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Follow-Up After Gastrectomy for Cancer: An Appraisal of the Italian Research Group for Gastric Cancer

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ABSTRACT

Background. The Italian Research Group for Gastric Cancer supports the practice of follow-up after radical surgery for gastric cancer.

Methods. This multicenter, retrospective study (1998–2009) included patients with T1-4N0-3M0 gastric cancer who had undergone D2 gastrectomy and lymphadenectomy, with at least 15 lymph nodes examined, and who had developed recurrent disease. Timing and site of recurrence were correlated to the actual scheduled follow-up timing and modalities.

Results. From eight centers, 814 patients with recurrent cancer and over 1,754 (46.4 %) patients undergoing gastrectomy were investigated (median follow-up 31 months). The most frequent sites of recurrence were local/regional lymph nodes (35.4 %), liver (24.3 %), peritoneum (30.3 %), lung (10.4 %) and intraluminal (7.5 %). Ninety-four percent of the recurrences were diagnosed within 2 years and 98 % within 3 years. Thoracoabdominal computed tomography (CT) scan and (18)F-fluoro-2-deoxy-D-glucose positron emission tomography (18-FDG-PET) detected more than 90 % of recurrences, abdominal ultrasound detected 70 % and tumor markers detected 40 %, while <10 % were identified by physical examination, chest X-ray, and upper gastrointestinal endoscopy. Twenty-six percent of patients with recurrence were treated, but only 3.2 % were treated with potentially radical intent.

Conclusion. Oncological follow-up after radical surgery for gastric cancer should be focused in the first 3 years, and based mainly on thoracoabdominal CT scan and 18-FDG-PET.

Gastric cancer is one of the most common cancers in the world. Unlike other tumors of the gastrointestinal tract, surgery remains the mainstay of therapy. However, after radical gastrectomy, a significant proportion of patients have a recurrence[1–5] and this is almost always a fatal event. A lot of studies have investigated the clinical significance of follow-up after curative surgery, and all agreed that early detection of recurrence in asymptomatic patients does not guarantee any benefit in terms of survival.[6–11]

The attitude adopted by the Italian Research Group for Gastric Cancer (IRGGC) after primary treatment was to always provide an intensive, clinical, and instrumental follow-up,[12] aimed either at early diagnosis of recurrence or at treatment of dietary changes/nutritional deficits

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related to gastrointestinal reconstruction, at least in the first postoperative years. However, in light of the literature, this practice should be critically analyzed. The Scientific Committee of the IRGGC promoted a survey about timing, methods, and results of follow-up schemes currently in use, in order to clarify what control tools are more likely to be useful, within what time cancer recurrence can be expected, and what proportion of patients can actually benefit from a therapy of relapse.

PATIENTS AND METHODS

Eight centers participated in this survey. The period under consideration was 1998–2009 (patients alive with follow-up lower that 24 months were not included). The global caseload of gastric cancer in this period, including all patients undergoing R0 gastrectomy for adenocarcinoma, with examination of at least 15 lymph nodes, amounted to 1,754 cases. Median follow-up was 31 months (range 8–131). Data were prospectively collected in a common database. Starting from this series, in the present work all patients who have developed a cancer recurrence during the course of regular follow-up were included; patients with metastases at the preoperative staging were excluded. The schedule of follow-up used by the participating centers was the one officially recognized by the IRGGC, which was modulated on age and risk of recurrence, stratified into low, medium and high, according to a previously proposed and already prospectively validated score (see Accessory Table).[13,14]

The following data were collected for all 814 patients with recurrence: age, sex, tumor location and size, Lauren histotype, T and N stage [American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) 7th edition], grading, vascular and neural invasion, type of intervention, associated resections, number of retrieved nodes, 30-day mortality and morbidity, preoperative tumor markers [carcinoembryonic antigen (CEA)/carbohydrate antigen 19-9 (CA19-9)], recurrence-free survival, mode of recurrence diagnosis, tumor markers at recurrence (CEA/CA19-9), localization of recurrence (locoregional/lymph nodal, liver, peritoneal, endoluminal, lung, bone, etc.), treatment of recurrence, overall survival (OS), and cause of death. The sensitivity of diagnostic tools for recurrence diagnosis over the entire follow-up was evaluated as follows:

$$\text{Sensitivity over the entire follow-up} = \frac{\text{No. of recurrences diagnosed by an examination}}{\text{No. of patients who underwent follow-up including that examination}}$$

Sensitivity was computed regardless of the number and timing of repeated investigations.

