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EDITORIAL

Follow-up after curative resection for gastric cancer: Is it time to tailor it?

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Abstract

There is still no consensus on the follow-up frequency and regimen after curative resection for gastric cancer. Moreover, controversy exists regarding the utility of follow-up in improving survival, and the recommendations of experts and societies vary considerably. The main reason to establish surveillance programs is to diagnose tumor recurrence or metachronous cancers early and to thereby provide prompt treatment and prolong survival. In the setting of gastric malignancies, other reasons have been put forth: (1) the detection of adverse effects of a previous surgery, such as malnutrition or digestive sequelae; (2) the collection of data; and (3) the identification of psychological and/or social problems and provision of appropriate support to the patients. No randomized controlled trials on the role of follow-up after curative resection of gastric carcinoma have been published. Herein, the primary retrospective series and systematic reviews on this subject are analyzed and discussed. Furthermore, the guidelines from international and national scientific societies are discussed. Follow-up is recommended by the majority of institutions; however, there is no real evidence that follow-up can improve long-term survival rates. Several studies have demonstrated that it is possible to stratify patients submitted to curative gastrectomy into different classes according to the risk of recurrence. Furthermore, promising studies have identified several molecular markers that are related to the risk of relapse and to prognosis. Based on these premises, a promising strategy will be to tailor follow-up in relation to the patient and tumor characteristics, molecular marker status, and individual risk of recurrence.

Key words: Gastric cancer; Follow-up; Surgery; Gastric carcinoma; Chemotherapy; Surveillance; Recurrence; Markers; Imaging

Core tip: There is still no consensus on the utility, frequency and regimen of follow-up after curative resection for gastric cancer. Surveillance programs may allow the following: (1) the early diagnosis of recurrence; (2) the detection of adverse effects of a previous surgery; (3) the collection of data; and (4) the detection of psychological and social problems. This editorial discusses the main studies, systematic reviews and guidelines on this subject. Several studies have demonstrated that patients may be stratified according to the risk of recurrence. A promising strategy will be to tailor follow-up in relation to the patient and tumor characteristics, molecular marker status, and individual risk of recurrence.

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INTRODUCTION

The main goal of follow-up programs after curative surgery is the early detection of cancer recurrence, such that rapid and efficacious treatment may be administered and long-term survival may be improved[1]. Other objectives of follow-up are to identify treatment-related complications and to collect data concerning cancer history and treatment outcomes[2]. International guidelines recommend postoperative follow-up for the majority of cancers, even if the role of follow-up in improving overall survival has not been demonstrated for all types of tumors.

According to the GLOBOCAN data, gastric cancer represents the fifth most common malignancy in the world, with 952000 new cases estimated to have occurred in 2012. Stomach cancer is the third leading cause of cancer death in both sexes worldwide, with an estimated 723000 deaths in 2012[3]. In the United States, there were an estimated 26370 cases in 2016, with 10730 deaths[4].

Recurrence occurs within the first 3 years in the majority of cases, and fewer than 10% of recurrences occur after 5 years[1,5,6]. Survival after recurrence is poor, and in the majority of recurrence cases, potentially curative treatments are not possible[1,7].

There is still no consensus on the frequency and regimen of follow-up after curative resection. Moreover, controversy exists regarding the utility of follow-up in improving survival, and the recommendations of experts and societies vary considerably. The problem of cost-effectiveness has also been raised[8]. The objective of this editorial is to review the current literature concerning follow-up after curative resection for cancer. We discuss the rationale of follow-up, the methods of follow-up, including clinical examination, biochemical analyses and radiological tools to detect gastric cancer recurrence, the main articles evaluating the role of follow-up in improving overall survival and the current guidelines of the most important international societies. Furthermore, the role of molecular analysis in predicting gastric cancer recurrence is analyzed, and future directions of research are suggested.

