High Risk of Rectal Cancer and of Metachronous Colorectal Cancer in Probands of Families Fulfilling the Amsterdam Criteria

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Objective: To investigate the risk of metachronous colorectal cancer (CRC), its impact on survival, and the risk of rectal cancer in a cohort of probands meeting the Amsterdam criteria.

Background: Several determinants of decision-making for the management of CRC in patients with a putative diagnosis of Lynch syndrome are scarcely defined, and many of them undergo segmental bowel resection instead of the advised total colectomy.

Methods: A retrospective cohort study was conducted on 65 probands of the Amsterdam-positive families who had surgery for primary CRC and at least 5-year surveillance thereafter. The rates of metachronous CRC and of rectal cancer were evaluated, together with their association with preoperatively available clinical predictors. Differences in overall survival between patients with and without metachronous CRC were evaluated using a time-dependent Cox model.

Results: Seventeen patients (26.2%) had metachronous CRC. No clinical feature was associated with an increased risk of its development. The risk of death in patients with metachronous CRC was 6-fold increased. Neither a 2-year interval endoscopic surveillance after surgery, nor total colectomy was associated with a significant reduction in metachronous CRC. Eighteen patients (23.7%) had rectal cancer at first presentation, 5 patients of the remainder (10.6%) developed rectal cancer after primary colon resection. Two patients undergoing total colectomy developed a metachronous rectal cancer (18.2%). A first-degree family history of rectal cancer was associated with an increased risk of rectal cancer.

Conclusions: Probands of families fulfilling the Amsterdam criteria carry a high risk of rectal cancer and of metachronous CRC. Total proctocolectomy, or total colectomy and a 1-year interval of proctoscopic surveillance should be advised when a high risk of rectal cancer can be predicted.

Keywords: Amsterdam criteria, colorectal surgery, familial colorectal cancer type X, Lynch syndrome, proband, rectal cancer

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The diagnosis of Lynch syndrome relies on the detection of germline mutations in mismatch repair genes.[1,2] Families qualifying for mismatch repair gene testing are generally selected starting from a single subject presenting with colorectal cancer (CRC), or another Lynch-associated cancer, whose personal and/or family characteristics fulfil specific criteria, such as the Amsterdam criteria or the revised Bethesda guidelines[3]: this first subject is defined as the proband or index patient.

In patients with a mismatch repair-mutation-proved Lynch syndrome, total colectomy with ileorectal anastomosis is advised when colon cancer develops.[4,5] Probands presenting with CRC, however, often undergo primary intestinal surgery without a defined mismatch repair gene status, because of the time required to perform molecular/gene testing. Accordingly, even when selection is carried out utilizing the more specific Amsterdam criteria,[6] we may expect that both mismatch repair–mutation-positive (Lynch syndrome) and mismatch repair–mutation-negative (familial CRC type X) subjects[7,8] are included among probands at the time of primary surgery.

Specific evidence on the risk of metachronous cancer, its impact on survival, and on the prophylactic value of total colectomy is scarce for this heterogeneous group of subjects. Consequently, surgical decision-making is guided prevalently by considerations similar to that adopted in sporadic cancer, such as tumor site/multiplicity, comorbidity, and life expectancy of patients.[9] This approach, together with a frequently overlooked family history,[10] may explain the high proportion of patients with putative Lynch syndrome and primary CRC undergoing a segmental resection of the colorectum.[11]

To improve the surgical decision-making in probands, mandatory information should encompass the risk of metachronous cancer in the colon and in the rectum, and the impact of metachronous CRC on survival. To these aims, we reviewed the data at the time of first diagnosis and the long-term outcomes of a cohort of probands with Amsterdam-positive criteria who underwent primary CRC surgery.

PATIENTS AND METHODS

This retrospective observational study was conducted on a cohort of unrelated consecutive patients with putative Lynch syndrome as identified by the Amsterdam criteria from the Brescia and Padua Hereditary CRC Registries.

The protocol was approved by the Institutional Review Boards at both institutions. All patients had consented to the anonymous use of their data for scientific purposes when they were originally included in the registries.

All data were collected retrospectively from computerized registry databases, and further verified directly with patients on outpatient visits during 2010, or with other family members in the case of previous death of the proband.

