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ORIGINAL ARTICLE

Recurrent desmoids determine outcome in patients with Gardner syndrome: a cohort study of three generations of an APC mutation-positive family across 30 years

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Abstract

Purpose Screening of Gardner syndrome (GS) patients is tailored towards prevention of colorectal cancer (CRC). However, many patients suffer from desmoid tumors, which are challenging to treat due to invasive growth and local recurrence. The aims of our study were to determine the effectiveness of screening in GS and analyze outcome of desmoid tumors by treatment modality.

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Methods This was a cohort study of a family of 105 descendants with GS. All family members who agreed were screened by endoscopy, and colorectal resection was performed upon pending malignancy. Resectable desmoids were excised, whereas large tumors were treated by a combination of brachytherapy (BT) and radiotherapy (RT). Main outcome measures were the incidence of CRC and overall and disease-specific mortality (ClinicalTrials.gov ID NCT01286662).

Results Thirty-seven of 105 family members have GS. Preventive colorectal resections were performed in 16 patients (15 %), with one death due to gastric cancer. In four patients who denied screening endoscopy, invasive tumors of the colon (three patients) and stomach developed. Of 33 desmoid tumors, 10 (30 %) were located in the mesentery, 17 (52 %) in the abdominal wall, and 6 (18 %) in extra-abdominal sites. Excision of 12 desmoids was performed in eight patients. Four desmoids were treated by BT and RT and showed full or partial remission.

Conclusions Provided adequate screening, good long-term control of colorectal tumors is achievable. However, desmoid tumors determine survival and quality of life in many patients. Our data suggest good local control using a combination of brachytherapy/radiotherapy in large desmoids unsuitable for surgical resection.

Keywords Colorectal cancer · Adenomatous polyposis · Colon · Rectum · Familial · Desmoid

Introduction

In 1950, Eldon J. Gardner first described a kindred of patients presenting with familial adenomatous polyposis

(FAP) in combination with various skin and soft tissue tumors [1]. Although the term “Gardner syndrome” (GS) describes more of a historically coined variant of FAP rather than a distinct subtype of the disease [2–4], the term is usually reserved for patients in whom extraintestinal manifestations are especially prominent and relevant during the course of their disease [5–7].

Since 1978, our group of physicians has been treating a family of GS patients in the remote southeastern part of Switzerland. Similar to ethnic subgroups with little genetic admixture such as the Amish community in Northern America, this kindred has been living in an area of alpine Switzerland with minimal migration of residents, thereby passing on the distinct genetic Gardner subtype in a manner allowing population-based genetic analysis. Affected family members present with the phenotype of an attenuated form of FAP (AFAP), distinguished from classic FAP by the presence of fewer colonic adenomas, a lower cancer penetrance, and an older age distribution of adenomas as well as carcinomas. In most cases, the syndrome is caused by autosomal mutations in the APC gene. These mutations have been verified since the early 1990s. In this kindred, the APC germ line mutation c.5942delA was identified; this mutation leads to a frameshift at codon 1981 and results in a premature stop codon (p.Asn1981IlefsX62) [8].

As in most FAP patients, the mainstay in the management is repeat clinical and endoscopic screening to ensure timely colonic resection (usually in the form of subtotal colectomy or proctocolectomy with ileal pouch-anal anastomosis—IPAA) in patients developing malignancy. Experts on hereditary gastrointestinal cancer recommend initial sigmoidoscopy in individuals with positive genetic testing and a classical FAP variant at the age of 10–12 years [9]. The same is recommended in patients with a positive family history and negative genetic testing, whereas in AFAP members with an identified mutation, initial colonoscopy is indicated at the age of 18–20. Thereafter, repeat endoscopy should be performed every 2 years; once adenomas are detected, annual colonoscopy should be performed until colectomy [9]. In addition, 10–15 % of GS patients develop desmoid tumors which frequently develop following surgical resection in accessible areas such as the abdominal wall, or in sites unsuitable for resection like the intestinal mesentery. Despite their lack of metastatic potential, desmoids cause significant morbidity and mortality due to their ability to surround, compress, and erode adjacent tissues, providing a challenge to surgeons and oncologists alike. Affected patients suffer from prolonged and often lethal courses.