RATIONALE OF FOLLOW-UP

The main reason to establish surveillance programs after curative gastrectomy is to diagnose tumor recurrence or metachronous cancers early to thereby provide prompt treatment and prolong patient survival. In the setting of gastric malignancies, other reasons have been advocated, including (1) the detection of adverse effects of a previous surgery, such as vitamin and iron depletion or malnutrition or digestive sequelae[9]; (2) the collection of data to evaluate the efficacy and outcomes of treatments; and (3) the detection of psychological and/or social problems subsequent to the disease and the provision of appropriate support to the patients[10].

Gastric cancer recurrence may be classified into five patterns[11-14]. The first is the locoregional pattern, defined as tumor relapse at the resection margin (proximal, including the esophagus or the proximal stomach, and distal, including the duodenal stump) or in the adjacent tissue of the surgical bed. The second is the nodal pattern, which is relapse within the regional and distant lymph nodes, including the retropancreatic, retrocrural and para-aortic nodes. The third pattern is peritoneal recurrence, with intraperitoneal tumor spread. The fourth pattern is hematogenous relapse, defined as metastatic lesions in distant organs (*e.g.*, liver, lung, or bones). Finally, some tumors have a mixed pattern of recurrence, including different synchronous routes of relapse.

The majority of patients relapse within the first 3 years, with a median time to recurrence ranging from 14 to 29 mo in recent series[13-17]. After laparoscopic gastrectomy, similar times to recurrence and patterns have been demonstrated[16,17].

Among clinicopathological prognostic factors, the Italian Research Group for Gastric Cancer identified nodal status, nodal ratio, and stage, and proposed a prognostic score that was able to predict the likelihood of recurrence for high-risk patients better than the TNM stage[14].

The majority of gastric cancer recurrences are

not surgically curable. The majority of patients with liver metastases are not candidates for resection, and treatment for peritoneal carcinosis is experimental[18,19]. Chemotherapy is the primary treatment for recurrent gastric carcinoma and may prolong survival and improve the quality of life. The median survival with chemotherapy is poor, ranging from 6 to 13 mo[13-21].

Follow-up also plays a role in evaluating and treating the long-term adverse effects of gastrectomy[1]. Proper follow-up allows the detection of digestive problems, such as dyspepsia, nausea, vomiting, early satiety, reflux, and anorexia, which occur in approximately 30% of patients. Furthermore, postgastrectomy syndromes, such as dumping syndrome, bile reflux, Roux-en-Y stasis syndrome and afferent and efferent loop syndromes, can be identified and treated[22]. Malabsorption may cause iron deficiency anemia (approximately 30% of patients), megaloblastic anemia due to vitamin B12 deficiency, and bone diseases (osteopenia, osteoporosis)[23,24].

METHODS OF FOLLOW-UP

Follow-up is based on the case history, clinical examination, blood tests, including tumor marker assays, imaging and endoscopy.

Tumor markers

The level of tumor markers is commonly used during follow-up because the assay is simple and inexpensive to perform[25,26]. However, the specificity and sensitivity are low. Markers are less useful in patients without an increase in the preoperative level of a tumor marker. As reported by Takahashi *et al*[27] 54.7% of patients had a first-time increase in carcinoembryonic antigen (CEA) levels at recurrence, and 40% had a first-time increase in carbohydrate antigen 19-9 (CA19-9) at recurrence. In that study, the sensitivity of the two markers for recurrence was 85.0%[27]. In contrast, when the preoperative level of CEA was elevated, the CEA level increased again at the time of recurrence in more than 90% of patients. Additionally, the CA19-9 level increased again at recurrence in more than 90% of patients who had high preoperative levels[27]. In a study by Kim *et al*[28] on 1117 patients, CEA and/or CA72-4 were found to be independent risk factors for recurrence. According to the findings of Choi *et al*[29], increased CEA was more frequent in cases of liver recurrence, whereas increased CA 19-9 was more frequent in cases of peritoneal recurrence. Furthermore, it has been reported that the elevation of tumor markers occurs earlier than imaging abnormalities (approximately 2-5 mo)[27,30].