The OS after gastrectomy and relapse was assessed. Timing of recurrence was divided into very early (1–6 months), early (7–18 months), late (19–36 months) and very late (>37 months). The survival curves of patients having their recurrence diagnosed in these different periods were compared. When performed, treatment of recurrence was classified into potentially radical (treatment of a local recurrence that could achieve a theoretical state of no residual disease) or palliative (hepatic transarterial chemoembolization, systemic chemotherapy alone). The survival of patients treated with potentially curative therapy, palliative therapy, or best supportive care were compared. Finally, the treatment of recurrence was stratified and distinguished between the periods 1998 and 2001, 2002 and 2005, and 2006 and 2009.

The present work was approved by the Institutional Review Committees and meets the guidelines of the Italian governmental agency.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Software Computer Sciences (SPSS Inc., Chicago, IL, USA) for Windows (version 17.0). Fisher's exact test and Chi square test were used to evaluate significance of differences in type of treatment as a function of time of recurrence or calendar period, as well as differences in site and timing of recurrence among different calendar periods. Disease-free survival (DFS) was defined as the time from the date of primary resection to the time of recurrence. OS was measured from the date of primary resection to the date of death or the last follow-up. In an ancillary analysis, OS was also computed from the date of recurrence detection. Survival curves were generated using the Kaplan–Meier method, and statistical significance was determined using the log-rank test. All p values were two-sided and a p value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the clinical and pathological data of this multicenter series, which reflects the characteristics of a typical series of Western patients with recurrent gastric

TABLE 1 Clinical and pathological features of primary cancer and recurrence of 814 patients with recurrent gastric cancer after curative resection, from eight centers participating in the Italian Research Group for Gastric Cancer

		N	%
Sex (M/F)	492/322		
Median age, years (range)	59 (28–91)		
Location	Upper	201	24.7
	Middle	184	22.6
	Lower	361	44.3
	Multiple	68	8.4
Mean size, cm (range)	5.36 (3–16)		
T	T1	31	3.80
	T2	95	11.6
	T3	539	66.2
	T4	149	18.3
N	N0	38	4.66
	N1	156	19.1
	N2	474	58.2
	N3	146	17.9
Lauren histotype	Intestinal	384	47.2
	Diffuse	328	40.3
	Other/mixed	102	12.5
Grading	G1	103	12.6
	G2	289	35.5
	G3	422	51.8
Vascular or neural invasion		516	63.4
Intervention	Subtotal gastrectomy	357	43.8
	Total gastrectomy	457	56.2
Number of mean nodes (range)	29.1 (15–85)		
Associated resections (splenectomies)		171 (149)	21.0 (18.3)
30-day mortality		18	2.2
Major morbility		194	23.8
Preoperative tumor markers increased[a]	CEA	78	9.6
	CA19-9	140	17.2
Recurrence site[b]	Local/nodal	288	35.4
	Hepatic	198	24.3
	Peritoneal	247	30.3
	Pulmonary	85	10.4
	Endoluminal	61	7.5
	Bone	29	3.6
	Other	73	9.0
Recurrence timing	≤6 months	171	21
	7–18 months	513	63
	19–36 months	114	14
	>37 months	16	2
Recurrence therapy[b]	None	599	73.6
	Hepatic resection	14	1.7
	Percutaneous ablation	7	0.9
	Radiotherapy	6	0.7
	Local recurrence resection	9	1.1
	HIPEC	4	0.5
	TACE	5	0.6
	Chemotherapy	208	25.6
Recurrence therapy aim	Potentially radical	26	3.19
	Palliative	189	23.2

M male, *F* female, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *HIPEC* hyperthermic intraperitoneal chemotherapy, *TACE* transcatheter arterial chemoembolization