The aim of our present study was twofold. First, we wished to investigate whether early genetic testing, repeat clinical and endoscopic testing, and prophylactic colectomy were associated with acceptable morbidity and mortality in GS. Secondly, we wished to better characterize extraintestinal manifestations

with an emphasis on treatment and outcome of desmoid tumors in our GS population.

Methods

Study design, eligibility criteria, and outcome variables

Prognostic cohort study: Since 1978, our group of physicians has been following a family of 105 members (43 women) from three generations of Gardner syndrome patients living in southeastern Switzerland. They are all direct descendants of a couple who lived at the end of the nineteenth century, and of which we know that five of their eight children died from gastrointestinal cancer [10]. They all suffer from an identical mutation of the APC gene that is being passed from one generation to the next. Both family members with confirmed APC mutations and those unwilling to undergo genetic testing but showing typical phenotype (endoscopic presence of multiple adenomas) were eligible for this study and defined our sample size. Operations were performed at the local hospital in cooperation with pathology services from a regional referral center and (radio-) oncology and genetic counseling services from two national university hospitals. Outcome variables included overall survival, incidence of intestinal and extraintestinal neoplasms, and treatment-specific recurrence rates and survival.

Diagnostic criteria: molecular and genetic testing

All family members at risk for the previously identified APC germ line mutation (c.5942delA) were counseled and offered genetic testing by direct DNA sequencing [3, 4]. Genetic testing of our patient cohort was started in 1995 [11]. Routine testing was recommended in adolescents by the age of 16 in order to timely identify patients in need of endoscopic screening and to reassure individuals not carrying the mutation. All tests were performed twice from two different samples of whole blood drawn on different days to minimize false-positive testing.

Clinical and endoscopic screening program

In patients with positive APC gene mutations, endoscopic screening was recommended to begin at the age of 16 years. Colonoscopy was indicated in patients with confirmed APC mutation and those who did or could not undergo genetic testing but who were related to known carriers of the mutation. Colonoscopy was recommended every 2 years in patients without adenomas; once adenomas were detected, annual colonoscopy was recommended.

Gastroscopy was performed upon detection of colorectal adenomas, or earlier upon onset of any upper gastrointestinal

symptoms. The extent of duodenal polyposis was assessed using the Spigelman classification and patients were monitored accordingly [12]. In case of few, small duodenal adenomas, screening and endoscopic removal was continued, whereas resection was encouraged in multiple or dysplastic adenomas (Spigelman IV).

Treatment of colonic adenoma, carcinoma, and soft tissue tumors

Preventive resections were recommended to patients with confirmed dysplasia and/or endoscopically uncontrollable numbers of adenomas. Subtotal colectomy with ileorectal anastomosis (IRA) was the procedure of choice in our patients due to the clinical phenotype of GS with predominantly right-sided polyposis and no or only moderate involvement of the rectum. Despite the risk of late rectal cancer and the need for lifetime follow-up in patients with IRA, we and others believe that this procedure is justified in GS due to its technical simplicity, good functional results, and lower perioperative morbidity compared to IPAA [13].

Desmoids and other soft tissue tumors

Desmoids of the abdominal wall were treated by wide excision in symptomatic patients or those exhibiting rapid growth and were routinely followed by CT. Recurrent desmoids were treated by radical resection or a combination of percutaneous radiotherapy (RT) and brachytherapy (BT) if unsuitable for resection. Intra-abdominal desmoids were usually considered nonresectable due to invasive growth in the intestinal mesentery and their often multifocal and late clinical appearance.

Statistical analysis

The study is registered at the National Institute of Health's registry (ClinicalTrial.gov ID NCT01286662). Descriptive analyses and univariate statistical comparisons were performed using Sigma Stat 3.11.0, Systat Software, Inc.

Results

Thirty-seven of the 105 members of this family were diagnosed with Gardner syndrome, either by positive genetic testing (27 patients) or by their phenotype (10 patients). The mean age at time of testing was 30 years (range 5–73). Genetic testing was done in 52 family members (27 positive, 25 negative). The APC mutation status of the remaining 43 patients is unknown, either because they declined genetic testing, have not undergone colonoscopy for age reasons, or were lost to follow-up during the course of their lives (Table 1).

