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Detection of Recurrence After Surgery for Colorectal Cancer

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Of all patients operated for colorectal cancer, 1 in 3 will suffer from cancer recurrence, and most of these patients will die from disseminated disease. Postoperative follow-up aims at improving these grim figures. This sound idea has not been supported by any empirical data. In the current article, we discuss some theoretical issues concerning colorectal cancer follow-up, and present results of a cost-effectiveness analysis, used to model the natural history of colorectal cancer recurrence and the costs and effects of follow-up and re-operation. The expected results of three policies were calculated: no follow-up, selective follow-up and intensive follow-up. For most patients, follow-up will only lead to a significant increase in costs, without increase in (quality-adjusted) life expectancy. Colorectal cancer follow-up is not "evidence-based medicine".

Key words: follow-up, colorectal cancer, decision analysis, cost-effectiveness analysis
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INTRODUCTION

COLORECTAL CANCER represents 15% of all cancers in the U.S.A., and is the second cause of cancer-related mortality [1]. In the Netherlands, in 1990, it was the third most frequent cause of death in men (after lung cancer and prostatic cancer), with a mortality of 24 per 100 000 for all age groups, and the second most frequent in women (after breast cancer), with a mortality of 28 per 100 000 [2].

Approximately 1 in 3 colorectal cancer patients die from the complications of unresectable primary disease. Of those treated by surgery with curative intent, a similar proportion die at a later stage from cancer recurrence [3]. Several approaches have been taken to reduce these grim figures, including primary screening, more aggressive primary surgery, adjuvant chemotherapy, and intensive follow-up in combination with aggressive surgery for recurrent cancer. However, for the latter, there are no data in the medical literature that justify the use of follow-up. In a meta-analysis that we performed of all published, comparative, non-randomised studies, we found no overall benefit of follow-up. Although a slight advantage was found for those follow-up regimens that included measurement of carcinoembryonic antigen (CEA) levels, this difference was possibly caused by selection bias [4]. So far, definitive data from prospective controlled trials have been lacking. The preliminary results of three trials currently running or recently terminated demonstrate no advantage of colorectal cancer follow-up [5–7].

In spite of this total lack of evidence, postoperative follow-up after colorectal cancer surgery is practised throughout the world [8, 9]. Although follow-up serves at least two other important purposes—that of quality control and of patient support—its formal justification is improvement of the results of cancer treatment. Follow-up scenarios are based on guidelines, mostly generated by a local consensus procedure in some form. Specialised colorectal cancer surgeons, in general, perform more intensive follow-up than general surgeons [8]. Few currently accepted medical practices comply so little with the requirements of "evidence-based medicine".

Research concerning the value of postoperative follow-up is hampered by the fact that many tests can be used for follow-up surveillance, including laboratory tests (such as CEA, liver function tests, and faecal occult blood test), radiology (chest and colonic X-ray, liver ultrasound and computed tomography (CT) scanning) and colonoscopy. All these tests can be performed at many different intervals: monthly, quarterly, semi-annually, annually or biannually. If eight different tests can be used separately or in combination at five varying intervals, this provides a choice from more than 30 000 (8^5) possible follow-up scenarios, of which a considerable number are realistic. Thus, before a controlled trial can be conducted to evaluate the value of colorectal cancer follow-up, one question needs to be answered initially "In assessing the value of follow-up, which intervention scenario should be compared with which control?" Only after this question has been answered, can we address the main policy-making question "How do the costs of colorectal cancer follow-up compare with its potential beneficial effects?"

The present study discusses intrinsic limitations of colorectal cancer follow-up, reviews present knowledge, and takes a novel approach to elucidate this complicated issue, using modern decision analysis and cost-effectiveness analysis techniques. The advantage of such an approach is that many follow-up regimens can be tested in "simulated controlled trials", using simulated patients and interventions instead of real ones. Only after a feasible trial has been identified that is expected to lead to significant results with an acceptable number of patients, can such a trial be conducted in the real life situation. Simulations

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are thus performed not as a substitute for empirical studies, but to identify the best possible scenarios that deserve actual testing. In this way, many vain research efforts can be avoided, minimising morbidity, mortality and costs.