Endoscopic surveillance

Endoscopic surveillance aims to detect intraluminal recurrence, metachronous tumoral lesions, precancerous gastric stump diseases and anastomotic strictures. The role of endoscopic surveillance is fundamental after the endoscopic treatment of early gastric cancer. Hahn and colleagues reviewed a series of 1347 patients who underwent curative endoscopic submucosal dissection (ESD) for early gastric cancer[31]. These authors found an annual incidence of recurrence of 0.84% at the previous endoscopic resection site and 2.48% at other sites in the stomach. Surveillance endoscopy at an interval of $\leqslant$ 12 mo permitted the detection of lesions at an earlier stage[31]. For these reasons, the majority of authors recommend endoscopy exams with short time intervals after the endoscopic resection of early stage gastric cancer[32]. The incidence of gastric stump recurrence or metachronous cancer ranges between 1% and 7% depending on the study and geographical area[33]. The time to the development of tumoral lesions in the remnant stomach is variable, ranging from months to decades[34]. Endoscopic surveillance may allow early diagnosis and potentially curative treatment, with survival advantages for resectable patients[35].

Imaging modalities

Computed tomography (CT) represents the most-used imaging technique for the surveillance of patients with previous gastric cancer. However, only a few studies have evaluated the ability of CT to detect recurrence after gastrectomy. The accuracy is reported to be approximately 60%-70%, with a low predictive value in cases of peritoneal recurrence[36]. Many reports have investigated the role of positron emission tomography (PET)/CT[37-40]. One meta-analysis[37] that included fourteen studies (828 patients) has shown the usefulness of PET/CT in this setting: the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio of 18F-fluoro-2-deoxy-D-glucose PET (18F-FDG PET) or PET/CT were 0.85 (95%CI: 0.75-0.92), 0.78 (95%CI: 0.72-0.84), 3.9 (95%CI: 2.9-5.4), 0.19 (95%CI: 0.11-0.34), and 21 (95%CI: 9-47), respectively. On a per-lesion basis, the pooled sensitivity was 0.75 (95%CI: 0.61-0.86). The area under the SROC curve of PET/CT per patient was 0.86.

One study compared CT and PET/CT during the follow-up of 139 patients, 28 of whom had recurrence[41]. The authors did not find statistically significant differences between the sensitivity, specificity and accuracy of PET/CT (53.6%, 84.7%, and 78.4%, respectively) and those of CT (64.3%, 86.5%, and 82.0%, respectively) for detecting tumor recurrence, except in the detection of peritoneal carcinomatosis. Among 36 recurrent lesions, 8 lesions (22.2%) were detected only with PET/CT, and 10 lesions (27.8%) were detected only with CT. PET/CT detected secondary malignancies in 8 patients. According to this study, additional PET/CT or CT scans may improve the detection rate of tumor recurrence and provide other

critical information, such as an unexpected secondary malignancy. Integrated PET/CT has an accuracy ranging from 75% to 97%. However, with both CT and PET, the accuracy is lower for detecting peritoneal disease. Inoue *et al*[42] have proposed the use of second-look laparoscopy and have shown that this approach is feasible in patients at a high risk of relapse.

WHAT IS THE EVIDENCE?

No randomized controlled trials have been published on the role of follow-up after the curative resection of gastric carcinoma, and there is no proven evidence that follow-up can provide a survival advantage due to the early identification and treatment of tumor recurrence.