Table 1 Prevalence of Gardner syndrome in the study cohort

Established diagnosis of GS	Genotype positive—27 (26 %) Phenotype positive—10 (10 %)
Diagnosis of GS ruled out	Genotype negative—25 (24 %)
Juvenile family members at risk w/o genetic testing or colonoscopy ^a	9 (8 %)
Adult family members at risk who decline genetic testing and colonoscopy	10 (10 %)
Lost to follow-up	24 (22 %)
Entire cohort	105 family members (100 %)

GS Gardner syndrome, w/o without

^a Endoscopy planned at age 16

Thirty-two of the 37 GS patients were screened using colonoscopy. The five remaining patients denied screening endoscopy. The youngest patient undergoing endoscopy was 12 years, and the youngest patient showing colonic polyposis was 14 years old. The most prevalent endoscopic findings of the gastrointestinal tract are listed in Table 2. In our series, patients most frequently presented with attenuated polyposis with a predominantly right-sided affection of the colon, mainly the cecum and the ascending colon. In 18 patients, few polyps (100 or less) were observed, whereas five patients showed up to 1,000 polyps. The rectum was mildly affected in 14 cases. Altogether, 18 patients (17 % of the entire kindred and 49 % of patients genotypically and/or phenotypically positive for GS) had to undergo colonic resections, and 7 patients had to undergo a total of 10 resections for extracolonic tumors. Overall mortality throughout the entire time period was six patients (16 % of all patients with Gardner syndrome), three of whom died from colorectal carcinoma, one from gastric carcinoma, and two from mesenteric desmoids tumors.

A total of 34 adult family members (32 %) either declined to undergo genetic testing or screening endoscopies

Table 2 Gastrointestinal tumors and polyps (36 patients, 93 tumors)

Site	Tumor	No. of patients
Stomach	Fundic gland polyposis	9
	Adenoma	15
	Ulceration/gastritis	9
	Dysplasia/adenocarcinoma	3
Duodenum	Adenomas	13
Jejunum	Adenocarcinoma	1
Ileum	Polyps	3
Colon	Adenomas/polyps	23
	Adenocarcinoma	2
Rectum	Adenomas/polyps	14
	Adenocarcinoma	1

or were lost to follow-up in the course of the entire observation period (Table 1). In addition, two patients with histologically confirmed colorectal carcinoma refused surgical treatment.

Outcome related to colorectal adenoma and carcinoma

Of the entire cohort, 18 patients underwent colorectal resections. Sixteen underwent preventive resections (15 colectomies with ileorectal anastomosis and one left colectomy) due to endoscopic findings of either too numerous or dysplastic adenoma and two patients because of colorectal cancer (CRC) without previous suspicion of dysplastic adenoma (one proctocolectomy and one resection of the transverse colon). Of all patients with colorectal resections, 16 remained free of recurrence for a mean 93 months (range 14–387), whereas two patients died from recurrent CRC. Both patients either refused screening endoscopy or surgical resection at a premalignant state. One patient died from gastric cancer and two from mesenteric desmoids after 48 months (range 24–103). Most importantly, however, none of the patients who underwent screening endoscopy followed by preventive colectomy for suspicious endoscopic findings died from intestinal neoplasms.

Treatment and outcome of desmoid tumors

Fifteen patients (5 women, 10 men) developed a total of 33 desmoids tumors (14 % of the entire family, 41 % of Gardner patients at a mean age of 43 years [31–77 years], Table 3). Most desmoids (17 tumors, 52 %) were found in the abdominal wall (Fig. 1a). Ten patients suffered from solitary mesenteric desmoids (30 %, Fig. 1b). Six desmoids (18 %) were located in extra-abdominal locations (back, groin, thigh, buttocks). Sixty-one percent occurred in context with previous surgery (mainly laparotomy) after a median interval of 39 months after surgery (range 6–94 months). Thirteen desmoids developed in patients without prior surgery (one mesenteric desmoid, six abdominal wall desmoids, six others). Ten abdominal wall desmoids could be treated by wide excision alone (Fig. 2), with three recurrences in one single patient within 28 months. Complications in patients with progressive mesenteric desmoids were ureteric obstruction in two patients and bowel obstruction in two patients with stage III mesenteric desmoids, one of whom was treated by small bowel resection and intestinal transplantation.