Only probands of families fulfilling the Amsterdam I or II criteria[12] were eligible for the study, a proband (also known as index case) being defined as the first member of a family being suspected of Lynch syndrome by the Amsterdam criteria, and undergoing formal registration at 1 of the 2 Institutions. Further inclusion criteria were the following: adherence of family history to the Amsterdam I or II criteria with documented histology of cancers running in the family, personal history of surgery for CRC, and at least 5 years of documented surveillance and follow-up after primary surgery. Probands undergoing proctocolectomy as a primary procedure were excluded from the study.

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Endpoints of the study were the following:

(1) The rate of metachronous carcinomas in the colon and rectum; the association with preoperatively available parameters was also investigated.
(2) The rate of rectal carcinoma, both primary and metachronous, and its association with clinical factors.
(3) The impact of metachronous colorectal carcinomas on survival.

The following patient, family, tumor, and management variables were considered in the study: age at primary surgery, sex, personal history of extracolonic cancers at primary surgery, personal history of rectal adenoma at primary surgery, pattern of family history (Amsterdam I vs Amsterdam II criteria), presence of first-degree family members with rectal carcinoma, site (the right colon defined as proximal to the splenic flexure, left colon, and rectum), stage of primary carcinoma (according to TNM, 7th Edition, with American Joint Committee on Cancer (AJCC) groupings), coexistence of synchronous CRC at primary presentation, pattern of primary procedure (extensive vs segmental resection), surgical center (Brescia/Padua Registry vs elsewhere), and pattern of endoscopic surveillance (appropriate vs inappropriate).

Extensive resection included total and subtotal colectomy with ileo-rectal or ileo-sigmoid anastomosis, respectively, whereas segmental resection included both segmental colectomy (including anterior resection and abdomino-perineal resection of the rectum) and left or right hemycolectomy.

Surveillance of the remaining colorectum with colonoscopies every 2 years or less throughout the period from primary surgery to data analysis or death, was defined as appropriate surveillance; any longer (even if episodically) endoscopic interval was defined as inappropriate surveillance.

Data on molecular-genetic testing are reported hereafter, even if no proband of the study cohort had his microsatellite or mismatch repair gene status available at the time of primary surgery. From 1997 to 2005, all index patients of Amsterdam-positive families were offered microsatellite instability tumor testing, and MutL homolog 1 (MLH1), MutS homolog 2 (MSH2) mutational testing if they had an microsatellite instability-high tumor.

STATISTICAL ANALYSIS

Descriptive

Most continuous variables had nonnormal distribution (as evaluated by Kolmogorov-Smirnov tests). For reasons of uniformity, summary statistics for all continuous variables are, therefore, presented as medians and interquartile ranges. Group differences were analyzed with Wilcoxon-Mann-Whitney tests or Fisher exact tests as appropriate.

Survival

Different models were applied to answer different questions. Survival was defined as the time from enrollment to the first of 2 events: metachronous cancer or death from any cause, whichever came first. Cox proportional hazards regression models were applied to further evaluate the effects of the different prognostic parameters measured in our patients. Scaled Schoenfeld residuals were used to verify the assumption of proportionality of the Cox model.

We have also studied how the onset of a metachronous cancer changes the risk of death in our patients, using a Cox model with the onset of a metachronous cancer as a time-dependent covariate, a so-called illness-death model.

The statistical analysis has been performed using the open-source statistical package R.[13] All statistical tests were 2-tailed and performed at a P value of 0.05.

RESULTS

Patient Characteristics

The study cohort was composed of 65 probands enrolled between 1976 and 2005 (35 of them were recruited at the Brescia Registry, 30 of them at the Padua Registry). These 65 patients came from 65 unrelated families with no mutation overlap among them. Their baseline clinical data are summarized in Table 1.

The index procedure for primary CRC was performed at 1 of the 2 Registry-associated university hospitals in 24 individuals, whereas it was carried out elsewhere in 41 cases.

