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Decision analysis in the management of duodenal adenomatosis in familial adenomatous polyposis

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Abstract

***Background*—Patients with familial adenomatous polyposis are not only at high risk of developing adenomas in the colorectum but a substantial number of patients also develop polyps in the duodenum. Because treament of duodenal polyps is extremely difficult and it is unknown how many patients ultimately develop duodenal cancer, the value of surveillance of the upper digestive tract is uncertain.**

***Aims*—(1) To assess the cumulative risk of duodenal cancer in a large series of polyposis patients. (2) To develop a decision model to establish whether surveillance would lead to increased life expectancy.**

***Methods*—Risk analysis was performed in 155 Dutch polyposis families including 601 polyposis patients, and 142 Danish families including 376 patients. Observation time was from birth until date of last contact, death, diagnosis of duodenal cancer, or closing date of the study.**

***Results*—Seven Dutch and five Danish patients developed duodenal cancer. The lifetime risk of developing this cancer by the age of 70 was 4% (95% confidence interval 1–7%) in the Dutch series and 3% (95% confidence interval 0–6%) in the Danish series. Decision analysis showed that surveillance led to an increase in life expectancy by seven months.**

***Conclusions*—Surveillance of the upper digestive tract led to a moderate gain in life expectancy. Future studies should evaluate whether this increase in life expectancy outweighs the morbidity of endoscopic examination and proximal pancreaticoduodenectomy.**

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Keywords: familial adenomatous polyposis, duodenal cancer, surveillance, decision analysis, pancreaticoduodenectomy.

Familial adenomatous polyposis (FAP) or Bussey-Gardner polyposis is an autosomal dominant disease due to a mutated adenomatous polyposis coli (APC) gene and is characterised by the development of hundreds of adenomas in the colon.[1–3] Since the disease was first recognised, there have been numerous reports of other lesions outside the colon. The spectrum of lesions reported in FAP includes multiple osteomas of the cranium and mandibles, multiple epidermoid cysts of the skin, dental abnormalities, desmoid tumours of the abdominal wall and abdomen, bilateral patches of congenital hypertrophy of the retina pigment epithelium, and fundic gland polyposis.[4 5]

During the 1970s, an increasing number of case reports of FAP patients with malignancy of the periampullary region and proximal duodenum appeared.[6 7] These reports focused attention on the upper gastrointestinal (GI) tract and led to series of reports on gastroduodenoscopy of groups of polyposis patients. Most recorded that at least two thirds of the polyposis patients also had duodenal adenomas.[8–15] The first question to arise at that time was: do the adenomas of the duodenum follow the adenoma-carcinoma sequence observed in the colorectum? At present, there is ample evidence suggesting that this is the case. Duodenal or periampullary adenocarcinoma has been found to occur in patients with FAP at a much higher frequency compared with the general population[16 17] and 40% of patients with duodenal cancer have synchronous duodenal adenomas.[18]

Despite this information it is still unknown how many patients with duodenal polyps ultimately develop duodenal cancer. As such information should be available before the introduction of a large scale surveillance programme for patients with polyposis, we evaluated the lifetime risk of duodenal cancer in a large series of patients with polyposis from the Polyposis Registries in The Netherlands and Denmark. In addition, a decision analysis model was developed for prediction of whether surveillance of the upper GI tract would lead to an increased life expectancy.