Recurrences of abdominal wall desmoids were treated by repeat local excision. Six patients stayed recurrence-free for a mean follow-up of 70 months (range 6–120 months). The remaining one patient decided to discontinue follow-up, and his status is unknown. From 2006 onwards, two desmoids were treated by high-dose radiation (HDR) brachytherapy and two others by a combination of HDR brachytherapy and

percutaneous radiotherapy. All were recurrent desmoids which were unsuitable for resection due to their large size at presentation. Desmoid tumors treated in this manner showed complete and partial remission in two cases each, with an average length of follow-up of 19 months (range 13–25 months, Fig. 3). Indications for BT were large tumors requiring plastic coverage if resected and patients denying surgery. In addition, desmoids had to be of adequate size to be properly exposed to the applicators (Fig. 4). Clinoril and tamoxifen was used in five patients with mesenteric desmoids that were unsuitable for resection, or in patients reluctant to undergo surgical therapy.

Osteoma and other extracolonic manifestations

A disproportionate number of GS patients developed a variety of both benign and malignant extracolonic tumors, including a renal cell carcinoma, pancreatic insular carcinoma, Hodgkin and non-Hodgkin lymphoma, uterus myoma, adrenal incidentaloma, cervical carcinoma, and one endometrioma. Eight patients developed a total of 12 osteoma which were located in the skull (seven), spine (two), and pelvic bone (three). Two such tumors were located in the mandibula of separate patients and required surgical excision due to progressive growth. No case of thyroid carcinoma occurred in our patient cohort.

Discussion

Since Elrond J. Gardner's original description in the 1950s, a number of case reports and small series have been published which describe this unique variant of FAP. Most authors agree on the need for early screening endoscopy followed by colectomy upon detection of dysplasia or endoscopically uncontrollable adenomatosis [9, 14, 15]. Less consent, however, exists on the management of associated desmoid tumors. In our present study, we have been privileged to follow on a large number of patients in a socially and geographically "contained" environment, providing us the unique opportunity to study not only problems related to colonic adenomatosis and its consequences, but also the occurrence and management of extracolonic manifestations in a large number of patients. In summary, we believe to contribute to the following issues related to Gardner syndrome patients:

Screening Our data show that early screening endoscopy in patients with identified APC gene mutation, and subsequent prophylactic colectomy in patients with dysplasia or substantial adenomatosis reliably prevents the occurrence of CRC in Gardner patients. In fact, none of the members of this family willing to participate in our surveillance program

Table 3 Overview of desmoid patients

Patient no.	Gender	Cause of death	Age at diagnosis	Location and number of desmoids	Abdominal surgery before desmoid occurrence	Occurrence in context with previous surgery	Time of desmoid occurrence after surgery (month)	Incidence without previous surgery	Resection of AWD	Resection of MD	Recurrence (month postop)	Brachytherapy/ radiotherapy	Remission after BT
1	w		73	2 (buttocks)	Cholecystectomy, hysterectomy, colectomy	No	2						
2	w	CRC	36	1 AWD	Resection of pancreatic tumor	Yes (1)	82	1			3 (12, 19, 28)		
3	w	MD	52	MD	Colectomy	Yes (1)	37						
4	m	MD	41	1 AWD, MD	Colectomy	Yes (2)	23, 23	1			1 (6)		
5	m		54	MD	Colectomy, splenectomy	Yes (1)	61						
6	w		56	3 AWD, MD, back, groin	–	No	6	2			2 (29, 69)	HDR-BT (14 Gy) + RT (20 Gy)	Partial
7	w		53	2 AWD, MD, 1 thigh	Colectomy	Yes (3)	38, 38, 38	1					
8	w		42	4 AWD	Colectomy, hysterectomy	Yes (4)	13, 37, 48, 48	1			1 (95)	HDR-BT (35Gy)	Complete
9	m		40	1 AWD	Colectomy	No		1			1 (?)		
10	m		41	MD	Colectomy	Yes (1)	22		1		1 (4)		
11	m		63	4 AWD	Colectomy	Yes (4)	46, 46, 94, 94	1			1 (50)	HDR-BT (35 Gy) HDR BT (35 Gy)	Complete Partial
12	w	Gastric cancer	63	1 AWD, MD	Lipoma excision abdominal	Yes (2)	24, 72	2	1		1 (72)		
13	w		32	2 AWD	–	No		1	2		2 (120)		
14	w		31	1 other (back)	–	No							
15	w		38	MD	Colectomy	Yes (1)	Unknown						