[a] Normal values are CEA <5 ng/dl and CA19-9 > 37 UI/dl

[b] Some patients had more than one recurrence and received more than one treatment

cancer. The sites of recurrence were divided as follows: local/regional lymph nodes (35.4 %), peritoneum (30.3 %), liver (24.3 %), lung (10.4 %), intraluminal (7.5 %), bone (3.6 %), and other locations (9.0 %). The median time to recurrence was 13.2 months; 94 % of recurrences were diagnosed within 2 years (21 % within 6 months, 49 % within 12 months, 84 % within 18 months, and 98 % within 36 months). Of the 814 patients with recurrence, 215 (26.4 %) had a treatment of relapse, aimed at local control in 39 cases; the treatment was potentially radical in 26 cases, while in the remaining 189 patients, the treatment had only a palliative purpose.

Table 2 describes the methods of recurrence diagnosis, and the relative effectiveness. Only thoracoabdominal computed tomography (CT) scan and (18)F-fluoro-2-deoxy-D-glucose positron emission tomography (18-FDG-PET) could identify more than 90 % of recurrences (93.6 and 91.0 %, respectively), while abdominal ultrasound, tumor markers, and diagnostic laparoscopy demonstrated an intermediate ability in the diagnosis of recurrence (69.6, 39.5 and 69.0 %, respectively). Chest X-ray, upper gastrointestinal endoscopy, and clinical visit were shown to have a very low (<10 %) diagnostic yield.

The survival of patients who developed recurrence after curative surgery for gastric cancer is shown in Fig. 1. Obviously, this is a group of patients with particularly poor prognosis; almost none of the patients, except some anecdotal cases, were alive 5 years after gastrectomy (Fig. 1a), and almost none were alive 3 years after relapse (Fig. 1b).

TABLE 2 Performance of diagnostic tests in detecting gastric cancer recurrence

Diagnostic technique	No. of patients examined (%)	No. of recurrences detected	Percentage of detected recurrences (95 % CI)
Clinical assessment	797 (97.9)	26	3.3 (2.1–4.7)
Abdominal ultrasound	728 (89.4)	507	69.6 (66.2–73.0)
Chest X-ray	721 (88.6)	38	5.3 (3.8–7.2)
Upper GI endoscopy	749 (92.0)	61	8.1 (6.3–10.3)
Tumor markers	623 (76.5)	246	39.5 (35.6–43.4)
CT scan	582 (71.5)	545	93.6 (91.3–95.5)
Total body 18-FDG-PET scan	211 (25.9)	192	91.0 (86.3–94.5)
Laparoscopy	29 (3.6)	20	69.0 (49.2–84.7)

Percentage of detected recurrences is computed as the number of recurrences detected to the number of patients undergoing that examination in the postoperative follow-up. Exact confidence intervals were computed

GI gastrointestinal, *CT* computed tomography, *18-FDG-PET* (18)F-fluoro-2-deoxy-D-glucose positron emission tomography

