What Follow-Up for Early Gastric Cancer Patients Radically Treated?

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Abstract: *Introduction*: At the present state of knowledge, submitting patients radically operated for Early Gastric Cancer (EGC) to an imaging-based oncological follow-up doesn't improve survival.

Materials and Methods: The present study was performed consulting the available Literature in PubMed and Embase. Manuscripts published in the period 1990-2012 were selected. A research inboard the Italian Research Group for Gastric Cancer (IRGGC) was also managed.

Results: After radical resection for EGC, the 5-years risk of recurrence is 1.7%-6.8%; the risk of another tumor is 1.2%-4.8%, so follow-up could be useless in almost 90% of cases. However, a lot of patients actually require to be followed over time after the intervention; furthermore, follow up is the only practice that should provide reliable data about time and mode of recurrence. Indeed, many high quality and high volume centers all around the world, and 100% of the 8 IRGGC Centers involved in this survey keep their patients currently under control. Looking for a rational approach, follow-up has to be especially considered for N+ patients, it has to last 5 years long and it must be based on CT with i.v. contrast medium injection alternating to abdominal ultrasonography.

Conclusions: Despite the absence of a clear survival advantage, the practice of follow-up after radical gastrectomy for EGC should be supported.

Keywords: Early gastric cancer, surgery, follow-up, prognosis, CT scan, chemotherapy.

INTRODUCTION

After curative surgery for gastric cancer, it is not currently clear whether to keep the patient in instrumental routine follow-up offers an advantage in terms of quality of life and survival [1, 2]. This is especially true in the case of early gastric cancer (EGC), considering the high probability of cure that radical surgery may enable [3].

There are multiple reasons for refer patients operated for EGC to clinical and instrumental seriated checks: first of all, the diagnosis of recurrence in an asymptomatic phase should allow to treat less advanced recurrence cases and this may translate into better survival results. Second, there are nutritional complications of gastrectomy that patients might fail to recognize, the treatment of which has beneficial consequences on the quality of life. Finally, the majority of patients feel protected and safe by having to meet their physicians at regular intervals.

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However, there are also a number of considerations adverse to follow-up: no scientific paper has ever shown that it leads to a significant improvement in the survival time, thus actually this is only a hope for the future; furthermore, the diagnosis of recurrence in an asymptomatic stage, in the absence of effective treatments courses, is equivalent to an anticipation of the diagnosis of death; finally, in this period of limited resources, we must consider the costs of protocols based on repeated routine examinations.

The present paper aims to analyze the existing literature on the issue of follow-up, specifically focused on the patient affected by EGC treated in a radical way.

MATERIALS AND METHODS

Electronic literature searches were conducted using Medline and Embase, from 1980 to 2012. “Early Gastric Cancer”, “Follow-up”, “Recurrence”, “Prognosis” were entered as key-words. Included were all the studies meeting the following: patients with gastric adenocarcinoma; reported outcomes of follow-up after gastrectomy; main or subgroup analysis specifically focused on EGC patients; peer-reviewed

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journals; English language. Reviews, meta-analyses, systematic reviews, editorials, letters and guidelines were also included. All titles were reviewed by 2 investigators (GLB and SM).

Three hundred and eleven abstracts were selected, whose argument could contain useful references, of which 41 papers were read in full and 16 were accepted as being centered on the above subject. Among the 16 articles, none were randomized controlled trials (RCTs) or prospective studies [4-12].

The present paper was presented at the international conference “Bertinoro, a meeting point for High Grade Dysplasia and Early Gastric Cancer between East and West toward the 10th IGCC. Diagnosis and treatment”, held in Bertinoro (Forlì, Italy), November the 30th and December the 1st , 2012.

RESULTS AND DISCUSSION

Let's take a common clinical scenario: a 53-years old man, in good general clinical conditions and without a significant previous medical history, is diagnosed by upper GI endoscopy as having antral ulcerated adenocarcinoma of approximately 2 cm in maximum diameter, whose preoperative staging, performed by contrast-enhanced CT scan, is cT1-2N0M0; the patient underwent subtotal gastrectomy with D2 lymphadenectomy and was discharged home on 7th post-operative day; histological examination revealed a Lauren intestinal-type gastric adenocarcinoma, G2, stage pT1smN0(0/21)M0. What follow-up protocol might we offer to this man?

