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, PET (optional)		HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, PET (optional)
	HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, PET (optional)				HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, endoscopy PET (optional)		HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, PET (optional)		HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, ET (optional)		HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, endoscopy PET (optional)		HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, PET (optional)		HP exam, lab tests, chest and abdominal CT, CEA, CA 19-9, B12, endoscopy PET (optional)
Jagiellonian University, Krakow, Poland	liver US, chest X-ray, endoscopy				liver US, chest X-ray, endoscopy				liver US, chest X-ray, endoscopy		liver US, chest X-ray, endoscopy		liver US, chest X-ray, endoscopy		liver US, chest X-ray, endoscopy
	HP exam, lab tests, abdominal CT, CA 19-9, B12, iron				HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy				HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy		HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy		HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy		HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy
Odette Cancer Research, Sunnybrook Research Institute, Toronto, Ont., Canada	HP exam, lab tests, abdominal CT, CA 19-9, B12, iron				HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy				HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy		HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy		HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy		HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy
	HP exam, lab tests, abdominal CT, CA 19-9, B12, iron				HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy				HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy		HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy		HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy		HP exam, lab tests, abdominal CT, CA 19-9, B12, iron, endoscopy
Leiden University Medical Center, Leiden, The Netherlands	HP exam				HP exam				HP exam		HP exam		HP exam		HP exam
	HP exam				HP exam				HP exam		HP exam		HP exam		HP exam
Städtisches Klinikum Solingen, Solingen, Germany															
no schedule															
HP exam = History and physical examination; US = ultrasonography.															

the majority of the centers with a considerable gastric cancer caseload and high level of care apply a policy of clinical and instrumental surveillance with the aim of a timely diagnosis of tumor recurrence and to minimize the nutritional sequelae of gastrectomy. The rationale for this relies on three factors:

- (1) The distinct feeling that being subjected to seriated scheduled checks does not represent a source of stress for many patients, but rather has the potential of reassuring them.
- (2) The hope that biomedical research will soon offer therapeutic weapons for the metastatic and/or relapsed patients, with results similar to those currently available for patients with colorectal cancer.
- (3) The process of improving the standard of quality in surgical oncology cannot be separated from a daily evaluation of the results of therapies by comparing these results between different surgical schools and different patterns of complementary therapies, and this evaluation is made possible only by reliable data on recurrence and survival.

Follow-up schedules based on more solid ground are definitely needed, and this should be done by identifying the tests and examinations with the best reliability and sensitivity and by limiting them to a period in which recurrence is likely.

Surgical oncologists could speculate that patients may receive some benefit by postoperative surgical surveillance if early detection of recurrence leads to any proven survival advantage and/or increased quality of life. Whether there is a preclinical phase in which early detection of recurrence can improve outcome (implying that followed-up patients may have better overall outcomes than unscreened) represents a question apparently suitable for a randomized controlled trial, which is commonly considered as the most rigorous method of determining whether a cause-effect relationship exists between an intervention and its outcome [55]. Although a large randomized trial could determine whether one recommend-

ed follow-up program confers a survival benefit, this is unlikely to be rewarding until effective treatments for most patterns of recurrence are available. In fact, at the moment, clinical trials on the efficacy of surveillance strategies with high-risk patients will be doomed to show no efficacy if survival is their primary endpoint because survival after recurrence is poor regardless of the time of diagnosis. At the same time, follow-up strategies in low-risk patients with good long-term prognosis (i.e. early gastric cancer) necessitate an excessively long time to demonstrate clear improvements in outcome. In both cases, huge sample sizes, money, and time are almost insurmountable obstacles.

Consensus methods are alternative means of dealing with conflicting or scarce scientific evidence. The focus of consensus methods lies where unanimity of opinion does not exist, owing to a lack of scientific evidence or when there is contradictory evidence about an issue. Consensus methods overcome some of the disadvantages normally found with decision-making in groups or committees, which are commonly dominated by one individual or by coalitions. The consensus method attempts to assess the extent of agreement and to resolve disagreement [56]. Currently, in our opinion, an appropriately designed and methodologically based consensus conference may be a proper tool to establish the best way to adequately perform follow-up in gastric cancer patients.

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