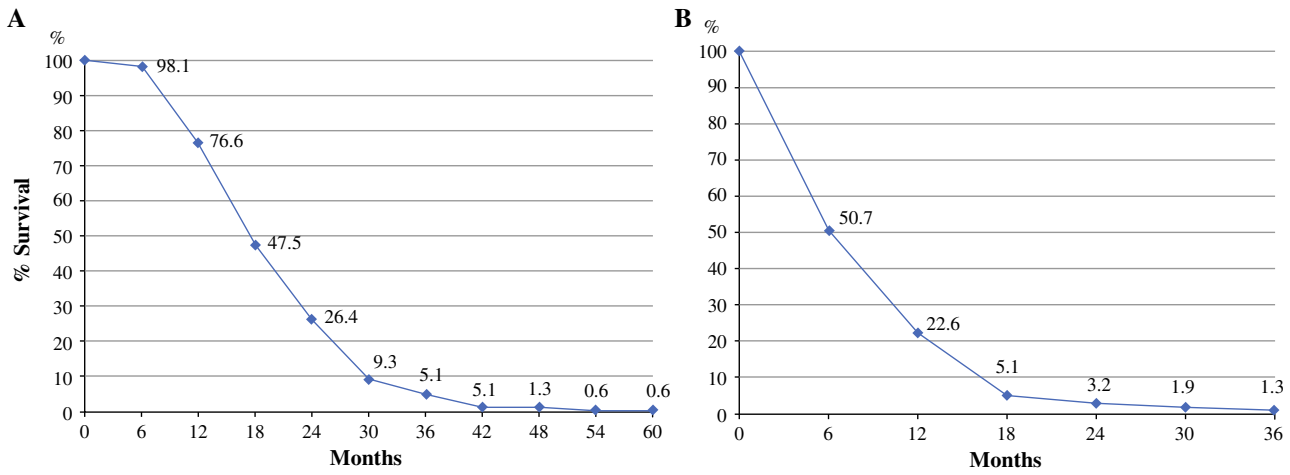
The likelihood of receiving treatment, either potentially radical or palliative, was independent from the time of recurrence (19.2, 25.3, 29.7 and 25 % for patients with very early, early, late, and very late relapse, respectively). By contrast, as reported in Fig. 2, survival after recurrence was significantly related to the timing of recurrence. The survival 12 months after recurrence was 65.3, 32.2 and 17.7 %, and the survival 24 months after recurrence was 38.4, 6.3 and 2.6 % for patients undergoing potentially curative treatment of recurrence, palliative chemotherapy, and no treatment, respectively (overall, $p = 0.039$; $p = 0.021$ for radical therapy versus no treatment, $p = 0.043$ for radical therapy vs. palliative chemotherapy, and $p = 0.038$ for chemotherapy versus no treatment).

Within the analyzed period, there was a significant change in the percentage of patients with recurrent gastric cancer who were offered treatment of relapse (Table 3), characterized by an increase in the rate of treated patients in the last 4 years compared with that in the two previous periods ($p < 0.001$). In particular, the rate of patients treated with palliative chemotherapy slightly increased from 1998–2001 to 2002–2005 ($p = 0.159$) and nearly doubled in the subsequent period ($p < 0.001$).

DISCUSSION

If there is one issue concerning the treatment of gastric cancer in which the literature is quite unanimous, it is the futility of follow-up, as clearly expressed in a number of retrospective series from both the Eastern[7–9] and Western Centers,[6,10,15,16] and in a systematic review.[11] In particular, it should be noted that a diagnosis of recurrence in the asymptomatic phase is unable to improve survival and, in certain instances, worsens the quality of life of patients from the psychological point of view, by anticipating by some months the diagnosis of death.

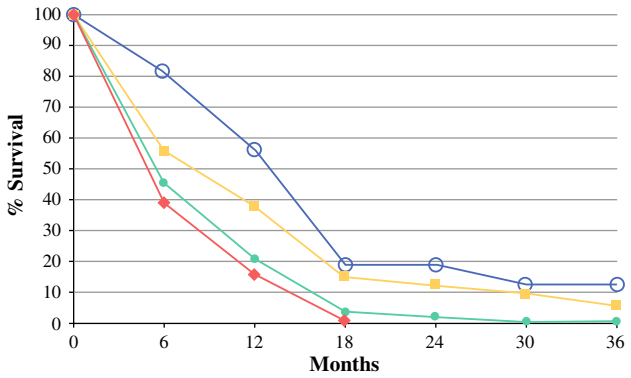
In the present paper we report a 10-year picture of follow-up after curative surgery for gastric cancer in eight centers belonging to the IRGGC. A number of suggestions



m	0	6	12	18	24	30	36	42	48	54	60
pts	814	799	624	387	215	76	41	11	11	5	5

m	0	6	12	18	24	30	36
pts	814	413	184	41	27	16	11

FIG. 1 Overall survival of 814 patients with recurrent gastric cancer, computed as either **a** time since R0 gastrectomy or **b** time since recurrence



m pts		0	6	12	18	24	30	36
	≤6 months (171)	171	66	27	2	0	0	0
	7-8 months (513)	513	231	105	19	10	3	2
	19-36 months (114)	114	63	43	17	14	11	7
	≥37 months (16)	16	13	9	3	3	2	2