CRC colorectal cancer, AWD abdominal wall desmoid, MD mesenterial desmoid, HDR-BT high dose radiation brachytherapy, RT radiotherapy

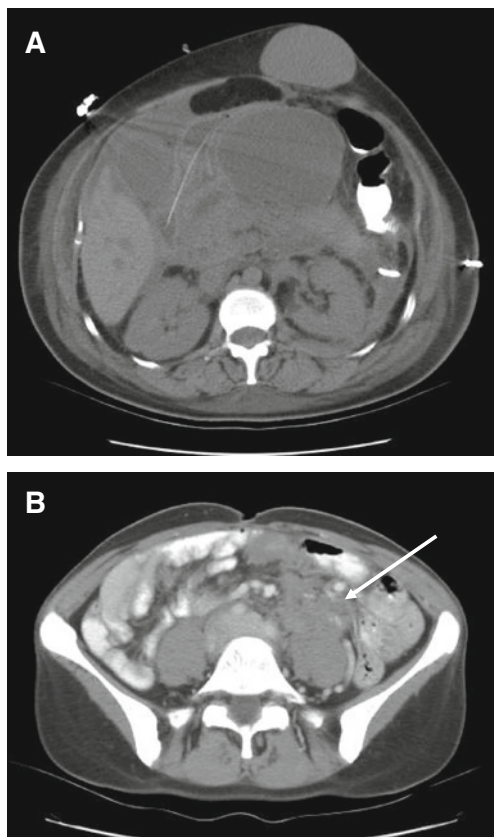


Fig. 1 Desmoids of the abdominal wall (a) and the intestinal mesentery (b). CT scanning; note the epifascial location in (a) and the proximity to the mesenteric root in (b)

with genetic testing, screening endoscopy, and prophylactic colectomy developed CRC. These encouraging results support the findings of Heiskanen et al., who found a mortality

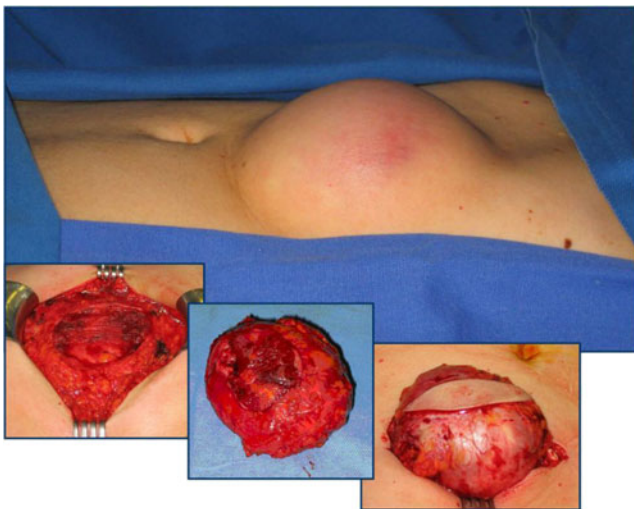


Fig. 2 Surgical treatment of desmoid tumors. En bloc resection of skin, subcutaneous fat, desmoid tumor, and adjacent abdominal wall musculature and fascia due to locally invasive growth and frequent recurrence

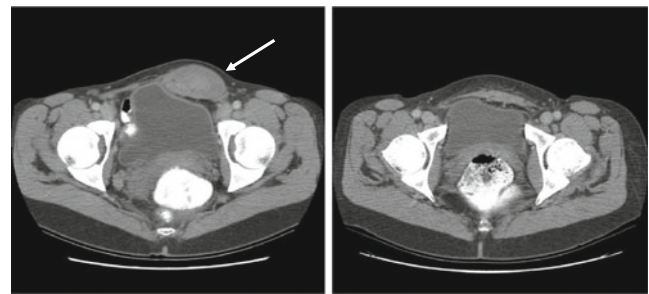


Fig. 3 Brachytherapy of desmoid tumors before (left) and 2 years after brachytherapy (right). Good remission with only residual thickening of rectus sheath after brachytherapy

rate in FAP patients with family screening approaching that of the normal population up to 18 years after colectomy [16].