A primary extensive colorectal resection was performed in 11 patients (16.9%); 6 of them (54.5%) had synchronous colon carcinomas. A diagnosis of synchronous colon cancer was the only

TABLE 1. Baseline Characteristics of the Study Cohort and Risk of Metachronous Colorectal Cancer

Characteristic	Total Population	Metachronous Cancer	No Metachronous Cancer	*P*
Total number of patients	65	17	48	
Female sex, no. patients (%)	27 (41.5)	7 (41.2)	20 (41.7)	1.000
Median age at surgery, years (interquartile range)	47 (15)	46 (14)	47 (16)	0.259
Criteria for patient inclusion, no. patients (%)				0.381
Amsterdam I	44 (67.7)	10 (58.8)	34 (70.8)	
Amsterdam II	21 (32.3)	7 (41.2)	14 (29.2)	
Primary colorectal cancer site, no. cancers (%)				0.987
Right colon	28 (36.8)	8 (40.0)	20 (35.7)	
Left colon	30 (39.5)	8 (40.0)	22 (39.3)	
Rectum	18 (23.7)	4 (20.0)	14 (25.0)	
Primary colorectal cancer AJCC stage, no. cancers (%)				0.225
Stage I	20 (26.3)	3 (15.0)	17 (30.4)	
Stage II	40 (52.6)	15 (75.0)	25 (44.6)	
Stage III	14 (18.4)	2 (10.0)	12 (21.4)	
Stage IV	2 (2.6)	0	2 (3.6)	
Patients with synchronous primary colorectal cancers, no. patients (%)	11 (16.9)	3 (17.6)	8 (16.7)	1.000
Index surgical procedure, no. patients (%)				0.713
Extensive colorectal resection	11 (16.9)	2 (11.8)	9 (18.8)	
Segmental colorectal resection	54 (83.1)	15 (88.2)	39 (81.2)	

preoperative factor associated with an increased propensity for extensive surgery ($P = 0.015$). In 9 patients, the extensive procedure was a total colectomy with ileo-rectal anastomosis, whereas the remaining 2 individuals had a subtotal colectomy with ileo-sigmoid anastomosis. A segmental resection was carried out in the remaining 54 patients (83.1%).

There were 13 patients with extracolonic tumors (20%), 9 of them had a diagnosis of extracolonic cancer before their diagnosis of primary CRC, whereas the remainder had the extracolonic cancer diagnosed after their CRC was diagnosed. Five patients (7.7%) had endometrial cancer; 4 of them had it diagnosed before primary CRC.

The median surveillance time after surgery was 10 years (interquartile range: 13) ranging from 5 to 31 years (except 2 patients who died of primary colon cancer 24 and 35 months after surgery) for a total of 814 person-years. Forty-six patients (70.8%) underwent appropriate endoscopic surveillance after primary surgery, whereas inappropriate surveillance was applied in 19 subjects (29.2%).

Microsatellite instability testing was conducted in 62 patients (3 patients refused testing). Microsatellite instability was found in the CRC tissue of 46 patients (74.2%). Thirty-one of them had a pathogenic MLH1 or MSH2 mutation (67.4%).

Metachronous Colon or Rectal Cancer

Cumulatively, 17 patients (26.2%) had at least 1 metachronous CRC after a median of 6 years (interquartile range: 7) since their primary surgery. The rate of metachronous CRC was similar at the Brescia and Padua Registries ($P = 0.579$).

In the group of 18 patients with primary rectal cancer (median surveillance: 13.5 years, interquartile range: 13), the rate of metachronous colon cancer was 22.2%, with 4 patients developing 6 colon carcinomas (4 in the right colon, 2 in the left colon) a median of 15 years (interquartile range: 18) after primary surgery.

In the group of 47 patients with primary colon cancer only (median surveillance: 9 years, interquartile range: 12), the rate of metachronous CRC was 27.7%, with 13 patients developing 5 rectal cancers and 10 colon carcinomas (8 in the right colon, 2 in the left colon) a median of 5 years (interquartile range: 5) after primary surgery. Among this subgroup, 2 out of 11 patients undergoing extensive surgery developed a metachronous rectal cancer (18.2%), whereas 11 out of 36 patients undergoing segmental resection had a metachronous CRC (30.6%, $P = 0.701$).

None of the patient, tumor or treatment variables were significantly associated with the rate of metachronous CRC.

