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Follow-up of patients with colorectal cancer: numbers needed to test and treat

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Abstract

Follow-up after curative treatment of patients with colorectal cancer has as its main aims the quality assessment of the treatment given, patient support, and improved outcome by the early detection and treatment of cancer recurrence. How often, and to what extent, the final aim, improved survival, is indeed realised is so far unclear. A literature search was performed to provide quantitative estimates for the main determinants of the effectiveness of the follow-up. Data were extracted from a total of 267 articles and databases, and were aggregated using modern meta-analytic methods. In order to provide one more colorectal cancer patient with long-term survival through follow-up, 360 positive follow-up tests and 11 operations for colorectal cancer recurrence are needed. In the remaining 359 tests and 10 operations, either no gains are achieved or harm is done. As the third aim of colorectal cancer follow-up, improved survival, is realised in only few patients, follow-up should focus less on diagnosis and treatment of recurrences. It should be of limited intensity and duration (3 years), and the search for preclinical cancer recurrence should primarily be performed by carcino-embryonic antigen (CEA) testing and ultrasound (US). The focus of colorectal cancer follow-up should shift from the early detection of recurrence towards quality assessment and patient support. As support that is as good or even better can be provided by a patient's general practitioner (GP) or by specialised nursing personnel, there is no need for routine follow-up to be performed by the surgeon.

Keywords: Colorectal cancer; Follow-up; Recurrence; Survival

1. Introduction

Most patients, who have been operated upon for colorectal cancer, undergo some form of oncological follow-up, which means that they are followed on an outpatient basis for many years. Follow-up serves at least three main purposes:

1. Quality assessment: by checking on treatment outcomes, negative as well as positive, such as complications of treatment, cancer recurrences and disease-free survival
2. Support: by checking and providing help for the somatic, psychological, and/or social problems that patients may experience after having been diagnosed with and treated for cancer, and
3. Improved survival: by the preclinical detection of asymptomatic recurrence, with the hope of providing better outcome than if recurrence had been detected later as a result of symptoms.

Although the latter purpose, improved survival, has been investigated in different types of studies, it is still not clear to what extent it can really be achieved, and what follow-up should be implemented to best serve this purpose [1,2]. Earlier, we demonstrated that a survival benefit due to follow-up is dependent on the joint fulfilment of many conditions [3]. Thus there must be at least an asymptomatic recurrence leading to a positive test for follow-up to be effective. In addition, the patient must be free from extensive metastases and fit enough to undergo surgery. Surgery must be with curative intent, and the patient must survive a resection that is microscopically radical (R0). Finally, the patient should, after hospital discharge, not die early from other causes, nor should he/she develop a second manifestation of cancer-recurrence in the near future.

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In this study, we reanalyse the available information on treatment and follow-up of patients, and use this information to assess the probabilities that the above conditions are met, i.e. that patients experience a long-term survival benefit as a result of follow-up. This approach provides a first impression on the order of magnitude of the effectiveness of follow-up with respect to its third aim of improved survival. In a separate paper, we will use these and other data as input for a formal decision model that allows for a more formal cost-effectiveness analysis of the various follow-up strategies that may be provided to patients with colorectal cancer.

2. Patients and methods

2.1. Literature search

To collect the data needed to assess the effectiveness of colorectal cancer follow-up with respect to improved survival, a quantitative literature analysis was performed using the following MESH-based search "Colorectal Neoplasm's" [MESH] AND (FOLLOW-UP [TI] OR MONITORING [TI] OR SURVEILLANCE [TI]). Additional searches were performed using different combinations of search terms pertaining to organ systems (COLON, COLORECTAL, or RECTUM), disease (CANCER, (LOCOREGIONAL) RECURRENCE, METASTASIS, and/or LIVER, LUNG) or intervention ("CarcinoEmbryonic antigen" [MESH], "Tomography, X-Ray Computed" [MESH], "Ultrasonography" [MESH], etc.).

Searches were made more specific by limiting the search to the abstract title or title by use of tags such as [TIAB] or [TI]. In addition, the 'related articles' -facility of Pub Med was used where appropriate. All retrieved articles were entered into a database (Reference Manager 9.5), and screened by abstract.