With respect to the surgical management of colorectal polyposis, two main options exist: colectomy with IRA and proctocolectomy with IPAA. Given the phenotypic presentation of our cohort, we have consistently utilized IRA in these patients, most of whom have experienced excellent functional outcome and quality of life. Due to this phenotype's distinct affection of the right-sided colon, we and others see no need for IPAA due to its higher morbidity and lower postoperative quality of life [17]. There was also no need for a secondary conversion to IPAA as none of our patients developed significant rectal polyposis, adenoma, or cancer. In fact, it is our observation that the numbers of rectal polyps appeared to decrease after colectomy even though we are lacking data to confirm this assumption. In addition, life-long repeat endoscopic surveillance and ablation of polyps is mandatory following both IRA and IPAA, since carcinoma may also develop in the pouch [18, 19]. In patients who had undergone colectomy, mortality mainly arose from desmoid tumors and extracolonic gastrointestinal malignancies, which supports previous studies on the causes of mortality in FAP [16, 20, 21].



Fig. 4 HDR brachytherapy applicators. Seven applicators in situ during treatment of a desmoid of the lower abdominal wall considered unsuitable for resection and direct closure

We found that desmoids develop in a significant percentage of patients. The greatest challenge posed by these tumors is their locally invasive growth in sites precluding radical resection. Several potential risk factors for the development of desmoids are being discussed in the literature, and previous surgery is believed to promote growth of desmoids [22]. Two thirds of the desmoids in our patients occurred after a mean interval of 34 months after colectomy. Partly, these results may be influenced by the fact that the mean age at diagnosis of desmoid tumors is 48 years (range 31–73 years), whereas colectomy is usually performed at a younger age of 44 years (range 30–61 years), thereby maybe implicating a false causative relationship. In addition, no desmoids at all were detected in seven colectomy patients during a mean follow-up of 104 months.

The location of the genetic mutation also seems to influence the development of desmoids (higher risk in mutations beyond codon 1444, or in mutations at the 3'-end of the codon) [23]. Our results, however, show pronounced intra-familial variations of the phenotype with a seemingly unpredictable clinical course, indicating the influence of genetic factors other than the APC mutation itself [11].

Best results were obtained in patients with abdominal wall desmoids at an early stage appropriate for radical resection and direct closure. Resection of desmoids was generally recommended in symptomatic patients and those exhibiting rapid growth, whereas observation with frequent follow-up was done in patients with small, asymptomatic desmoids and those unwilling to undergo resection. Alternatively, we used HDR brachytherapy with good success in four patients with large recurrent tumors unfit for resection. No recurrence was observed throughout their follow-up. Despite our limited experience, we believe that HDR brachytherapy may provide an alternative to resection in patients that are unfit for surgery or in whom the size or location of the desmoids precludes radical resection, since HDR brachytherapy is known to improve local control of desmoid tumors [24].

The greatest therapeutic challenge was desmoids arising within the intestinal mesentery. In these patients, operative treatment is associated with serious morbidity and mortality arising from intestinal ischemia following radical resection, anastomotic failure, or late small bowel obstruction. Furthermore, evidence exists that resection of mesenteric desmoids may in fact stimulate tumor growth, which is why treatment is often directed only at relieving specific local consequences such as small bowel obstruction or ischemia [25, 26]. Chemotherapy has so far not been part of our treatment rationale in desmoid patients due to its controversial benefits; however, two recent trials have shown improved progression-free survival rates in patients with nonresectable desmoids treated with doxorubicin or imatinib, thereby potentially offering a true benefit in this difficult to treat subgroup of patients [27, 28].