PATIENTS AND METHODS

The present decision analysis and cost-effectiveness analysis simulate the natural course of colorectal cancer recurrences, as represented by different patterns of seeding of recurrences and metastases, and by different rates of growth over time. In addition, as a separate overlay, we created the potential to simulate different follow-up regimens, using different combinations of tests such as blood chemistry, CEA, endoscopy, X-ray and ultrasound, with their different sensitivities and specificities for recurrences at different sites, size and numbers. We also represented re-operative surgery, using generally accepted indications for further resection, and published resectability rates, cure rates and mortalities as determined by patient characteristics and disease stage. The analysis was executed as a first order Monte Carlo simulation of a Markov analysis, using currently available decision support software (SmlTree 3.0B). The technical details concerning the modelling of colorectal cancer disease, follow-up, treatment, outcome and costs are described elsewhere [10]. Using the decision tree, we simulated many trials, with trial sizes varying between 5000 and 100 000 patients per arm. Each individual simulated patient was followed in 3 month cycles until the end of his or her life, health and disease being represented by three main health states: (1) no evidence of (recurrent) disease; (2) incurable recurrence; and (3) death.

In the preliminary calculations reported here, we compared three scenarios: (1) no follow-up, in which case recurrences and metastases are only detected on the basis of symptoms; (2) selective follow-up, in which CEA is performed quarterly, and colonoscopy annually; and (3) intensive follow-up, in which CEA is performed quarterly, while colonoscopy, chest X-ray and liver function tests are performed annually.

RESULTS

In a simulated trial of 3 × 20 000 patients (with a mean age of 65 years at first operation), follow-up provided no increase in quality-adjusted life years (QALYs) (7.41 ± 4.38 QALYs and 7.43 ± 4.39 QALYs for selective and intensive follow-up, versus 7.51 ± 4.50 QALYs for no follow-up). Costs increased from Dfl. 2400 ± 1960 for no follow-up, to Dfl. 6190 ± 3170 and Df. 7450 ± 3330 for selective and intensive follow-up, respectively, implying increases in costs of 1.58 and 1.65-fold, respectively. Sensitivity analyses were performed for age and tumour stage using trial simulations of 3 × 5000 per analysis. Results of sensitivity analysis for age are shown in Figure 1, suggesting that older age, like favourable tumour stage, decreases the effectiveness of colorectal cancer follow-up even further. No marginal cost-effectiveness of the follow-up scenarios tested so far was below the acceptable range of Dfl. 50 000 per quality-adjusted life year gained, that justifies the routine use of colorectal cancer follow-up.

DISCUSSION

In the calculations performed so far, we could not demonstate any beneficial effect of follow-up on the results of colorectal cancer treatment. Disappointing as these results may be, these calculations are in agreement with even the most recent empirical data [11]. Given these persistently negative results, we reconsidered the conditions that have to be met before follow-up of colorectal cancer patients may improve their quality-adjusted life expectancy cost effectively. These "conditions of benefice" have materialised from our experience of building a simulation model based on empirical data, and are listed below with their respective empirical data.

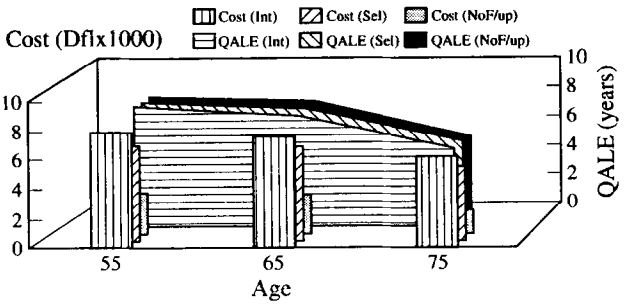

Figure 1. Relationship between patients' age at initial operation for colorectal cancer, and the costs and effects (expressed in Dutch guilders and in quality-adjusted life years) of three follow-up policies (intensive follow-up (Int), selective follow-up (Sel) and no follow-up (No F/up)).

Condition 1

After curative surgery for colorectal cancer, patients are at risk of developing recurrences, of which at least some should be localised and amenable to treatment with curative intent.

The presently available published data indicate that this condition holds true to a different extent for different recurrence sites. Operability and resectability at operation vary greatly per site, from over approximately 60% and 55%, respectively, for local and hepatic recurrences [12–19] to below 10% for lung and other sites [20–23].

Condition 2

The process of seeding and growth of colorectal cancer recurrences and metastases should involve two synchronous but counteractive mechanisms. The first mechanism would then be a shift in detection from undetectable recurrence, through detectable preclinical recurrence, to symptomatic recurrence. The second mechanism would be a counteractive change in the potential for successful treatment from curable recurrence, through palliatively resectable recurrence, to irresectable recurrence.