2.2. Information categories and paper selection

For further data extraction and processing, only those articles that compiled with the following criteria were selected.

- studies that described colorectal cancer patients undergoing active follow-up
- in which
  - only such patients were reported, or
  - these patients, and their characteristics and outcomes could be identified separately from others, and
- that reported primary data on one or more items from the five categories of information, and
- in which calculated fractions and/or other variables were derived from a minimum number of at least 10–50 cases, depending on the type and availability of data per variable, and
- that did not duplicate results from earlier publications.

Data extracted from these 'suitable' articles were divided into five main categories (patient, disease, diagnosis, treatment and outcome). These data categories were then further divided into subcategories and into individual parameters as follows:

1. patient, with subcategories sex and age
2. (cancer) disease, with subcategories:
   - stage at initial treatment (Dukes' and TNM)
   - recurrence rate, both overall and per site, subdivided into the four sites: (1) local or locoregional recurrence, (2) liver metastasis, (3) lung metastasis and (4) other recurrence, and quantified by recurrence rate
   - recurrence characteristics per site, characterised by the size of the largest detected recurrence and number of cancer recurrences per site
3. diagnostic testing, with subcategories for diagnostic techniques and sites of recurrence, quantified by the parameters sensitivity and specificity per test,
4. treatment of cancer recurrence, with subcategories for sites of recurrence, and quantified by the parameters operable fraction, operative mortality, resectability (R0, R1, R2), long-term survival and factors determining that survival per treatment,
5. outcome, including survival and mortality, life expectancy and quality of life.

Data were extracted from the original publications and entered in a spreadsheet (Excel 2000), using different sheets per data-(sub-)category, columns for parameters, and rows for articles. Best estimates of parameter values were calculated by combining reported data using customary meta-analytic techniques.[1]

[1] Most variables (such as proportions, probabilities and real variables) were aggregated using weighted means or inverse variance weighted means technique. Incidence rates of recurrence and other events were calculated from *N*-year cumulative incidence. Diagnostic characteristics of tests were quantified in terms of sensitivity and specificity, likelihood and Odds Ratios, and were combined using Mantel–Haenszel Odds Ratio and summary receiver operating characteristic (ROC) curve methods [232]. Posttreatment survival outcomes were standardised into yearly mortality rates and into 5-year cumulative mortality and survival, using a modification of the DEALE method to transform mortality rates into fractional survival and vice versa wherever necessary [233,234]. The extent to which various determinants influence long-term outcome was quantified by calculating its Odds Ratio for 5-year mortality. Odds Ratios of determinants for cancer mortality were combined using both the Mantel–Haenszel Odds Ratio technique and summary ROC-curve methods.

3. Results

Using the search terms described above, a database was created consisting of over 2500 articles, including 980 articles resulting from the initial MESH search. Analysis of the abstracts resulted in 485 suitable articles from which 196 parameters were extracted into the spreadsheet database. Additional information was obtained from three databases on patients who underwent follow-up after surgery for colorectal cancer, one from Erlangen (courtesy Dr A. Altendorf-Hofmann), and two from Leiden [4–6].

3.1. Patients

To assess the characteristics of these patients, we selected only those 'suitable' articles that

- described patients who had undergone treatment with curative intent for primary colorectal cancer
- specified the follow-up strategy or strategies used, and
- reported quantitative own data on survival per follow-up strategy.

This left a total of 75 articles or a series reporting on 36 123 patients. Patient characteristics are given in Table 1.

3.2. Disease

Stage of primary cancer was reported by Dukes' classification in 24 articles describing 11 799 patients, and by TNM classification in 16 articles describing 9492 patients. Stage distribution of primary cancer is shown in Table 2a and b.

Thus, of the patient series described 1 out of every 8 patients had a Dukes' A tumour at initial treatment approximately half had Dukes' B cancer, and approximately 1 out of 3 had Dukes' C, Dukes' D and M1 patients were excluded, as their treatment is considered to be palliative instead of curative in the majority of cases.