Those who would bring an intensive follow-up, based on clinical and major instrumental examinations such a s CT scan (for example, checks every 3 months for 1 year, every 6 months up to 3 years and every 12 months up to 10 years after surgery), would accept to unnecessarily perform 90-95% of examinations, since the likelihood of relapse is comprised between 1.7% [12] and 6.8% [13], and the likelihood of a second tumor ranges from 1.2% [12] and 4.8% [14]; on the other hand, those who would propose an intermediate follow-up protocol, i.e. clinical, biochemical and ultrasound (for example, every 6 months for 2 years and every 12 months up to 5 years), would accept the fact that about 50% of recurrences would not be detected by these tests: it is well known that " Overall, classical practice of follow-up, mainly based upon outpatient clinical assessment, chest x-ray and ultrasonography, has a poor ability of detecting asymptomatic recurrences“ [1]. Finally, those who suggest not to do any follow-up at all, comes up against the common practice, accepted and basically requested by patients and surgeons itself: "Globally, surgeons want to follow-up the patients, and patients ask to be followed for longtime. Moreover, post-operative nutritional deficits remain a concern "[15].

In the absence of scientific data providing evidence-based indications on this topic, it may prove to be worthwhile to come back to personal feeling and experience of the surgeon; thus, it may be useful to note how do centers with high volume of gastric cancer activity and high-quality care behave. According to a recent national survey in Korea [16], and to the official position of the Italian Research Group for Gastric Cancer [17], there are some merely theoretical remarks according to which patients need to be regularly followed after gastrectomy: first of all, the hope that biomedical research will offer in the future therapeutic weapons for the metastatic and/or relapsed patients, with results similar to those currently available for patients with colorectal cancer [18]. Moreover, 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. Finally, it has been demonstrated (and we’ve got the distinct feeling) that being subjected to seriated scheduled checks do not represent a source of stress for most patients, but this has rather the potential of reassuring them [19].

On the other hand, it is certainly needed that follow-up schedules are founded on more solid rationale, by identifying those tests and examinations with the best reliability and sensitivity, and by limiting them to a period in which recurrence is likely. We therefore need to define which patients will be subjected to oncological follow-up, for how long, with what means and with what purpose.

As regards the patient selection, there are several retrospective series analyzing the prognostic factors of recurrence in patients operated on for EGC; Lai, for example (79 recurrences out of 2923 cases), reported that the presence of lymph node metastases and elevated gross appearance, if present in the same patient, increased the likelihood of recurrence from 2.7% to 17.1% [14]. In the series of Huang [22 recurrences out of 323 cases), however, poorly

differentiated EGC, micro vascular infiltration and lymph node metastasis were significantly related to recurrence rate [13]. Considering other series [12, 20, 21], the only parameter that is consistently related to the probability of recurrence is the presence of nodal metastases, while other factors (degree of differentiation, vascular infiltration, gross appearance, number, location, depth, age and familiarity) were significant only in some series. We can therefore conclude that follow-up should be primarily offered to patients radically treated for EGC with nodal metastases.

As for the length of follow-up, in the series published by Lai, 60.7% of recurrences were discovered within 2 years, 77.3% within 3 years, and 91.1% within 5 years; Youn, Lee and Yamamoto report that the proportion of recurrences diagnosed within 5 years is more than 90% [21-23]; nevertheless, it should be mentioned a paper by Sano, where this percentage decreases to 40% at 3 years and 77% at 5 years, with 23% of recurrences diagnosed beyond the 5 years [24]. With this exception, it can be considered that after 5 years "the death rates from nongastric cancers were significantly higher than those for recurrent gastric cancers. The validity of what is effectively screening for other cancers is dependent on national priorities" [2].