FIG. 2 Overall survival, computed as time since recurrence, in 814 patients with recurrent gastric cancer, according to the timing of recurrence. Significant differences were detected between patients relapsing within 6 months and patients relapsing after 19–36 months ($p = 0.048$) or thereafter ($p = 0.031$). The differences between the other survival curves were not statistically significant

TABLE 3 Trends in treatment for patients with recurrent gastric cancer in three consecutive periods in eight centers belonging to the IRGGC

Period	*n*	R0 treatment [*n* (%)]	Palliative treatment [*n* (%)]	No treatment [*n* (%)]	*p* value
1998–2001	297	9 (3.03)	42 (14.14)	246 (82.8)	
2002–2005	281	6 (2.13)	56 (19.92)	219 (77.9)	0.159[a]
2006–2009	236	11 (4.66)	91 (38.55)	134 (56.7)	<0.001[b]
Total	814	26 (3.19)	189 (23.2)	599 (73.6)	<0.001[c]

p values were computed using Fisher's exact test

IRGGC Italian Research Group for Gastric Cancer

[a] Significance of differences between 1998 and 2001, and 2002 and 2005

[b] Significance of differences between 2002 and 2005, and 2006 and 2009

[c] Significance of differences over the entire period

clearly emerged. First, after the first 3 years the likelihood of diagnosing a recurrence is low enough to suggest the practice of follow-up planned for many years to be largely unjustified.[17,18] Although 16 patients whose recurrence was diagnosed after 36 months had better survival than those with early recurrence, it does not appear that this small group of patients (1.96 %) received treatment of relapse more frequently than others (25 %, compared with an average of 26.4 % for the whole series). Considering the limited resources, it seems appropriate to concentrate efforts and costs on the first 36 months after surgery, in order to identify 98 % of patients with cancer relapse. After that, follow-up may be continued only on a voluntary basis, or in a very selected subgroup of patients having a high risk of late recurrence. This statement is partially in contrast to that recently reported by Korean and Japanese authors,[18–20] who consider recurrences after 3 years as fairly frequent (9 % in the series of Nashimoto et al.[19]), and not quite rare after 5 years (23 % in the early gastric cancer series of Sano et al.[21]). However, Western experiences are different; in a previous IRGGC series of 272 patients with recurrence, only 3.3 % of cases were diagnosed after 5 years,[13] and in the present series only 6 % of recurrences were discovered 2 years after gastrectomy. A possible explanation of this difference in recurrence timing is related to the different early gastric cancer rate, which is actually as high as 50 % in the Eastern series; early gastric cancers eventually recur in a later period; thus, this may represent a subgroup of patients for which a longer period of surveillance is warranted. However, the advantage of performing regular instrumental controls in the long term should be analyzed in light of screening programs, considering that the incidence of new tumors of other organs is even higher. As such, why should only the stomach, and not the lung, colon, prostate, etc., be investigated?

Second, what is the ideal follow-up schedule? Patterns of examinations used in various centers differ substantially in timing and mode, as evidenced by the fact that in some series the rate of relapse detected in the asymptomatic phase is only 20 %,[6] while in others it is 45–50 %[8,16] or even more than 75 %.[7] As clearly expressed in Table 2, from our data the only instruments characterized by a good ability for showing a recurrence are contrast-enhanced thoracoabdominal CT scan and whole-body 18-FDG-PET, while abdominal ultrasound and tumor markers have intermediate figures. On the contrary, clinical examination, standard chest X-ray, and upper gastrointestinal endoscopy can detect recurrence in a very limited number of cases—as low as below 10 %. In our series, upper gastrointestinal endoscopy was positive in 8.1 % of patients with recurrence, resulting in an impressive rate of negative procedures. In a previous study specifically designed to evaluate the usefulness of endoscopy in the follow-up of patients undergoing total gastrectomy, 0/212 early gastric cancer and 24/622 advanced gastric cancer cases had an anastomotic recurrence, or, expressed with our method, 0/2 recurrent early gastric cancer cases (0 %) and 24/233 recurrent advanced gastric cancer cases (10.3 %) were detected by upper gastrointestinal endoscopy.[23] Moreover, in a fair percentage of cases, CT and/or 18-FDG-PET could at least raise the suspicion of intraluminal recurrence. In a recent IRGGC series of 98 multifocal early gastric cancer cases treated by distal gastrectomy, no case of gastric