Cardoso *et al*[43] published a systematic review on this topic in 2012. In this study, the authors searched the literature from 1999 to 2009 and selected five retrospective studies that reported data on follow-up after gastric resection and included a total of 810 patients[44-48]. Follow-up was performed using several modalities, including the following: history and physical examination, abdominal ultrasonography, CT, endoscopy, endoscopic ultrasound (EUS), chest radiography, blood counts, chemistry profile, tumor marker assays, barium enema, and bone scintigraphy. Only one study reported that DFS was significantly shorter in the intensive follow-up group than in the standard follow-up group (11.5 mo *vs* 19.2 mo, $P = 0.02$)[44]. In the included studies, survival post-recurrence was significantly longer in the asymptomatic than in the symptomatic patients. However, no significant differences were found concerning overall survival according to the two studies reporting the information. Therefore, the authors of the systematic review concluded that there is no evidence that follow-up may provide any survival benefit after gastric cancer resection and that further prospective studies are required to determine whether a subgroup of patients may benefit from more intensive follow-up.

Two studies included in the review reported data on overall survival according to follow-up intensity. The first, a retrospective study by Tan *et al*[44] was published in 2007 and included the data from 102 patients submitted to curative gastrectomy in Singapore from 1995 to 1998. Forty-nine patients were intensively followed-up, whereas 53 received the standard follow-up. Intensive follow-up was defined as employing regular physical examinations, serum tumor marker assays and performing CT scans more than once every 12 mo. The preoperative characteristics of the patients in the two groups were similar. Neoadjuvant therapy was not administered, and adjuvant therapy was administered to 36 patients, 30 in the intensive follow-up group and 6 in the standard group ($P < 0.01$). Recurrences were detected significantly earlier in the intensive follow-up group. However, no significant difference in overall survival was found between the two groups (43% *vs* 34% at 5 years for intensive and standard follow-up, respectively, $P = 0.36$). The second study was published in 2003 by Kodera *et al*[48] from Nagoya. This retrospective study included 211 patients with relapsing gastric cancer, treated between 1985 and 1996. In this analysis, patients were divided into groups with and without cancer-related symptoms at the time the recurrent disease was diagnosed. Survival was analyzed in these two groups. The follow-up program consisted of an interim history, physical examinations, blood tests and tumor marker assays, repeated every 3 mo for the first postoperative year and every 6 mo thereafter for at least 5 years. Either abdominal ultrasonography or CT was performed every 6 mo, as was chest radiography. Endoscopy was performed annually to screen for cancer in the gastric remnant, beginning 1 to 1.5 years after surgery. In addition to this regular follow-up, patients consulted their doctors whenever the patients had clinical symptoms. Eighty-eight (45%) patients were asymptomatic at the time of diagnosis of a recurrence, whereas 109 had symptoms and consulted the physician or reported the symptoms during a scheduled follow-up. A greater proportion of the patients with asymptomatic recurrence was treated with chemotherapy and underwent resection of metastatic lesions (although these data were not statistically significant). Survival after the diagnosis of recurrent disease was better when the recurrence was detected at an asymptomatic stage ($P = 0.0001$). Longer survival in patients with asymptomatic recurrences was observed even in patients whose recurrences were not treated with chemotherapy. However, because symptomatic recurrences were diagnosed later after surgery than were asymptomatic recurrences, the overall survival after curative resection of the primary tumor was not significantly affected by the presence or absence of symptoms at the time of cancer recurrence. The authors conclude that the early detection of asymptomatic gastric cancer recurrence did not improve the overall survival of patients with recurrence after curative resection. Until the development of a more effective treatment for this disease, close follow-up may offer no survival benefit. Both of these studies and, consequently, the systematic review (the conclusions of which are based on these two articles) have several limitations: the retrospective nature of the studies, the period of treatment (prior to 2000), the protocol and administration of perioperative treatment, and the obsolescence of imaging modalities to detect recurrence.