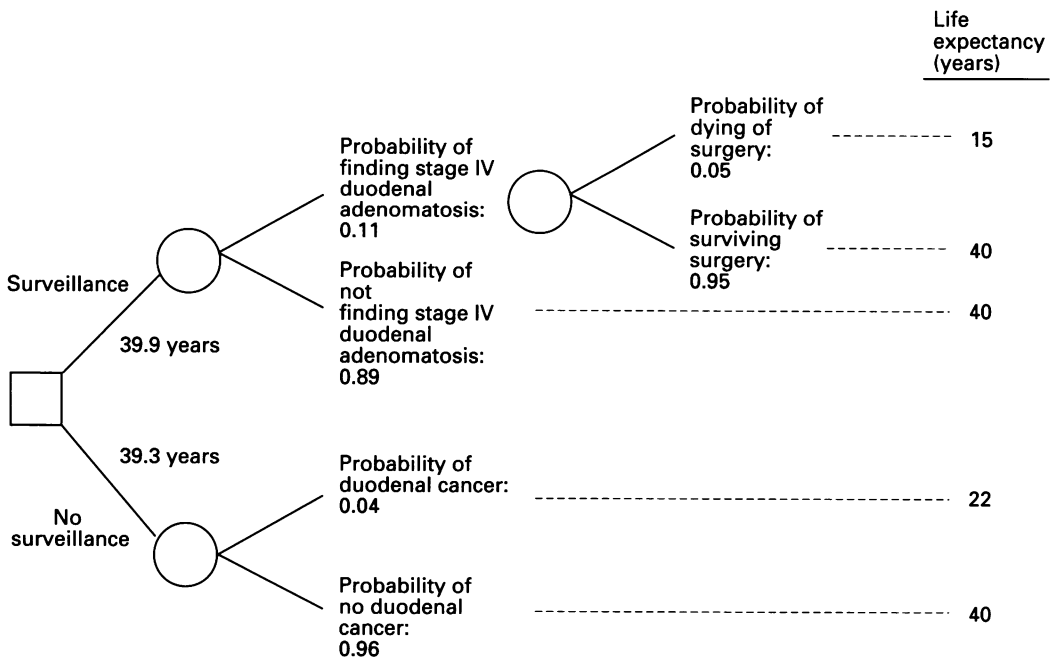
Methods

THE DUTCH AND DANISH POLYPOSIS REGISTRIES

Families suspected of FAP are referred to the registries from all parts of both countries.[19] Personal data, results of investigation, pathology reports, and results of treatment are collected for the registries. The criteria used for the diagnosis of an FAP family were that there should be at least one relative with more than 100 colorectal adenomas, or that linkage or mutation analysis had proven that the APC gene was responsible for the disease in the family.

RISK ANALYSIS

For risk assessment, patients with polyposis were studied with respect to risk of the



Decision tree for a 30 year old man with familial adenomatous polyposis.

development of duodenal cancer from birth until death. The data were analysed by life table analysis methods. Observation time was until date of last contact, death, date of diagnosis of a duodenal cancer, or closing date of the study, 31 December 1995.

DECISION ANALYSIS

We applied the technique of decision analysis to a hypothetical male polyposis patient, 30 years of age, who had undergone colectomy and ileorectal anastomosis. The first step was to identify all the alternative actions, treatments, and outcomes that could occur for the patient in question. On the basis of this, a decision model (shown in the Figure) that displays these elements in their proper time sequence was developed. Points where the tree branches ("nodes") are square ("choice nodes") when they imply a decision under the control of the physician, and round ("chance nodes") if a chance outcome occurs.

Results

RISK ANALYSIS

On 31 December 1995, the Dutch Popyposis Register included about 200 families with FAP. Data collection was completed in the first 155 families and these families were selected for the present study. The 155 families included 711 patients with FAP. The diagnosis of FAP was confirmed by pathology and/or medical reports in 601 patients. One hundred and eighteen patients died; the cause of death is known in 91% of the patients. Among the 601 patients, seven developed duodenal cancer (including one suspected case). The mean age at diagnosis of duodenal cancer was 47 years (range 39–53). The cumulative risk of developing duodenal cancer by age 70 was 4% (95% confidence interval 1–7%). The number of patients at risk by age 70 was 27.

On 31 December 1995, the Danish Polyposis Register included 142 FAP families with a completed data collection, including 454 patients of whom 376 had a histologically verified FAP. The cause of death is known for all 160 deceased patients. In five patients data were insufficient. Of the remaining 371 affected patients, five developed duodenal cancer; the mean age at diagnosis was 51 years (range 43–77). The cumulative risk of developing duodenal cancer by age 70 was 3% (95% confidence interval 0–6%). The number of patients at risk by age 70 was nine.