Data about cancer recurrence, either overall or at any of the four specified sites, were reported in 53 articles complying with our criteria, describing 24 305 patients (Table 3). In these articles, mean follow-up time varied from 1.9 to 10 years, while overall cumulative cancer recurrence varied from 11.3 to 84%.

Thus, nearly 4 out of 10 patients (37.5%) will have a recurrence within 5 years, while approximately 6 out of 10 will still be cancer-free 5 years after initial surgery. Approximately 1 out of every 8 patients will experience local recurrence, approximately 1 out of every 5 will develop metastatic disease to the liver, and approximately 1 out of every 12 will experience pulmonary metastatic disease.

Table 1
Patient characteristics

Patient characteristics	Value	Articles (*n*)	Patients (*n*)	References
Male sex	0.537	39	18 304	[4–43]
Age: Mean (S.D.)	66.7 (14.2)	36	15 956	[4–8,10,13–15,18–20,24–27,30–41,43–50]

Just over half of the patients were male, with a mean age of approximately 67 years. S.D., standard deviation.

Table 2
Distribution of cancer stages by (a) Dukes' classification and (b) TNM classification at initial treatment

	Proportion	Articles (*n*)	Patients (*n*)	References
(a) Dukes' stage				
A	0.124	24	11 799	[4–6,8,14,19–21,25,26,28,30,33,35,37,40–43,45,48,51,52]
B1	0.176			
B2	0.352			
Any B	0.528			
C1	0.050			
C2	0.298			
Any C	0.348			
(b) TNM stages				
T1	0.060	16	9492	[4,5,14,16,19,21,31,35,37,39,40,42,43,45,48]
T2	0.231			
T3	0.615			
T4	0.094			
N0	0.599			
N1	0.200			
N2	0.098			
N3	0.103			

3.3. Testing

Many different tests have been proposed for the follow-up of colorectal cancer patients. For each of these tests, sensitivities and specificities for the various recurrences have been reported.

However, the concept of sensitivity is an ambiguous one with respect to cancer recurrence. Most cancer recurrences have been present from the time of first treatment as minimal residual disease, undetectable due to low tumour volume. Therefore, the disease-free state after initial cancer treatment may only be the result of false-negative testing for minimal residual disease. However, such false-negative results are in general not included in the calculations of test sensitivity. Only when residual disease has grown into detectable cancer recurrence is it included in the subset from which test sensitivity is calculated. Thus, test sensitivity has a relative meaning only, being a measure of how sensitive a test is in comparison to the set of all tests available for the same purpose.

Test characteristics were investigated separately for the four sites described above, and were subdivided into three subcategories of laboratory tests, imaging and endoscopies. Test characteristics sensitivity and specificity were calculated per site. These data on test accuracy were combined with data on cancer recurrence rate per site to provide an additional set of three clinical test-characteristics: (1) the probability of a positive test per 3-month test visit (pTpos), (2) probability of true- and false-positive test (TP and FP), and (3) the ratio false- versus true-positives (FP/TP). Results are shown in Table 4a–d for each of the four sites of recurrence.

From Table 4, it can easily be seen that, with the exception of endoscopy, most positive follow-up tests will more often be false-positive than true positive. Best FP/TP ratios will occur with endoscopy and endo-ultrasound for local recurrence (0.6 and 4.0, respectively), all other tests being false-positive 10 or more times more often as true positive.

In the search for liver metastases, best FP/TP ratios can be expected from liver imaging tests (ultrasound and CT-scanning outperforming MRI) and CEA tests. The other laboratory liver function tests are useless for follow-up, with FT/TP ratios in the range of approximately 15–70.

Data on the diagnostic accuracy of tests for pulmonary metastases from colorectal cancer are scarce, and suffer from inadequate comparisons to a (pseudo-)gold standard.

There are even less data available on the diagnosis of other recurrences than data on pulmonary metastases. This is not surprising as it is clinically useless to put much effort into the diagnosis of cancer recurrence that is not limited to one of the three sites described above.