The most recent studies report interesting results. Park *et al*[49] in 2016 reviewed the clinical data of 376 patients with intra-abdominal recurrence after curative gastrectomy. These patients were classified according to the surveillance interval. A total of 101 patients (26.9%) composed the 3 mo or less group, while 137 (36.4%) composed the 3- to 6-mo group, and 108 (28.7%) composed the 6- to 12-mo group. The

remaining 30 patients (8%) with a surveillance interval longer than 12 mo were excluded. The 3 mo or less group and the 3- to 6-mo group had higher proportions of stage 3 cancers and early recurrences within 24 mo after gastrectomy than did the 6- to 12-mo group [stage 3 cancer: 87.1% (3 mo) *vs* 81.0% (3-6 mo) *vs* 60.2% (6-12 mo), $P < 0.001$]. The recurrence rates within 24 mo after gastrectomy were 86.1% (3 mo) *vs* 78.8% (3-6 mo) *vs* 57.4% (6-12 mo) ($P < 0.001$). The proportion of patients with symptoms at the time of recurrence did not differ among the three groups ($P = 0.122$). The post-recurrence survival did not differ among the three groups ($P = 0.057$). According to the authors, although the detection of recurrence before symptoms enabled the prolongation of both post-recurrence survival and overall survival, shortening the surveillance interval to less than 6 mo was not useful in improving survival.

In 2016, Fujiya *et al*[50] retrospectively analyzed 218 patients with recurrent gastric cancer after curative gastrectomy. The patients were divided into an asymptomatic group ($n = 117$) and a symptomatic group ($n = 101$). Peritoneal recurrence was less frequent in the asymptomatic group (22.2%) than in the symptomatic group (62.4%).

The median time to recurrence was shorter in the asymptomatic group than in the symptomatic group (12.7 mo *vs* 18.9 mo, $P < 0.001$), and the median survival time after recurrence was longer in the asymptomatic group than in the symptomatic group (18.7 mo *vs* 7.5 mo, respectively, $P < 0.001$). The median overall survival time after gastrectomy was not significantly different between the groups (30.1 mo for asymptomatic recurrence *vs* 30.0 mo for symptomatic recurrence, $P = 0.132$). In a multivariate analysis, the overall survival after gastrectomy was not significantly different between the groups (HR = 0.86, $P = 0.402$). Among the patients with a nonperitoneal recurrence, the time to recurrence was similar between the asymptomatic and symptomatic groups (12.2 mo *vs* 15.2 mo, $P = 0.062$), but the survival time after recurrence was significantly longer in the asymptomatic group than in the symptomatic group (20.8 mo *vs* 7.5 mo, $P < 0.001$). The overall survival time after gastrectomy was significantly greater in asymptomatic patients with nonperitoneal recurrence than in symptomatic patients (35.9 mo *vs* 24.0 mo, $P = 0.039$).

According to this study, the detection of nonperitoneal recurrence before the appearance of symptoms may provide a survival benefit, and regular follow-up is recommended.

Lee *et al*[51] analyzed the data of 192 cancer patients with gastric cancer recurrence after curative resection. Of these patients, 126 (65.6%) had asymptomatic recurrences. The patients were divided into two groups: asymptomatic and symptomatic recurrence. The median recurrence-free survival did not differ between the two groups ($P = 0.507$), whereas the median post-recurrence ($P < 0.001$) and overall survival times ($P = 0.022$) were longer in the asymptomatic group, suggesting the utility of follow-up programs.

In 2005, Marrelli *et al*[52] proposed a scoring system to predict recurrence in patients with previous gastric cancer, with the aim of identifying the categories of patients at higher risk. These authors demonstrated that the risk of recurrence increased remarkably with the score values; the risk of recurrence was only 5% in patients with a score below 10 and rose to 95.4% in patients with a score of 91 to 100. Their model correctly predicted recurrence in 227 of 272 patients (sensitivity, 83.5%), whereas the absence of recurrence was correctly predicted in 214 of 264 patients (specificity, 81.1%); the overall accuracy was 82.2%. This scoring system was further validated with a group of 635 patients from 5 Italian Research Group for Gastric Cancer (GIRCG) centers[53]. In the validation group, the observed recurrence rates ranged from 5% to 92% in the different scoring strata. The area under the receiver operating characteristic curve was 0.889 (95%CI: 0.864-0.914; $P < 0.001$), indicating a high discrimination value of the score for recurrence. A good calibration was observed by comparing the predicted risk with the actual risk of recurrence. With a score cut-off value of 50, the sensitivity, specificity, and overall accuracy were 74%, 86%, and 81%, respectively. An inverse correlation between the time to recurrence and score level was also estimated ($R^2 = 0.119$, $P < 0.001$). In addition, Barchi *et al*[14] validated this scoring system on 185 patients with gastric cancer who underwent an operation with the intention of a cure, demonstrating that the GIRCG's prognostic score was more accurate than the TNM system in predicting recurrence mainly for high-risk patients, whereas the score did not have the same effectiveness for low-risk patients and overestimated the chance of recurrence even for disease-free patients.