When considering the impact of surveillance on the rate of metachronous CRC, 10 out of 46 patients (21.7%) undergoing appropriate (1- to 2-year interval) endoscopic surveillance developed a metachronous cancer, with a median interval from the last endoscopy to diagnosis of 14 months (range 11–24 months), whereas 7 out of 19 of those undergoing inappropriate surveillance (36.8%) had a metachronous cancer, with a median interval from the last endoscopy to diagnosis of 36 months (range 29–40 months). The rate and the stage of metachronous CRC were similar in patients undergoing appropriate and inappropriate surveillance ($P = 0.228$ and $P = 0.114$, respectively).

The Risk of Rectal Cancer

The cumulative rate of rectal cancer including patients with primary and metachronous rectal cancer was 35.4%, with no statistical difference between the Brescia and Padua Registries ($P = 1.000$).

Eighteen probands (27.7%) had rectal cancer at the time of primary surgery and 3 of them synchronously with colon cancer. As mentioned above, 5 probands developed a metachronous rectal cancer a median of 6 years (interquartile range: 9) after primary surgery (2 of them after total colectomy and the remainder after segmental colectomy).

When testing the variables available at the time of primary surgery as predictors of either primary or metachronous rectal cancer (Table 2), only a family history of rectal cancer was significantly associated with it ($P < 0.001$). Accordingly, a proband of an Amsterdam-positive family including family members with rectal cancer has a 20-fold risk of developing rectal cancer sometime in their life compared with a proband without a family history of rectal cancer (odds ratio: 20.22; 95% confidence interval: 4.78–85.55).

The Impact of Metachronous CRC on Survival

All patients who died in our series died of CRC, either primary or metachronous. Three patients (6.3%) died from their primary cancer, whereas four of those with metachronous colorectal cancer died (23.5%).

As the period of surveillance after primary surgery was longer in patients with metachronous cancer (median: 18 years, interquartile range: 16) than in patients without metachronous cancer (median: 9 years, interquartile range: 10, $P = 0.033$), the 10-year mortality after primary surgery was 6.3% in patients without metachronous cancer, and 11.8% in those with metachronous cancer ($P = 0.299$). However, when applying a time-dependent Cox or proportional hazards model, the development of a metachronous CRC carried a 6-fold increase in the risk of death (hazard ratio: 5.994, standard error: 0.769, $P = 0.020$).

Among the factors that may influence the risk of cancer-related death, we found that with a 58.8% rate of stage III to IV, metachronous carcinomas were significantly more advanced than primary carcinomas, where the rate of stage III to IV cancers was 23.1% ($P = 0.038$).

TABLE 2. Risk of Primary or Metachronous Rectal Cancer

Characteristics	Rectal Cancer	Colon Cancer Only	*P*
No. patients	23	42	
Primary rectal cancer	18		
Metachronous rectal cancer	5		
Female sex, no. patients (%)	8 (34.8)	19 (45.2)	0.444
Mean age at surgery, years (range)	49 (18)	46 (13)	0.978
Criteria for patient inclusion, no. patients (%)			0.175
Amsterdam I	13 (56.5)	31 (73.8)	
Amsterdam II	10 (43.5)	11 (26.2)	
Family history of rectal cancer, no. patients (%)	14 (60.9)	3 (7.1)	<0.001
Personal history of rectal adenoma (%)	2 (8.7)	4 (9.5)	1.000
Patients with synchronous primary colorectal cancers, no. patients (%)	5 (21.7)	6 (14.3)	0.500
Personal history of extracolic cancer, no. patients (%)	2 (8.7)	7 (16.7)	0.474

DISCUSSION

The surgical management of primary CRC in probands of families fulfilling the Amsterdam criteria is controversial. In particular, the decision on the extent of primary colorectal removal is not straightforward as several important determinants for planning are lacking.

First, at the time of primary surgery, probands do not have a precise syndromic diagnosis. Lynch syndrome or familial CRC type X may be classified according to mismatch repair gene status.[7,8] Unfortunately, as of yet, the time required to complete genetic assessments remains difficult to predict. This uncertainty influences the scenario of the information/counseling phase before surgery weighing on both the emotional factors of the patient and the perception of potential clinical/legal risks of clinicians. As a consequence, most patients presenting with a diagnosis of CRC undergo primary surgery without a genetic categorization, and their surgical planning must take into consideration both possible diagnoses.