A point of interest is the phenotype–genotype correlation in GS: Since 1992 several attempts have been made to correlate specific APC mutations with clinical phenotypes and explain clinical variability on the basis of different mutations. However, there is considerable variability in the expression of specific phenotypes within families and even among individuals with identical mutations [29, 30]. In our family, the mutation is located on exon 15, codon 1981 which causes an attenuated form of polyposis with fewer adenomas (100 or fewer).

Finally, although sophisticated screening and surveillance programs are available, a considerable number of individuals refuse participation or are reluctant to act once their disease has been diagnosed. We have encountered this denial frequently and have sadly had to observe progression into fatal cancer in three patients. While the problem of noncompliance pertains to many problems in medicine, the high percentage of individuals that remain reluctant to undergo preventive testing remains of great concern. In our opinion, this phenomenon emphasizes the need for a continuous follow-up of all individuals at risk through the same credible group of physicians and emphasizes the need for a sustainable physician–patient relationship throughout the life of any Gardner patient.

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References

1. Gardner EJ, Stephens FE (1950) Cancer of the lower digestive tract in one family group. *Am J Hum Genet* 2:41–48
2. Bodmer WF, Bailey CJ, Bodmer J, Bussey HJ, Ellis A, Gorman P, Lucibello FC, Murday VA, Rider SH, Scambler P (1987) Localization of the gene for familial adenomatous polyposis on chromosome 5. *Nature* 328:614–616
3. Groden J, Thliveris A, Samowitz W, Carlson M, Gelbert L, Albertsen H, Joslyn G, Stevens J, Spirio L, Robertson M (1991) Identification and characterization of the familial adenomatous polyposis coli gene. *Cell* 66:589–600
4. Kinzler KW, Nilbert MC, Su LK, Vogelstein B, Bryan TM, Levy DB, Smith KJ, Preisinger AC, Hedge P, McKechnie D (1991) Identification of FAP locus genes from chromosome 5q21. *Science* 253:661–665
5. Galiatsatos P, Foulkes WD (2006) Familial adenomatous polyposis. *Am J Gastroenterol* 101:385–398
6. Gardner EJ, Richards RC (1953) Multiple cutaneous and subcutaneous lesions occurring simultaneously with hereditary polyposis and osteomatosis. *Am J Hum Genet* 5:139–147
7. Gardner EJ, Plenk HP (1952) Hereditary pattern for multiple osteomas in a family group. *Am J Hum Genet* 4:31–36