A final study from Baiocchi *et al*[54] included 814 patients with recurrent cancer. Ninety-four percent had recurrence within 2 years, and 98% had recurrence within 3 years. In this study, thoracoabdominal CT and 18F-FDG PET detected more than 90% of recurrences, whereas abdominal ultrasound detected 70%, and tumor marker assays detected 40%. Less than < 10% of tumor relapses were identified by physical examination, chest X-ray, and upper gastrointestinal (GI) endoscopy. Twenty-six percent of patients with recurrence were treated, but only 3.2% were treated with the intention of a cure. On the basis of these results, the authors affirmed that follow-up should be focused on the first 3 years and based mainly on thoracoabdominal CT and 18F-FDG PET.

GUIDELINES

Different protocols have been proposed by scientific societies and groups. The lack of strong evidence is

responsible for the heterogeneity of the guidelines.

NCCN

The NCCN recommends a systematic follow-up for all patients. A history and physical examination should be undertaken every 3 to 6 mo for 1 to 2 years, every 6 to 12 mo for 3 to 5 years, and annually thereafter[55]. However, a CBC, a chemistry profile, radiologic imaging, or upper GI endoscopy should be performed if clinically indicated. Monitoring and treatment of vitamin B12 and iron deficiency is recommended in surgically resected patients.

ESMO

ESMO recommends regular follow-up for the investigation and treatment of symptoms related to previous treatments, for psychological support and for the early detection of recurrence[56]. A follow-up tailored to the individual patient and the stage of the disease is recommended. Furthermore, ESMO recommends dietary support for patients on either a radical treatment or palliative pathway with reference to vitamin and mineral deficiencies. If relapse or disease progression is suspected, then a clinical history, a physical examination and directed blood tests should be conducted.

Association of upper gastrointestinal surgeons of Great Britain and ireland, the british society of gastroenterology and the british association of surgical oncology

A regular review of patients following the treatment of esophageal and gastric cancer is recommended for symptom management, supportive care and surveillance. These organizations assert that although regular review may identify an early recurrence, there is no evidence for specific investigations or that such an approach can affect OS[57].

GIRCG

The GIRCG recommends routine follow-up for all patients for the following reasons: oncological (detection and management of cancer recurrence), gastroenterological (endoscopic surveillance and management of postgastrectomy symptoms), research (the collection of data on treatment toxicity, time to and site of recurrence, and survival and cost-benefit analyses), and pastoral (psychological and emotional support)[58]. The nutritional sequelae of gastrectomy, including, but not limited to, adequate vitamin B12 and iron, and calcium replacement should be investigated. Follow-up should be offered by members of the multidisciplinary team who managed the initial diagnosis, staging, and treatment, and modalities should be tailored to the individual patient, to the stage of their disease, and to the treatment options available. Cross-sectional imaging is recommended to detect asymptomatic recurrence. Upper GI endoscopy may be used to detect local recurrence or metachronous primary GC in patients who have undergone a subtotal gastrectomy. Routine screening for the asymptomatic recurrence of GC may be discontinued after 5 years, as recurrence beyond that interval is infrequent.

