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In Search of an Ideal Follow-Up in Colorectal Cancer Resected for Cure – A Ten-Year Experience

Summary Two different follow-up programmes were compared in a prospective study of 86 patients with carcinoma of the colon and rectum. Thirty-four patients had an intensive instrumental follow-up (CAT scan, ultra-sonography, chest X-ray etc.) and 52 patients had a simplified follow-up (CEA, history and physical examination). No differences were observed in the number of recurrences, median period of diagnosis of recurrence and number of reoperations with curative intent within two years after operation. An intensive instrumental follow-up and a simplified follow-up were equally effective in the early detection of colorectal cancer recurrences. A simplified follow-up with a moderately aggressive surgical attitude appears to be an effective compromise to detect and remove localised recurrences.

(Keywords: Colorectal cancer, CEA, follow-up)

Résumé Les auteurs rapportent les résultats d'une étude prospective portant sur 86 malades ayant un carcinome colique ou rectal; cette étude ayant pour but de comparer deux types différents de suivi. 34 malades furent suivis de façon intensive à l'aide d'examen complémentaires (scanner, échographie, radio thoracique etc.) et 52 eurent un suivi simplifié (ACE, interrogatoire, examen clinique). Au cours des deux années suivant l'intervention chirurgicale, il n'y eut aucune différence entre les deux groupes en ce qui concerne le nombre de récurrences, le laps de temps moyen avant un éventuel diagnostic de récurrence et le nombre de réinterventions à but curatif. Les deux méthodes de suivi se sont avérées également efficaces quant à la détection précoce des récurrences. Un suivi simplifié et une attitude chirurgicale modérément agressive semblent être un compromis efficace permettant de détecter et de traiter les récurrences cancéreuses locales.

(Mots clés: Cancer colorectal, ACE, suivi)

Resumen Dos programas diferentes de control fueron comparados en un estudio de 86 pacientes con carcinoma del colon y recto. A 34 pacientes se les hizo un control intenso instrumental (CAT scan, ultrasonografía, rayos X de pecho, etc.) y a 52 pacientes un control simplificado (CEA, historia clínica y examen físico). No se observaron diferencias ni en el número de recurrencias, a los dos años después de la operación, ni período de diagnósticos de recidivas y número de reoperaciones con intención curativa. Un control completo instrumental y uno simplificado dieron una eficacia igual en la localización precoz de las recidivas del cáncer colorrectal. Un control simplificado con una actitud quirúrgica moderadamente agresiva parece ser un trato eficaz para detectar y extirpar recidivas localizadas.

(Palabras clave: Cáncer colorrectal, CEA, control)

Introduction

In a previous paper, the role of sequential carcinoembryonic antigen (CEA) determinations and instrumental follow-up for the early detection of resectable recurrences in a group of patients operated on between 1979 and 1983, was retrospectively evaluated. On that occasion, we observed that to detect early recurrences, CEA-guided follow-up (which included history and physical examination) was possibly as effective as an intensive instrumental follow-up [1]. We therefore undertook a prospective study on patients operated on with curative intent of colorectal cancer. This was done to confirm the role of sequential CEA determinations, physical examinations and history as effective and inexpensive diagnostic tools in the early detection of recurrences.

This paper reports the results of this experience and summarises the results of ten years of follow-up.

Patients and Methods

Patients

One hundred and fifty patients (80 men, 70 women) aged between 36 and 83 years (mean 62.8 years) with localised primary invasive colorectal cancer (Dukes stage: 54 A, 47 B, 49 C) who were operated on with curative intention between January 1979 and June 1989 participated in an active follow-up programme for a period ranging from 24 to 150 months (mean: 58.9 months).

Between January 1979 and December 1983, 64 patients (Group 1) were monitored with a CEA assay and instrumental follow up (Tab. 1). Between January 1984 and June 1989, 86 patients (Group 2) were allocated to two different follow-up programmes, depending on the facilities available for instrumental examinations in the place where they lived. The follow-up schedule of 34 patients (Dukes stage: 10 A, 11 B, 13 C) was identical to that reported in Table 1. In 52 (Dukes stage: 11 A, 24 B, 17 C), the follow-up had the same scheduled time but was based only on history, physical examination and CEA increases. A study of the colon (X-ray or endoscopy) was made in all patients either before or shortly after the operation.

CEA Assay

Until December 1983, CEA was analysed using a double antibody method (CEA k Pr Sorin-Biomedica) which had a detection limit of approximately 2.5 ng/ml. From January 1984, CEA was tested using a monoclonal antibody radioimmunoassay sandwich solid phase (CEA-M-K Sorin Biomedica kits).