remnant relapse was observed at a mean follow-up of 9 years (range of 1–28).[24] Thus, it is time to reflect on the role of endoscopy in gastric cancer follow-up. From a pragmatic point of view, it may not be performed routinely during follow-up, but should be carried out on patients with warning signs (dysphagia, anemia, melena, hematemesis, etc.) or in cases with suspicious CT scan or 18-FDG-PET.

Tumor markers and abdominal ultrasound have been shown to have an ability to diagnose a recurrence of 39.5 and 69.6 %, respectively. Both are non-invasive and less expensive than CT scan and 18-FDG-PET, and are known to be characterized by high specificity but a relatively low sensitivity. In a previous IRGGC study, CEA and CA19.9 were shown to have 44 and 56 % sensitivity, and 79 and 74 % specificity, respectively.[25] Similar data were reported by other series.[26–28] In all these papers, it is stressed that the accuracy of the diagnosis of recurrence is higher in patients in whom these markers are altered at preoperative stages, which are known to be a minority (21.4 % in our series). When the ability of tumor markers to diagnose a symptomatic recurrence before other imaging modalities was specifically evaluated, the results were discouraging.[27]

In recent years, significant data related to the risk of being affected by cancer induced by medical radiation raised concerns about the use of CT scan and 18-FDG-PET. In particular, it is actually stated that given a standard of at least two phases, thoracoabdominal CT scan and 18-FDG-PET combined with CT, the risk of developing a radio-induced tumor is ~ 1 in 1,500–2,000 examinations.[29,30] Thus, a patient who undergoes such examinations at least six times after surgery for gastric cancer (one every 6 months for 3 years) runs a risk estimated at one new cancer per 250 patients (0.004 %). It is clear that such a risk is totally inconsistent when compared with that of having a relapse (50 % approximately). The proposal of a prevalent use of CT in the follow-up of gastric cancer is consistent with more recent patterns reported in the literature.[9,17,31] In recent years, 18-FDG-PET has also gained an important role in the follow-up of cancer patients, but data are still inconsistent.[32,33]

Considering the retrospective non-randomized design of the study, patients receiving different treatments are not homogeneous. Those undergoing surgery for recurrence are usually younger and in good conditions, and have a relapse that is most often limited and late. However, the few studies that have stratified for treatment homogeneous groups of patients with recurrence showed that aggressive treatment can, in some cases, offer a chance for increased survival.[34] This is particularly true for metachronous liver metastases. Retrospective reports have been reported on a total of more than 150 patients undergoing hepatectomy, with 5-year survivals between 20 and 38 %,[35–37] suggesting that liver resection could be considered in patients in whom this may result in R0 resection. With regard to extrahepatic metastases, only a short Spanish series recently reported that 11 % of patients with recurrence were operated, with a median DFS time of 26 months.[38] The data presented here do not confirm these numbers since the number of patients treated for extrahepatic recurrence with potentially radical intent was only 12 (1.47 %). However, including both surgery, percutaneous ablations, and systemic chemotherapy, more than one of four patients with recurrent gastric cancer in our series received a type of therapy for relapse. It seems worthy of note that the temporal evolution of this attitude shows a significant increase in the percentage of patients receiving systemic chemotherapy. It is clear that to make sense of the oncological follow-up, it is crucial that the discovery of recurrence should prompt a certain type of treatment, and this, contrary to that widely held to date, seems to be the trend of recent years.

CONCLUSIONS

In the present paper, a critical analysis of follow-up after gastrectomy for cancer is presented, on the basis of the clinical experience of eight centers participating in the IRGGC, and with the aim of investigating the rational and limits of such a practice. Analyzing the results of multiple examinations in 814 patients with cancer recurrence, we conclude that oncological follow-up should be limited to the first 3 years after gastrectomy, and mainly based upon contrast-enhanced thoracoabdominal CT scan and 18-FDG-PET.

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