French guidelines: HAS

The French Haute Autorite de Sante recommends follow-up to detect recurrent or metachronous cancer, symptoms and adverse effects of treatment, to control the quality of life and to provide supportive care and social assistance[59]. Follow-up is recommended for at least for 5 years by the multidisciplinary team that cared for the patient and, after this period, by the general practitioner. Clinical examinations should be performed every 3-6 mo during the first 1-3 years, every 6 mo for the first 5 years, and then, after 5 years, performed once a year. Abdominal ultrasound or thoracoabdominal CT should be performed every 6 mo for 3 years and then every year for 2 years. GI endoscopy should be performed in the case of remnant stomach and precancerous lesions or *Helicobacter pylori* infections on initial biopsies (frequence of endoscopy is not specified). Blood tests for tumor markers are not recommended.

The American Society of Clinical Oncology and the Japanese Gastric Cancer Association have not provided guidelines for the follow-up of gastric cancer.

MOLECULAR BIOMARKERS

Recent research on gastric cancer has focused on molecular biomarkers. Some markers have prognostic significance; other markers are potential targets for novel chemotherapeutics. In the setting of surveillance, some of the biomarkers may represent potential prognostic indicators, able to differentiate patients according to the risk of recurrence, and potential early markers of tumor relapse. Among the prognostic markers, the expression of vascular endothelial growth factor, a regulator of angiogenesis, has been associated with a poor prognosis by several authors[60,61]. VEGF receptors are the targets of novel monoclonal antibodies that are currently being evaluated in clinical trials as potential treatments for advanced gastric cancer, such as ramucirumab and bevacizumab[62,63].

Several microRNAs, such as miR-328[64,65], have been found to be potential biomarkers for recurrence after curative resection, even though none are currently used in clinical practice.

The hypermethylation of various genes, such as cadherin 1, E-cadherin, hMHL1 and others, has been associated with the prognosis of gastric cancer[66].

Among the cell cycle regulators, cyclin E is considered a significant regulatory factor and useful prognostic parameter in gastric cancers[67]. Alterations in the *p53* gene are also associated with less favorable

prognoses in advanced gastric cancer[68]. Apoptosis-related factors are associated with the prognosis of gastric cancer patients. Bcl-2 and Fas expression are related to the progression and prognosis of gastric carcinoma[69,70]. The expression of markers such as VEGF or Bcl-2 is analyzed in the surgical specimen and may permit a better stratification of the risk of recurrence. Blood circulating biomarkers, on the other hand, may be quantified during follow-up with specific blood tests. We must point out that for novel biomarkers, the validation of a prognostic role to detect recurrence in a large cohort is still required.

Future studies will help to better characterize the role of each molecular factor and the ability of that marker to predict recurrence, allowing personalization of follow-up according to the individual risk of relapse.

CONCLUSION

Recommendations concerning the follow-up after curative resection of gastric cancer are heterogeneous, reflecting the absence of solid and high-grade evidence. The majority of international societies and authors recommend surveillance after gastrectomy on the basis of retrospective studies, although there is no consensus on how the follow-up should be conducted or how often the follow-ups should be scheduled. Surveillance permits the identification and treatment of postoperative digestive and nutritional problems, with a potential impact on quality of life. The ability of an early diagnosis to increase survival has not been demonstrated. Indeed, the outcomes after recurrence are poor according to the published series, even in cases of early diagnosis. The development of new agents based on new molecular targets may be a possible strategy to improve the survival of patients with recurrence. Several studies have demonstrated that it is possible to stratify patients submitted to curative gastrectomy into different classes according to the risk of recurrence. Prognostic scores may help clinicians to modulate the intensity and methods of surveillance.

In the future, better characterization of the molecular prognostic factors for gastric cancer will permit a better understanding of the biology of each resected gastric cancer and its risk of recurrence, enabling the establishment of a more individualized and tailored follow-up based on the tumor and patient characteristics. Tailoring the follow-up based on an accurate stratification of the recurrence risk may be a strategy to limit useless and expensive surveillance and to promptly identify recurrence patients who may benefit from treating the relapsing tumor, thereby improving survival outcomes.

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