Thus, in the course of follow-up many false-positive tests will occur. These false-positive test results will not only cause a lot of stress, but will also necessitate further testing to eliminate uncertainty about the presence or absence of recurrence, and will thereby induce considerable costs.

3.4. Treatment

The aim of follow-up is early treatment, ultimately leading to a better outcome. However, to achieve this aim, a detected recurrence must be considered operable, the patient must survive the operation, and the resection must be radical. To what extent these goals are achievable for recurrences at the four different sites is shown in Table 5a–d for each of the four sites of recurrence.

For each site, we calculated the proportion of all recurrences detected that is operated upon, as well as the proportion of those operated that is resected, what the operative mortality is, what proportion of all resections for recurrence is macroscopically, as well as microscopically, radical (R0), and what proportion of those undergoing and surviving R0-resection is still alive after 5 years.

Combining these individual parameters provides the proportion of all recurrences that is still alive 5 years after a R0 resection.

Thus, in only 2.4% of patients with local recurrence is a long-term cure achieved by follow-up.

Thus, the data for patients with liver metastases demonstrated significantly better survival results than the data for patients with local recurrence, with up to 8.5% of all patients with liver metastases being alive 5 years after a R0 resection.

From these data, it can be seen that the treatment of liver recurrence clearly offers the best chance of a long-term favourable outcome. The percentage of patients

Table 3
Cancer recurrence rates

Site	5-year cumulative	Rate/year	Rate/3 months	Articles (*n*)	Patients (*n*)	References
Local	0.123	0.026	0.007	53	24 305	[5–8,13,14,16,18–20,22–27,30,31,33,34,37,41,42,44,45,48–53,53–76]
Liver	0.189	0.042	0.010			
Lung	0.083	0.017	0.004			
Other	0.296	0.070	0.018			
Overall	0.375	0.094	0.023			

alive at 5 years after R0 surgery is only around 2–3% for all other recurrence sites.

If we average the data on diagnosis and treatment from Tables 2–5, we find there is an 8% chance of a positive test per 3-month visit, and that only 7% of these positive tests are true-positives. Subsequently, from all proven recurrences, 42% would be deemed operable, 57% of all operated recurrences would be resected with a curative intent (with an operative mortality of 3%), and 68% of these resections would be proven R0 by histology. Finally, of all patients with a R0 resection of recurrence, 29% would still be deemed cured after 5 years. These data are summarised in Fig. 1.

3.5. Outcome

The long-term outcome after treatment of recurrence differs strongly between patients, and is influenced by a number of factors, such as the initial stage of the cancer, and size and number of recurrence(s). The extent to which these determinants increase or decrease long-term cancer mortality is quantified by the positive and negative likelihood ratios (LRpos and LRneg) for yearly cancer mortality. Most favourable results can be expected in those subgroups with a low negative likelihood ratio for cancer mortality, as they will have lowest mortality and thus highest survival at 5 years. Results are shown in Table 6a–c, again for each site of recurrence.

Few adequate data are available on the prognostic factors for treatment of local recurrences.

Results show that the best survival can be expected in female patients with favourable initial Dukes' stage, who have a single small liver metastases with a low preoperative CEA, that can be resected with a margin of at least 1 cm. Worse outcome is expected in all other cases, especially in more than 3 liver metastases, and/or in the presence of recurrences at other sites.

In cases of pulmonary metastasis, the main determinant of long-term survival is the number of metastases present. When more than one metastases are present, deteriorating prognosis falls rapidly, further in case of large tumour size, and/or the presence of recurrence elsewhere.

Finally, we analysed to what extent long-term survival is influenced by the presence or absence of symptoms at the time of detection of recurrence. Results are shown in Table 7, and are not specified per site.