DECISION ANALYSIS

The decision tree for the 30 year old polyposis patient with corresponding probabilities is shown in the Figure. We assumed that the life expectancy of a 30 year old polyposis patient would be shortened due to desmoid disease, the mortality due to secondary rectal surgery, and the mortality due to rectal cancer. Therefore, we estimated that the average life expectancy of this 30 year old patient would be 40 years instead of 45 years. For staging of duodenal polyposis in most studies use was made of the so-called Spigelman classification.[14] This staging system is based on a set of arbitrary scores using postulated adenoma/cancer risk factors. These are the architecture ("villousness"), the degree of dysplasia, and the size and number of the duodenal polyps. Stage I represents minor disease and stage IV indicates major or advanced duodenal polyposis (Table I). When stage IV duodenal polyposis is found, surgical intervention may be considered. The probability of finding Spigelman stage IV is based on findings of two prospective studies on the natural history of duodenal adenomatosis.

TABLE I *Classification of duodenal adenomas according to Spigelman*[14]

	Points		
Polyps	*1*	*2*	*3*
Number	<4	5–20	>20
Size (mm)	0–4	5–10	>10
Histology	Tubular	Tubulo-villous	Villous
Dysplasia	Mild	Moderate	Severe

Spigelman stage I: 1–4; stage II: 5–6; stage III: 7–8; stage IV: 9–12 points.

One analysis was conducted at the St Mark's Polyposis Registry in London[14] and the other in five European countries.[15] The British study showed that 11 (11%) out of 102 FAP patients had stage IV duodenal polyposis. In the European multicentre study, 27 patients out of 310 (9%) had stage IV duodenal polyposis. In the multicentre study, 7% of the patients aged between 20 and 40 years, and 11% of those aged between 40 and 60 years had stage IV duodenal adenomatosis (personal communication, S Bülow). The cumulative risk of developing stage IV adenomatosis is therefore at least 11%. The mean age of the patients identified with Spigelman stage IV was 51 years in the British study and 38 years in the multicentre study. On these grounds we estimated that the average age of patients who reached stage IV duodenal polyposis would be 45 years. If a pancreaticoduodenotomy is performed and the patient dies as a result of complications of this procedure, the average life expectancy of a 30 year old patient would amount to 15 years. The perioperative mortality of pancreaticoduodenectomy has declined during the past decade and is now about 5%.

The cumulative risk of duodenal cancer by age 70 in the present series is 3–4%. The mean age at diagnosis of duodenal cancer in this study and in three others was about 50 years. The life expectancy of a patient who develops duodenal cancer is estimated at two years. Hence, the life expectancy of the hypothetical 30 year old patient is on average 22 years if he develops duodenal cancer.

We then worked our way back through the decision tree by "folding it back" from right to left. By multiplying the life expectancy by the probabilities of occurrence of each option, and summing them for each branch, we could assign life expectancies to the various nodes. The calculations showed that the option of surveillance led to an increase in life expectancy by seven months. The key variables – the cumulative risk of stage IV duodenal adenomatosis, duodenal cancer, and the risk of mortality due to pancreaticoduodenotomy – were varied over a plausible range to assess their impact on the outcome of the model (Table II). The probability of developing duodenal cancer appeared to be the most important variable.

TABLE II *The impact of various probabilities of developing duodenal cancer, stage IV duodenal adenomatosis, and perioperative mortality on life expectancy*

	Life expectancy (y)	
	Surveillance	*No surveillance*
Probability of duodenal cancer (%)		
4	39·9	39·3
10	39·9	38·2
15	39·9	37·3
Probability of stage IV duodenal adenomatosis (%)		
11	39·9	39·3
15	39·8	39·3
20	39·7	39·3
Probability of perioperative mortality (%)		
2	39·9	39·3
4	39·9	39·3
6	39·8	39·3

Discussion

After the realisation that a majority of patients with polyposis develop adenomas in the duodenum, many investigators recommended surveillance of the upper GI tract. However, before establishing such a surveillance programme, a more critical evaluation of the pros and cons of surveillance should be performed. In particular, the difficulties for effective treatment posed by duodenal adenomas make the benefit of surveillance of the upper GI tract questionable.