No formal data exist in the literature that confirm this assumption. Most studies do not demonstrate that earlier resection, or resection of asymptomatic recurrences provides better survival [4, 11]. Most recurrences will, because of their number and site, be incurable before they are detectable. Alternatively, a few metastases may remain curable up to their phase of symptomatic detectable disease [4, 14, 15]. Present data suggest that curability of colorectal cancer recurrences is, in general, not a time-dependent phenomenon.

Condition 3

Postoperative surveillance of colorectal cancer patients aims at detecting recurrences at an early stage when they are still resectable or curable, ideally without bringing forward the moment of detection of incurable disease.

Present data suggest that most recurrences, even when detected by follow-up in the preclinically detectable phase, are already beyond cure. These incurable recurrences are discovered

by follow-up indiscriminately from those that are amenable to treatment, and their detection will reduce the quality of life of asymptomatic colorectal cancer patients by confronting them with their incurable disease.

Condition 4

Benefits of colorectal cancer follow-up (increased quality-adjusted life expectancy through more frequent curative and palliative resections) should outweigh the non-monetary costs of early detection of incurability, re-operative morbidity and mortality, and false positive tests.

Re-operations carry a significant morbidity, and a mortality of around 3–5% [19, 24]. No empirical study has thus far demonstrated that these negative effects are outweighed by the positive effects of follow-up and re-operation [5–7]. However, it may be that these grim findings can, in part, be explained by some mechanisms that are open to improvement. Follow-up alone will never improve quality-adjusted life expectancy; re-resections will have to be performed if follow-up is to produce any advantage, and they will have to be performed with considerable skill, and at low morbidity and mortality. Unwillingness to do or undergo re-resections from surgeons or patients, lack of experience, or, on the contrary, the (too) liberal performance of re-resections in cases where no gains are expected, will prevent any potential advantage from materialising. Although unproven, it cannot be excluded that the discriminating use of a diagnostic therapeutic protocol of routine tests, pre-operative analysis, and re-operation in selected patients may produce gains that were not found previously, and our present endeavours are aimed at identifying the conditions under which these advantages could materialise.

Condition 5

The ratio between costs and effects of colorectal cancer follow-up should be sufficiently favourable to justify its routine use. Various calculations agree that colorectal cancer follow-up, in the way it has been used so far, is not cost-effective [13, 25–27].

Although our calculations have not yet identified an undisputed best follow-up scenario, and far more simulations will have to be performed, several conclusions can already be drawn concerning the clinical use of colorectal cancer follow-up. First, intensive follow-up of all patients operated on for colorectal cancer provides no benefit, involves considerable costs, and is highly cost-ineffective. Colorectal cancer follow-up is not "evidence-based medicine". Discriminating follow-up in selected patients might provide some benefits, but at considerable costs. Secondly, the costs and effects of colorectal cancer follow-up will be difficult to establish. Even if follow-up is performed in a selective way, using different optimal scenarios for different patient categories, our calculations suggest that the prospective evaluation of its costs and beneficial effect on QALYs would require a trial with more than 5000 patients per arm. Even then, such trials might only demonstrate cost differences. Thus, prospective research concerning the cost-effectiveness of colorectal cancer follow-up might itself not be cost-effective. Thirdly, even from our preliminary calculations, it is perfectly clear that follow-up serves no oncological purpose in patients who are elderly, not fit enough to undergo re-resection, or are not willing to undergo re-operation. Similarly, follow-up should not involve tests that mostly detect unresectable or incurable recurrences, or that lead to high rates of false positive test results, such as liver function tests and other blood chemistry and haematology tests.

If, as stated before, resectability and curability are, in most cases, characteristics of recurrent colorectal cancer, that are stable over relatively long periods of time, and depend on tumour characteristics more than on time, future research should be aimed at identifying the basis of these characteristics of resectability and curability, using molecular biological or other techniques. Improved insight into these mechanisms would strongly improve the cost-effectiveness of follow-up and resections, by providing the basis for a rational selection of patients for follow-up and re-operation. Until such time, our continuing efforts will be aimed at identifying the most effective and efficient follow-up regimen for colorectal cancer patients. It may very well be that this is a regimen where no or few routine tests are performed, but where follow-up primarily serves as a means of quality control and patient support.

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