Table 4
(a) Diagnostic characteristics of tests for local recurrence, (b) diagnostic accuracy of tests for liver metastasis, (c) diagnostic accuracy of tests for lung metastasis and (d) diagnostic accuracy of tests for other recurrences

		Sensitivity	Specificity	pTpos	TP	FP	FP/TP	Articles (*n*)	Patients (*n*)	References
Test for local recurrence										
Laboratory test	CEA	0.599	0.857	0.146	0.004	0.142	35.9	14	1305	[33,48,77–80,80–88]
	Haemoccult	0.572	0.928	0.075	0.004	0.071	18.9	3	187	[89–91]
Imaging	Ultrasound	0.378	0.500	0.499	0.002	0.497	199.6	1	59	[82]
	X-ray	0.600	–	–	–	–	–	1	10	[86]
	CT	0.849	0.922	0.083	0.006	0.077	13.8	17	1226	[81–83,92–104]
	MRI	0.948	0.821	0.184	0.006	0.178	28.5	5	155	[82,92,99,102,105]
Other	Endoscopy	0.491	0.998	0.005	0.003	0.002	0.6	5	1020	[23,25,55,91,106]
	endo-US	0.916	0.976	0.030	0.006	0.024	4.0	3	167	[99,103,107]
Test for liver metastasis										
Laboratory test	CEA	0.726	0.912	0.095	0.008	0.088	11.5	13	1293	[33,48,49,60,78,84–86,88,104,108–110]
	Alk Fos	0.298	0.920	0.082	0.003	0.079	25.3	3	379	[86,111,112]
	GGT	0.192	0.864	0.137	0.002	0.135	66.9	1	70	[33]
	LDH	0.469	0.918	0.086	0.005	0.081	16.5	2	309	[86,112]
	SGOT	0.072	0.977	0.024	0.001	0.023	30.6	2	365	[111,112]
	SGPT	0.077	0.955	0.046	0.001	0.045	55.7	1	70	[111]
Imaging	Ultrasound	0.573	0.966	0.040	0.006	0.034	5.6	19	1873	[86,111–128]
	CT	0.683	0.960	0.047	0.007	0.039	5.5	27	2229	[25,93,97,104,111,114–119,122–137]
	MRI	0.429	0.938	0.066	0.004	0.062	13.8	4	165	[114,116,136,138]
Test for lung metastasis										
Laboratory test	CEA	0.559	0.828	0.176	0.006	0.170	29.0	4	525	[48,88,108,130]
Imaging	X-ray	1.000	–	–	–	–	–	1	4	[86]
	CT	0.895	–	–	–	–	–	2	105	[104,139]
Test for other recurrence										
Laboratory test	CEA	0.701	0.730	0.274	0.007	0.267	36.3	1	380	[78]
Imaging	CT	0.278	–	–	–	–	–	1	18	[94]

pTpos, positive test per 3-month test visit; TP, true-positive test; FP, false-positive test; FP/TP, ratio of false-positives versus true-positives; CT, computed tomography; MRI, magnetic resonance imaging; CEA carcino-embryonic antigen; US, ultrasound; GGT, gamma glutamyl transferase; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; LDH, lactate dehydrogenase; Alk Fos, alkaline phosphatase.

Table 5
Characteristics of treatment for (a) local recurrence, (b) liver metastasis, (c) lung metastasis and (d) other recurrences

Treatment characteristic	Value	Articles (*n*)	Patients (*n*)	References
Treatment for local recurrence				
Proportion operated upon given detection	0.300	13	1035	[5,8,18,19,24,36,38,39,42,45,56,69,71,76,140–151]
Proportion irresectable given surgery	0.269	17	1258	[5,18,19,36,38,42,45,56,69,70,76,140–146,148]
Operative mortality	0.020	18	1407	[5,18,19,36,38,39,42,45,56,69,76,140–147,150]
R0, if resected	0.404	8	799	[5,18,56,72,75,140,141,143,144]
5-year survival after R0-resection	0.276	17	843	[5,8,18,39,56,69,71,76,140,142–148,150,151]
and thus alive 5 years after R0-surgery	0.024	28	2023	Previous in this table
Treatment for liver metastasis				
Proportion operated upon given detection	0.717	8	2490	[5,54,56,76,152–155]
Proportion irresectable given surgery	0.480	32	7414	[5,54,69,70,76,152,156–161]
Operative mortality	0.030	55	9909	[5,54,56,69,76,82,138,152–154,156–187,187–198]
R0, if resected	0.807	11	1783	[5,75,157,159,179,185,186,190,191,194,199]
5-year survival after R0-resection	0.290	37	6739	[54,69,76,157–159,162,164–167,169,171–173,175,178, 182,183,185–187,187–189,191–193,195–198,200–205]
and thus alive 5 years after R0 surgery	0.085	65	11 511	Previous in this table
Lung metastasis				
Proportion operated upon given detection	0.123	3	2029	[5,206,207]
Proportion irresectable given surgery	0.101	5	297	[5,69,70]
Operative mortality	0.013	8	499	[5,208–214]
R0, if resected	0.843	1	197	[5]
5-year survival after R0-resection	0.336	23	899	[53,69,206,208,210–228]
and thus alive 5 years after R0 surgery	0.031	14	1050	Previous in this table
Other recurrences				
Proportion operated upon given detection	0.300	2	236	[5,69]
Proportion irresectable given surgery	0.269	2	236	[5,69]
Operative mortality	0.020	1	173	[5]
R0, if resected	0.404	1	173	[5]
5-year survival after R0-resection	0.156	1	32	[5]
and thus alive 5 years after R0 surgery	0.024	2	236	Previous in this table