In the assessment of population screening, the criteria formulated by Wilson and Jungner[20] are usually applied. These criteria are also appropriate in the assessment of surveillance of high risk groups such as patients with polyposis. According to these criteria, the natural history of duodenal adenomas should be known, a curative treatment should be available, and there should be evidence that early treatment leads to an improved prognosis.

With respect to the natural history of duodenal adenomas, the most urgent question is "do the duodenal polyps have the same malignant potential as the colonic polyps?" Earlier studies[17] indicated that the relative risk of duodenal cancer in FAP was very high, but such information is less useful in the decision making process, because the incidence of duodenal cancer in the general population is extremely low. Much more important would be to know the lifetime risk of developing duodenal cancer. The present study revealed that the cumulative risk of duodenal cancer was less than 5% by the age of 70. Although prospective studies are needed to confirm our findings, such studies have the disadvantage that the screening examinations will inevitably lead to early detection of premalignant disease and to early surgical intervention, which will interfere with the assessment of the duodenal cancer risk.

The treatment of duodenal adenomas in our patients is limited by a number of factors. Endoscopic snaring may be made impossible by the presence of large numbers of polyps or by the usual sessile nature of the polyps. Endoscopic electrocoagulation, if repeated very often, will lead to considerable scarring, which in the periampullary area might cause strictures. Laser ablation of polyps via the endoscope can be used, but carries the risk of duodenal perforation. Polyp removal by (surgical) duodenotomy consisting of submucosal infiltration and local excision of all polyps is

not recommended, because a recent study has shown recurrence in all patients treated by this technique within a short time.[21] To summarise, the only curative treatment appears to be a proximal pancreaticoduodenotomy. Such an operation has considerable potential morbidity and mortality which makes the indication for and the timing of surgery extremely difficult. Criteria of size, rapid growth, polyp induration, or consistently severe dysplasia or villous change suggest that intervention is necessary. In the above mentioned British study, among the 10 patients with stage IV adenomatosis at the first endoscopy, one developed duodenal cancer and two other patients are suspected of having this type of cancer.[22] Thus surgery may be considered in patients that consistently have stage IV duodenal adenomatosis.

Evidence that early treatment leads to improvement of the prognosis is not yet available, and it will probably take a long time to collect such information. The best way to demonstrate the benefits of surveillance would be by randomised controlled studies showing a higher survival rate. Such studies will, however, be difficult to carry out in view of the extremely high risk of premalignant duodenal disease. Therefore, we decided to apply decision analysis to predict whether surveillance might lead to an increase in life expectancy. The calculations showed that surveillance increased the life expectancy by seven months if surgery was performed after detection of stage IV adenomatosis. Sensitivity analysis showed that the probability of duodenal cancer had the strongest effect on the outcome compared with the probability of developing duodenal adenomatosis stage IV or perioperative mortality.

To summarise, the present analysis revealed that surveillance may lead to a moderate gain in life expectancy. Therefore, before starting surveillance of the upper digestive tract, it is important to explain to the patients that the risk of developing duodenal cancer is relatively low and that the only curative treatment for severe duodenal adenomatosis is a major operation with substantial morbidity and mortality (in addition to the morbidity from duodenoscopy). On the basis of this information the patients may be able to decide whether the potential gain in life expectancy outweighs the adverse effects of surveillance and treatment. If the patient prefers to be under surveillance, the screening protocol should start by the age of 30 years. Starting at an earlier age can be considered to offer no clinical benefit, as reports of duodenal cancer before this age are extremely rare. The recommended interval between examinations is one to three years depending on the findings. Ideally, the results should be collected in a uniform manner at a regional or national registry which will permit future evaluation.

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