Instead, it appears very difficult to establish what diagnostic tools are better characterized by a favorable cost-benefit ratio. Guidelines actually provide only "complete history and physical examination (investigations are recommended as clinically Indicated by symptoms)" (NCCN) and "symptom-driven visits (directed investigations only in patients who are candidates for further treatment)" (ESMO) [25]; at the other end, in the current clinical practice of many centers around the world patterns of follow-up are very complex (Figure **1**). However, it may be worth considering that the most typical presentation of EGC recurrence is haematogenous, representing 63-83% of cases [12, 13, 21, 24, 26,], while lymph node/local and peritoneal recurrences represent respectively 13-20% and 10-32% of cases [14]. It therefore makes sense to search for EGC recurrence in asymptomatic phase mainly by contrast-enhanced CT scan [21, 27]: in the paper by Youn (85 recurrences out of 3883 cases), the CT scan allowed to identify recurrence in 81% of cases. Some recent papers have proposed the use of 18FDG-PET scan; for example, in a small chinese series of 23 cases, the accuracy of 18FDG-PET was found to be as high as 82 .6% and it changed the therapeutic strategy in 30.4% of cases [28]. By contrast, upper GI endoscopy can detect a very small number of recurrences; for instance, Lee [22] found a recurrence in the gastric stump in 0/212 EGC (and 24/622 AGC), and also in the multicenter experience of IRGGC, 0/98 patients with EGC which have been regularly given endoscopic surveillance had intraluminal relapse after a mean follow-up of 9 years

MILD

Months	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
Tumor markers*		X		X		X		X		X		X	X	X	X	X
Abdominal Ultrasound		X		X		X		X		X		X	X	X	X	X
Chest X-ray				X				X				X				
Thoraco-abdominal CT scan																
Endoscopy				X				X				X				X

* CEA, CA 19-9, CA 72-4
CT scan: increase of tumor marker levels, clinical or radiological suspicion of recurrence

MODERATE

Months	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
Tumor markers*	X	X	X	X	X	X	X	X		X		X	X	X	X	X
Abdominal Ultrasound		X				X				X			X		X	X
Chest X-ray																
Thoraco-abdominal CT scan				X				X				X		X		
Endoscopy				X				X				X				X

* CEA, CA 19-9, CA 72-4

INTENSIVE

Months	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
Tumor markers*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Abdominal Ultrasound													X		X	
Chest X-ray																
Thoraco-abdominal CT scan		X		X		X		X		X		X		X		X
Endoscopy				X				X				X				X

* CEA, CA 19-9, CA 72-4

Figure 1: Follow-up protocols proposed by the IRGGC, on the basis of recurrence risk and patients' compliance with follow-up. The model to calculate the IRGGC prognostic score can be downloaded from the website: www.gircg.it (With permission, Marrelli D, Caruso S, Roviello F. Follow-up and treatment of recurrence. In: G. de Manzoni, F. Roviello, W. Siquini (eds.), Surgery in the Multimodal Management of Gastric Cancer, Springer-Verlag Italia 2012).

[29]. Clinical examination, abdominal ultrasound, chest x-ray and tumor markers [30-32], even though potentially valuable in the follow-up of patients operated for EGC, have a significantly lower chance to detect a relapse.

But the most important point of discussion is the fate of patients to whom asymptomatic recurrence of EGC is diagnosed. Indeed, very few papers demonstrate that recurrence is still subject to some kind of treatment. Kodera reported a series in which the diagnosis of recurrence at an earlier stage allowed a greater proportion of patients to be treated with chemotherapy; a possible explanation is related to the fact that the performance status was higher in this subgroup of patients [8]. In addition, a recent small series was published by Villareal Garza, in which the percentage of curative redo-resections and chemotherapy was significantly higher in patients whose recurrence was detected in asymptomatic phase than in patients who were not submitted to regular follow-up (14.3% versus 1.3% and 70.5% versus 42.9%, respectively). However, the actual numbers in this series are really very low [33]. We should also mention another brief series of 26 patients who underwent exploratory laparotomy for suspected recurrence and a radical resection was possible in 50% of cases [34], and the series of 11 liver resections for metachronous liver metastasis presented by the IRGGC in 2009 [35].

In conclusion, although at the present state of knowledge there is no incontrovertible evidence about the role of oncological follow-up after radical gastrectomy for cancer, and many monocentric retrospective series have clearly demonstrated that early diagnosis of tumor recurrence in the asymptomatic phase has not resulted in an improvement in survival compared to late diagnosis motivated by symptoms, the daily practice of many centers at high volume of gastric cancer surgery and high quality of care, requires that the patient is not abandoned after surgery, but it is submitted to clinical and instrumental seriated checks with the aim to minimize the nutritional sequelae of gastrectomy and to lead to a timely diagnosis of tumor recurrence. To do so in a rational manner, mainly patients with N+ EGC should be subjected to seriated controls by CT scan and eventually 18FDG-PET, only in cases of a known 18FDG-avid tumor, for a maximum of 5 years.

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