Table 6
Determinants of cancer mortality after the treatment for (a) local recurrence, (b) liver metastases and (c) lung metastases

	LRpos	LRneg	OR (95% CI: 1.44–5.45)	Articles (*n*)	Patients (*n*)	References
Cancer mortality after local Tx						
Male sex	1.17	0.81	1.44	1	65	[150]
Dukes' $\geqslant$C	1.70	0.59	2.86	1	59	[150]
Preoperative CEA >5	1.87	0.69	2.69	1	95	[150]
Cancer mortality after liver Tx						
Male sex	1.18	0.80	1.47	8	1060	[54,162,164,171,192,193,198,229]
Dukes' $\geqslant$C	1.14	0.85	1.33	9	1173	[162,164,169,171,189,192,193,197,203]
>1 metastasis	1.60	0.77	2.08	16	2574	[54,69,158,165,169,171,172,178,183,189,192,193,196,198,203,229]
>3 metastases	2.20	0.86	2.56	10	1459	[54,164,171,172,178,182,183,186,197,198]
Size >5 cm	1.26	0.85	1.48	10	1406	[54,164,178,182,183,186,189,192,198,229]
Other metastases	3.04	0.81	3.74	10	1625	[54,158,162,164,172,175,183,185,192,200]
Margin <1 cm	1.67	0.61	2.75	10	1571	[54,158,164,182,183,189,192,198,202,203,229]
Preoperative CEA >5	1.54	0.42	3.67	2	281	[158,182]
Preoperative CEA >30	1.61	0.77	2.11	3	217	[157,178,182]
Cancer mortality after lung Tx						
Male sex	1.07	0.91	1.18	3	360	[210,211,222]
Dukes' $\geqslant$C	1.09	0.91	1.19	4	296	[210,211,222,224]
>1 metastasis	3.00	0.45	6.67	7	412	[69,210,211,213,222,224,227]
>2 metastases	3.07	0.20	15.33	2	166	[211,227]
Size $\geqslant 3$ cm	1.34	0.80	1.68	4	259	[210,213,222,227]
Other metastases	1.77	0.52	3.42	2	298	[210,222]

Tx, therapy; LRpos and LRneg, postive and negative likelihood ratios; OR, Odds Ratio.

Table 7
Preoperative symptoms as a determinant of cancer mortality after treatment for recurrence

Mortality after any re-Tx	LRpos	LRneg	OR	Articles (*n*)	Patients (*n*)	References
Symptomatic recurrence	2.29	0.67	3.44	6	938	[7,25,69,72,230,231]

re-Tx, treatment for recurrence; LRpos and LRneg, positive and negative likelihood ratios.

In the course of follow-up, the decision to perform surgery for cancer recurrence should be the result of a careful weighing of risks (as determined by the extent of disease, and the patient's health) and expected benefits (which depends on the factors described above).