The values obtained using these two methods showed good correlation ($r=0.997$) when tested with 40 serum samples containing different concentrations of CEA.

Any postoperative increase in antigen level greater than the limit defined by the between assay coefficient of variation (calculated on the basis of two standard deviations) was considered significant and prompted the assay to be

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repeated twice, initially after three weeks and again after six weeks.

If the CEA increase was confirmed, an extensive instrumental investigation was carried out. This included all the examinations reported in Table 1 and, occasionally, a chest computed tomographic (CT) scan, an intravenous pyelogram, a nuclear magnetic resonance scan and a bone scintigram. Instrumental investigation obviously followed any suspicions arising out of the history or physical examination. If recurrent neoplastic disease was confirmed by these investigations, the patient was evaluated for treatment; if recurrence was not confirmed, then he was invited to return at the following scheduled follow up visit.

Statistical Methods

The curve was plotted with the technique of Kaplan-Meier life tables [2]. All frequency comparisons were made by contingency tables and chi-square test. The two-tailed Student's t test was used to compare the means of continuous data.

Results

In the overall group of 150 patients, we observed 49 recurrences (33%). Of these, 39 patients (80%) were found in the first two years of follow-up. These could be divided as follows: ten (19%) were in A cancers, ten (21%) in B cancers and 29 (59%) in C cancers. Fourteen (9% of all cases) were local or locoregional recurrences, six were local with metastatic implants, 12 were metastatic to the lung, 10 were metastatic to the liver and seven were multiple metastases: bone, brain, retroperitoneum and peritoneum.

An exploratory operation with curative intent was done in 15 cases (31% of all the recurrences). Eventually, 11 (73% of the re-operated patients or 22% of all patients with recurrences) had the recurrences resected. The re-operations were as follows: perineal excision of recurrence 3,

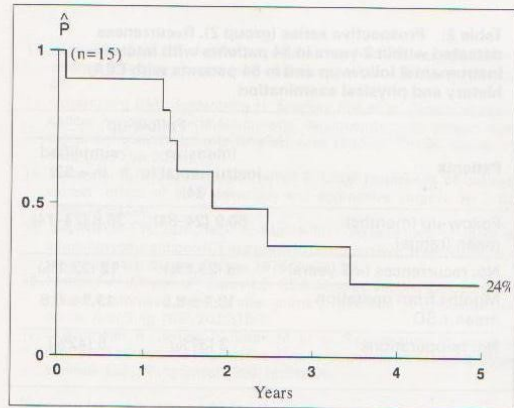


Fig.1: Survival curve of the 15 patients after re-operation for recurrence

Hartmann procedures 3, left hemihepatectomy 1, pelvic exenteration 1, abdominoperineal excision 1, lung lobectomy 1, and excision of lung metastasis 1.

In all, four of the patients with a tumour at the section margins were treated with complementary radio- or chemotherapy; one patient died postoperatively. The median survival of the group was 30 months (range: 0-72 months). The Kaplan-Meier estimated 5-year survival was 24% (Fig.1).

In this comparison of the outcome in 34 patients who had extensive instrumental follow-up and 52 who had only CEA coupled with history and physical examination the results showed no significant differences as regards the detection rate of recurrences in the first two years of follow-up, the time lapse between the operation and diagnosis of recurrence or the number of re-operations (Tab.2).

Table 1: Intensive instrumental follow-up schedule

Examinations	Preoperative	Post-operative (day)	Postoperative (months)																	
			3	7	14	1	3	6	9	12	15	18	21	24	30	36	42	48	54	60
CEA	*	* * *	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Liver sonography	*				*	*					*			*	*	*	*	*	*	*
Chest x-ray	*				*	*		*			*		*	*	*		*	*	*	*
Double contrast barium enema	*										*					*				*
Colonoscopy						*		*			*		*		*		*		*	*
Clinical examination	*	* * *	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Blood count*	*				*	*		*		*	*	*	*	*	*	*	*	*	*	*
Abdominal pelvic CT scan								*			*		*		*		*		*	*
Random perineal percutaneous needle biopsy (in rectal cancer)						*		*		*	*	*	*	*	*	*	*	*	*	*

* RBC, platelets, prothrombin, bilirubin, alkaline phosphatase, SGOT, SGPT, iron, proteins, WBC, and differential sedimentation rate

Table 2: Prospective series (group 2). Recurrences detected within 2 years in 34 patients with intensive instrumental follow-up and in 54 patients with CEA, history and physical examination