8. Dobbie Z, Spycher M, Mary JL, Haner M, Guldenschuh I, Hurliman R, Amman R, Roth J, Muller H, Scott RJ (1996) Correlation between the development of extracolonic manifestations in FAP patients and mutations beyond codon 1403 in the APC gene. *J Med Genet* 33:274–280
9. Vasen HF, Moslein G, Alonso A, Aretz S, Bernstein I, Bertario L, Blanco I, Bulow S, Burn J, Capella G, Colas C, Engel C, Frayling I, Friedl W, Hes FJ, Hodgson S, Jarvinen H, Mecklin JP, Moller P, Myrhoi T, Nagengast FM, Parc Y, Phillips R, Clark SK, de Leon MP, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJ, Wijnen J (2008) Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* 57:704–713
10. Simmen HP, Müller G, Roth A, Hasler T (1979) Das Gardner-Syndrom: Definition, Ausdrucksformen, Frühdiagnostik und Therapie. *Dtsch med Wochenschr* 104:799–803
11. Plasilova M, Russell AM, Wanner A, Wolf A, Dobbie Z, Muller HJ, Heinimann K (2004) Exclusion of an extracolonic disease modifier locus on chromosome 1p33-36 in a large Swiss familial adenomatous polyposis kindred. *Eur J Hum Genet* 12:365–371
12. Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RK (1989) Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 2:783–785
13. Bulow C, Vasen H, Jarvinen H, Bjork J, Bisgaard ML, Bulow S (2000) Ileorectal anastomosis is appropriate for a subset of patients with familial adenomatous polyposis. *Gastroenterology* 119:1454–1460
14. Heiskanen I, Luostarinen T, Jarvinen HJ (2000) Impact of screening examinations on survival in familial adenomatous polyposis. *Scand J Gastroenterol* 35:1284–1287
15. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S, Simmgang C (2003) Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. *Gastroenterology* 124:544–560
16. Belchetz LA, Berk T, Bapat BV, Cohen Z, Gallinger S (1996) Changing causes of mortality in patients with familial adenomatous polyposis. *Dis Colon Rectum* 39:384–387
17. da Luz MA, Church JM, Burke CA (2009) The evolution of prophylactic colorectal surgery for familial adenomatous polyposis. *Dis Colon Rectum* 52:1481–1486
18. Parc YR, Olschwang S, Desaint B, Schmitt G, Parc RG, Turet E (2001) Familial adenomatous polyposis: prevalence of adenomas in the ileal pouch after restorative proctocolectomy. *Ann Surg* 233:360–364
19. Vrouwenraets BC, Van Duijvendijk P, Bemelman WA, Offerhaus GJ, Slors JF (2004) Adenocarcinoma in the anal canal after ileal pouch-anal anastomosis for familial adenomatous polyposis using a double-stapled technique: report of two cases. *Dis Colon Rectum* 47:530–534
20. Arvanitis ML, Jagelman DG, Fazio VW, Lavery IC, McGannon E (1990) Mortality in patients with familial adenomatous polyposis. *Dis Colon Rectum* 33:639–642
21. Nugent KP, Spigelman AD, Phillips RK (1993) Life expectancy after colectomy and ileorectal anastomosis for familial adenomatous polyposis. *Dis Colon Rectum* 36:1059–1062
22. Gurbuz AK, Giardiello FM, Petersen GM, Krush AJ, Offerhaus GJ, Booker SV, Kerr MC, Hamilton SR (1994) Desmoid tumours in familial adenomatous polyposis. *Gut* 35:377–381
23. Eccles DM, van der LR, Breukel C, Bullman H, Bunyan D, Fisher A, Barber J, du BC, Primrose J, Burn J, Fodde R (1996) Hereditary desmoid disease due to a frameshift mutation at codon 1924 of the APC gene. *Am J Hum Genet* 59:1193–1201
24. Assad WA, Nori D, Hilaris BS, Shiu MH, Hajdu SI (1986) Role of brachytherapy in the management of desmoid tumors. *Int J Radiat Oncol Biol Phys* 12:901–906
25. Jones IT, Jagelman DG, Fazio VW, Lavery IC, Weakley FL, McGannon E (1986) Desmoid tumors in familial polyposis coli. *Ann Surg* 204:94–97
26. Lotfi AM, Dozois RR, Gordon H, Hruska LS, Weiland LH, Carryer PW, Hurt RD (1989) Mesenteric fibromatosis complicating familial adenomatous polyposis: predisposing factors and results of treatment. *Int J Color Dis* 4:30–36
27. Chugh R, Wathen JK, Patel SR, Maki RG, Meyers PA, Schuetz SM, Priebat DA, Thomas DG, Jacobson JA, Samuels BL, Benjamin RS, Baker LH (2010) Efficacy of imatinib in aggressive fibromatosis: results of a phase II multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial. *Clin Cancer Res* 16:4884–4891
28. Nieuwenhuis MH, Mathus-Vliegen EM, Baeten CG, Nagengast FM, van der BJ, van Dalsen AD, Kleibeuker JH, Dekker E, Langers AM, Vecht J, Peters FT, van Dam R, van Gemert WG, Stuijbergen WN, Schouten WR, Gelderblom H, Vasen HF (2011) Evaluation of management of desmoid tumours associated with familial adenomatous polyposis in Dutch patients. *Br J Cancer* 104:37–42
29. Giardiello FM, Krush AJ, Petersen GM, Booker SV, Kerr M, Tong LL, Hamilton SR (1994) Phenotypic variability of familial adenomatous polyposis in 11 unrelated families with identical APC gene mutation. *Gastroenterology* 106:1542–1547
30. Leppert M, Burt R, Hughes JP, Samowitz W, Nakamura Y, Woodward S, Gardner E, Lalouel JM, White R (1990) Genetic analysis of an inherited predisposition to colon cancer in a family with a variable number of adenomatous polyps. *N Engl J Med* 322:904–908