4. Discussion

The available literature data allows for several conclusions to be drawn concerning the value of colorectal cancer follow-up. First of all, diagnostic tests that are used to detect cancer recurrences are not very accurate, and will in general give rise to more false-positives than true-positives, false-positive test results being on average 16 (0.6–200) times more common than true-positives in many tests. False-positive test results will not only cause unnecessary stress, but will also necessitate additional testing to eliminate or at least reduce the uncertainty, thereby adding to both the patient burden and healthcare costs. Even if the test results are truly positive, only a limited number of patients will be deemed suitable for curative resection of cancer recurrence. More patients will only be informed that they have incurable cancer recurrence, and will hear this earlier because of the follow-up testing. Finally, of those who will undergo re-operation, some will be found to have irresectable recurrence at operation while in others the resection will be macroscopically or microscopically irradical. Some will also die from the surgery. This leaves a small proportion of those with cancer recurrence (varying from a maximum of 8.5% in cases of liver metastasis, to between 2 and 3% in other cases, who really derive a long-term benefit from testing and the ensuing treatment, these patients mostly being those that are treated for liver recurrence from colorectal cancer.

From Tables 2–5, we can calculate the number of positive follow-up tests and the number of treatments that are needed in order to provide one or more patient with a long-term cure by R0 resection of a colorectal cancer recurrence. The results of such calculations are shown in Fig. 1, and demonstrate that on average 370 positive follow-up tests and 11 operations are required to provide 1 patient with a long-term survival after treatment for cancer recurrence. More accurate estimates of the risks and benefits of follow-up are beyond the scope of this paper, and will be presented in a separate paper on the cost-effectiveness of colorectal cancer follow-up.

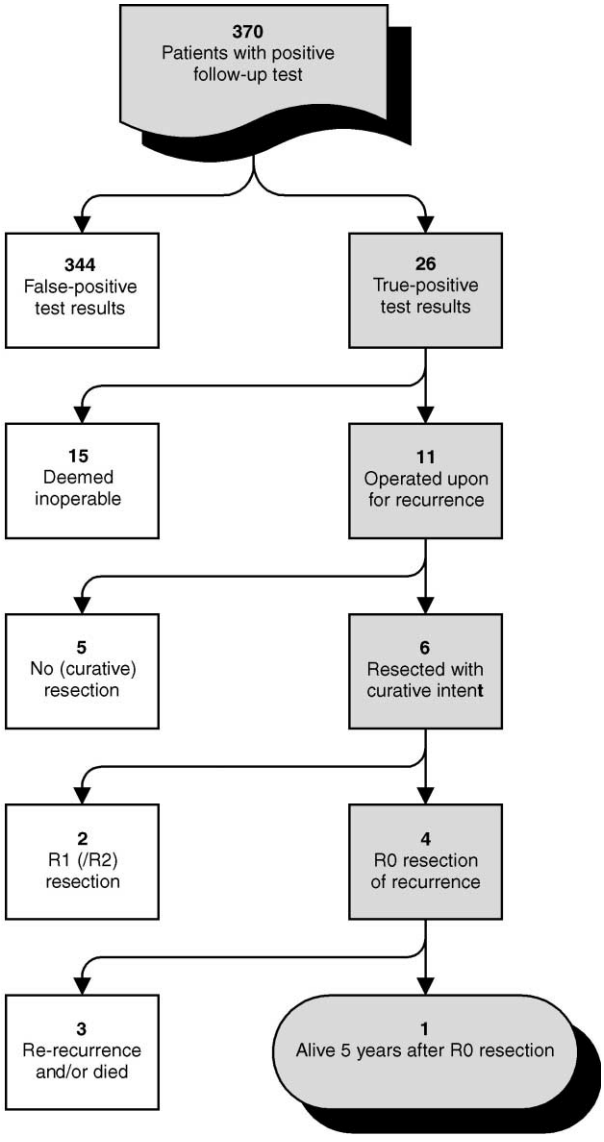

Fig. 1. Number of positive follow-up tests necessary to provide 1 patient with 5-year survival after a R0 resection of colorectal cancer recurrence.