Patients	Follow-up	
	Intensive instrumental (n = 34)	simplified (n = 52)
Follow-up (months) mean (range)	50.9 (24-84)	36.8 (24-74)
No. recurrences (< 2 years)	8 (23.5%)	12 (23.1%)
Months from operation mean \pm SD	13.1 \pm 8.5	13.7 \pm 5.8
No. re-operations	3 (37%)	5 (42%)

Table 3: Recurrences and re-operations within 2 years in the patients of previous series (group 1) compared with the 84 patients of recent prospective study (group 2)

Patients	Group 1 (1979-83) n = 64	Group 2 (1984-89) n = 86
Follow-up (months) mean (range)	80.3 (24-150)	42.4 (24-84)
No. recurrences (< 2 years)	19 (29.7%)	20 (23.3%)
Months from operation mean (range)	14.6 (5-24)	13.5 (3-24)
No. re-operations	3 (16%)	8 (40%)
No. resections	2 (66%)	7 (87%)

No patient with recurrence in the first two postoperative years presented spontaneously for a follow-up visit with symptoms of recurrence outside the scheduled times. CEA test (monoclonal) sensitivity and specificity examined in the 34 patients of Group 2 who had simultaneously CEA and instrumental investigations, revealed a 90% sensitivity and a 100% specificity. When we compared the 64 patients (group 1) operated during the 1979-83 period with the 86 patients (group 2) operated in the 1984-89 period, we found a similarity between (i) the recurrence rate in the first two years of follow-up and (ii) the time lapse between the operation and diagnosis of recurrence. However, the 1984-89 group (group 2) underwent a higher number of reoperations and a higher number of removals of recurrences (Tab.3). Nonetheless, the low number of patients with recurrences does not allow for any comparative analysis of the survival rate.

Discussion

In the last 15 years, colorectal cancer scheduled follow-up has become a common clinical procedure in many hospitals all over the world [3-8]. Despite the fact that it has never been demonstrated that an intensive control of the

patients operated on for colorectal cancer can ameliorate their prognosis compared with that of patients with no follow-up, the evidence that the sensitivity and specificity for recurrent cancer CEA assay was sufficiently high even in asymptomatic patients was so appealing that CEA monitoring on the one hand forced follow-up programmes to be adopted, and on the other hand, it became the leading examination in those programmes.

A few randomised studies are still under way [9,10]. Their objective is to assess the validity of CEA monitoring as opposed to other forms of follow-up, and determine the usefulness or uselessness of follow-up.

At the moment it is important to evaluate the diagnostic tools commonly employed (CEA, clinical examinations, instrumental examinations) so as to have an acceptable, simple, efficient, low-cost follow-up method. Our experience showed that a follow-up based on CEA, history and physical examination is as effective as instrumental intensive follow-up. Results showed that CEA sensitivity was high (90%). Specificity was also high (100%) if calculated on the basis of significant increases in marker value from postoperative nadir in three consecutive serum samples over a six-week period. In these conditions, when a complete instrumental work up did not demonstrate a recurrence, the neoplastic disease was revealed at a later date in multiple sites. This confirms that a CEA rise, depending on a recurrence, generally occurs late in the natural history of the disease as an expression of a discrete amount of cancerous tissue. Therefore, when a complete and accurate clinical investigation does not reveal or strongly suggest any site of relapse, the disease is probably present in disseminated small deposits [1]. Recent reports on the radioimmuno-guided (RIG) detection of recurrences in patients with a CEA rise and no clinical or instrumental evidence of recurrence confirms this opinion [11-13]. This is a reason why asymptomatic second-look surgery on the basis of CEA rise alone with neither clinical nor instrumental evidence of disease should be abandoned or at least performed only in trials which evaluate diagnostic procedures such as RIG gamma-probe detection.

Moreover, our experience, as well as that of others [14-17], also shows that a higher number of exploratory re-operations resulted in a higher rate of resectability. A moderately aggressive surgical approach to clinical or CEA-guided instrumentally-demonstrated recurrences seems to be a satisfactory compromise. The resectability rate of all the recurrences we observed was similar to that reported by other authors who used more complex follow-up programs [5] including asymptomatic second-look procedures [17]. The fact that the 5-year survival rate is similar (20-30%) in all experiences -with only one exception [3] - is enlightening.

In conclusion, as surgeons, our objective ought to be to identify localised recurrences amenable to removal. We believe that this can be achieved using simple diagnostic tools (CEA, physical examination and history) together with a moderately aggressive surgical attitude.

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