Second, scarce data are available on the risk of metachronous CRC for this heterogeneous group of patients. In fact, whereas most recent studies considered mismatch repair mutation carriers and nonmutants distinctly,[14,15] most previous investigations on metachronous CRC included both probands and family members,[16,17] though each one implies different syndrome awareness and decision-making for the appropriate primary surgical procedure.

Third, there is limited information on the risk of rectal cancer in both Lynch syndrome and familial colon cancer type X, leaving further uncertainty on the benefits of total colectomy with ileorectal anastomosis in these patients.[18–20]

The lack of answers to these issues is contributing to the adoption of a sporadic cancer-like strategy by applying segmental resection to treat CRC in most patients fitting the Amsterdam criteria.[9]

In our series, more than one fourth of probands belonging to the Amsterdam-positive families developed a metachronous CRC after a primary large-bowel resection. These data are not novel as comparable rates have been found both in patients selected by clinical criteria,[11,16,17] and in those selected by mismatch repair mutation.[14,15] Unfortunately, no reliable preoperative predictor of the risk of metachronous CRC has been found in the present or in previous studies.

In our series, even more emphasis is placed on the impact of metachronous bowel cancer by the 6-fold increase in the death rate associated with its development, and its frequently advanced stage. Moreover, in contrast with previous observations in patients with Lynch syndrome,[21] a surveillance interval of 1 to 2 years was not associated with significant prevention, or stage reduction of metachronous cancer.

Similarly to previous investigations,[14–17] these findings support the use of extensive colon resection for the treatment of primary colon cancer, though in our series, the reduction from 30% to 18% in the rate of metachronous cancer associated with total colectomy was not statistically significant. Moreover, the rate and timing of the diagnosis of rectal cancer question the appropriateness of total colectomy as a standard choice for all Amsterdam-positive patients with colon cancer.

Total proctocolectomy, either restorative or with ileostomy, is not generally advised,[4,5] on the one hand, because of its technical challenge and impact on quality of life, and on the other hand, previous data suggest that the risk of rectal cancer may be relatively low,[18] and that endoscopic surveillance every 1 or 2 years is adequate and safe in patients with Lynch syndrome.[21] However, a wide range of rectal cancer rates have been actually reported in the Amsterdam-positive families; specifically, the rate of primary rectal cancer ranging from 13% to 31%,[16,18–20,22] and the rate of metachronous rectal cancer ranging from 8% to 20%.[18–20] In our series, the rate of primary rectal cancer was 28%, and that of metachronous rectal cancer was 11%, along with previous figures supporting a substantial risk of developing rectal cancer in these individuals. Nonetheless, the short interval between the previous endoscopic surveillance and the examination that detected metachronous cancer, as well as the advanced stage of the latter, indicates that a 2-year interval of surveillance might be inappropriate if we are going to preserve the rectum.

Therefore, although agreeing that an extensive resection reduces the rate of metachronous colon cancer, we deem that a total proctocolectomy may be a valuable option not only for patients with primary rectal cancer, but also for those with primary colon cancer and a relative who has been diagnosed with rectal cancer. In fact, in our series, more than 60% of patients with rectal cancer, either primary or metachronous, had 1 or more first-degree family members with rectal cancer, whereas less than 10% of those with colon cancer only had a similar family history. Hopefully, future studies in larger series would eventually validate this predictor of rectal cancer risk, which has never been reported or possibly investigated, previously. As an alternative to proctocolectomy in high-risk patients undergoing rectum-preserving surgery, a 1-year interval of endoscopic surveillance of the rectal stump should be recommended, together with the use of techniques that may facilitate the detection of preneoplastic lesions, such as magnifiying and high-resolution endoscopy, chromoendoscopy,[23] and more advanced technologies (narrow-band imaging and endoscopic confocal microscopy).

Even if the small sample size and the retrospective design of our study do not allow us to draw conclusive remarks, we confirm that probands of families fulfilling the Amsterdam criteria carry a high risk of rectal cancer and a of metachronous carcinoma, both in the colon and in the rectum, impacting importantly on patient survival. Alternative options such as total proctocolectomy, or total colectomy, and subsequent yearly proctoscopic surveillance should be offered to those patients with an increased risk of rectal cancer, as predicted by family history.

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