Because of the limited effectiveness of follow-up with respect to identifying patients suitable for re-operation with curative intent, we believe follow-up of colorectal cancer patients should be performed, if at all, with an understanding of its risks and its limited effectiveness. More specifically routine follow-up is unwarranted in:

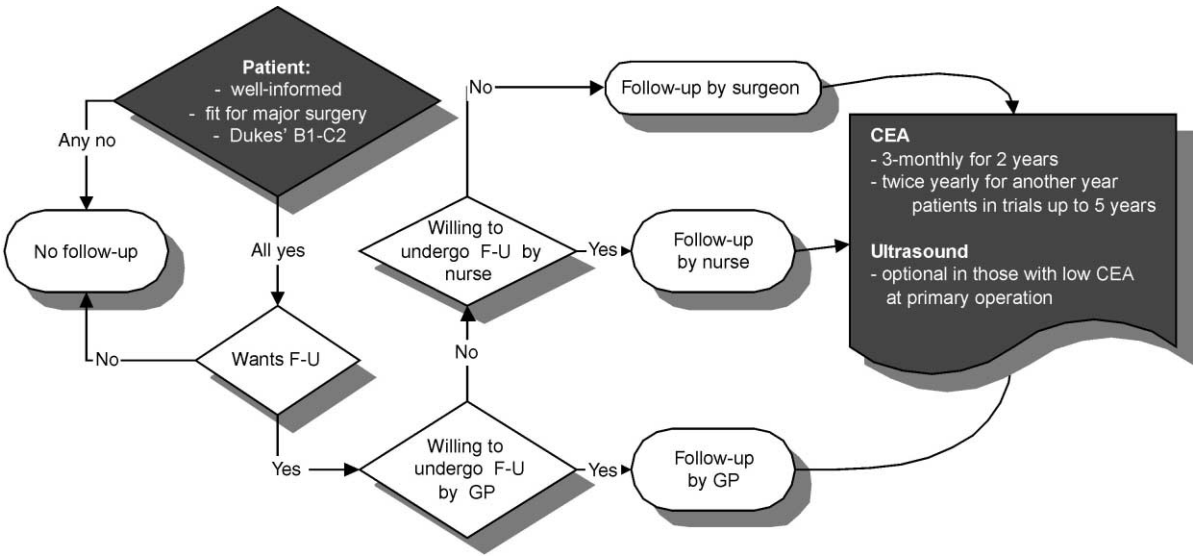

Fig. 2. Flow chart for selective follow-up. F-U, follow-up; GP, general practitioner.

- patients with Dukes' A (because their low risk of recurrence will increase the number of false-positives obtained) or Dukes' D cancer (as curative surgery is the exception rather than the rule);
- those who are (biologically) too old, or not fit enough to undergo major surgery;
- those who do not wish to undergo follow-up testing because they consider the benefits too low.

The limited effectiveness of follow-up with respect to a survival gain underlines the two other purposes of follow-up (quality assessment and patient support). Patients have to come to terms with the fact that they have had cancer, and may experience somatic, psychological and social side-effects from their cancer and its treatment. They will want a 'safe haven', where their problems can be reported and dealt with.

Such support may well be provided by the surgeon in a conventional outpatient setting. However, if surgical expertise is no longer required after an uneventful recovery, follow-up may as well be performed by others. Depending on the local situation, quality and quantity of support may be even better if provided by a specialised nurse or by a patient's general practitioner (GP) than by the many different surgical interns or residents that a patient may encounter in the outpatient clinic of a large surgical oncological department.

A summary of the above principles is shown in Fig. 2, signifying that if follow-up is performed, it:

- should be of limited duration (3 years), as the risk of false-positive test results will increase over time while the recurrence rate declines (80% of all recurrences occur within the first 2 years),
- should primarily be based on CEA, possibly in combination with liver imaging methods ultrasound or CT scan,
- may, depending on considerations of capacity, efficiency and support, be performed by personnel other than the surgeon.

By limiting the duration and intensity of follow-up for colorectal patients, by offering it only to suitable patients, and by taking it out of the hands of surgeons in selected cases, the risks and costs will decrease and the benefits may increase.

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