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Chapter 13

Is colorectal surveillance indicated in patients with *PTEN* mutations?


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IS COLORECTAL SURVEILLANCE INDICATED IN PATIENTS WITH PTEN MUTATIONS?

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ABSTRACT

**Background and aim:** Patients with germline phosphatase and tensin homologue (PTEN) mutations develop hamartomatous lesions in several organs and are at increased risk of various malignancies. We assessed the lifetime risk of benign and malignant gastrointestinal lesions in patients with a proven PTEN mutation.

**Method:** Data on sex, mutation, dates of birth, last contact, and diagnosis, location, and type of gastrointestinal lesions were collected from nine countries. The lifetime risk of gastrointestinal lesions was calculated by Kaplan-Meier methods.

**Results:** A total of 156 patients (67 males, 43%) from 101 families with a PTEN mutation were included. Patients were born between 1928 and 2008. Benign gastrointestinal polyps were reported in 49 patients (31%) at a mean age of 38 years (range 18-62 years) and were most often hamartomas. Twenty-two patients (44%) had upper as well as lower gastrointestinal lesions, 14 (29%) had only colonic lesions, and 13 (27%) had gastrointestinal lesions at unknown sites. The cumulative risk of developing benign gastrointestinal polyps was 70% at age 60. Four patients (two males) developed colorectal carcinoma (CRC) at 53, 57, 59, and 62 years, respectively. The cumulative risk of developing CRC was 18% at age 60. Except one carcinoid in the small intestine, no upper gastrointestinal cancers were observed.

**Conclusion:** Benign gastrointestinal lesions are common in PTEN mutation carriers. We show a three- to fourfold increased lifetime risk of CRC, compared to the general population. Colorectal screening of patients with germline PTEN mutations is recommended, starting at age 40 years.

**What is new in this paper?**

Patients with a germline PTEN mutation have a significant risk of developing benign colorectal tumors (70% cumulative risk at age 60) and colorectal cancer (18% cumulative risk at age 60). Surveillance of the colorectum is recommended from age the age of 40 years.
INTRODUCTION

PTEN hamartoma tumor syndrome (PHTS) is the collective term for clinical syndromes caused by germline mutations in the tumor suppressor Phosphatase and tensin homologue, deleted on chromosome ten (PTEN).

The PTEN gene is located at chromosome 10q23.31. PTEN acts as a tumor suppressor by counteracting the important cancer promoting PI3K/Akt signaling pathway. PTEN is also involved in regulation of genomic instability, DNA repair, stem cell self-renewal, cellular senescence, and cell migration/metastasis.[1]

Clinical syndromes caused by PTEN mutations include Cowden syndrome, Lhermitte-Duclos disease, Bannayan-Riley-Ruvalcaba syndrome, and Proteus-like syndrome. A common characteristic of these syndromes is the development of hamartomatous tumors which can arise from all embryonal layers and therefore occur at various sites of the body. Although histologically benign, some lesions have serious consequences, for example Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma), a hamartomatous overgrowth of cerebellar tissue which can cause mass effects in the posterior fossa. Beside the benign tumors, PHTS patients have an increased risk of developing cancer, particularly cancer of the breast and thyroid.[2] Surveillance protocols have been established to allow timely detection of (pre)malignant lesions.[3]

Although colorectal hamartomas and other types of polyps in the gastrointestinal tract are common, there are no consistent guidelines for gastrointestinal surveillance in PHTS patients. It is notable that information on cancer risks in the PTEN hamartoma tumor syndrome are generally derived from studies of individuals who fulfill published clinical criteria for Cowden Syndrome but who do not necessarily have an identifiable PTEN mutation. In this type of study, several have reported increased risks of colorectal polyps and cancer in such patients.[2-5]

In the present study we assessed the lifetime risk of benign and malignant lesions in the gastrointestinal tract in a large international cohort of PTEN mutation carriers and discuss the need for colorectal surveillance in these patients.

PATIENTS AND METHODS

Clinical and genetic data on patients with a germline PTEN mutation were obtained from clinical genetic centers from nine countries (USA, France, Norway, United Kingdom, Germany, Switzerland, Australia, Denmark, The Netherlands). Patients had given informed
consent for using clinical data for research purposes and data were gathered anonymously. The data collected included information on date of birth, date of last contact, type of \textit{PTEN} mutation, and details on gastrointestinal lesions, including year of diagnosis and type of the lesions. The \textit{PTEN} mutations reported in the study cohort were considered to be deleterious based upon the type of the mutation (nonsense, frameshift, or splice site mutation), or upon existing literature on this mutation. For mutations that have not been described evidence for pathogenicity was obtained by mutation prediction software and/or co-segregation of characteristic phenotype within families. Patients with a \textit{PTEN} and \textit{BMPR1A} contiguous deletion, known to cause a different phenotype with early onset juvenile polyposis, were excluded. A minority of patients had a missense mutation with uncertain pathogenicity, therefore a second statistical analysis without the data of these patients has been performed to determine whether the results were different.

Descriptive results were reported as mean (range) for continuous variables and number (percentage) for categorical variables. The lifetime risk of benign and malignant gastrointestinal lesions was calculated by Kaplan-Meier methods. The observation time was from the date of birth until CRC, gastrointestinal polyps, death, or date of last contact, whichever came first. For the calculations, all patients were in the denominator, assuming that all patients had had gastrointestinal examinations. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 16.0 (Chicago, Ill, USA).

\section*{RESULTS}

A total of 156 patients with documented deleterious \textit{PTEN} mutations from 101 families were included. Sixty-seven (43\%) were male. The patients were born between 1928 and 2008. The mean age at the date of last contact was 33 years (range 1-73 years). Forty-three patients (28\%) were younger than 18 years at the date of last contact. Four patients had died at a mean age of 48 years (range 42-68 years), all of them had cancer.

In 49 patients (31\%), benign gastrointestinal lesions were reported. There was no familial clustering of polyps. The mean age at diagnosis of gastrointestinal lesions was 38 years (range 18-62 years). All patients were above age 18 at the first diagnosis of gastrointestinal polyps. The polyp types included hamartomas (n=42), ganglioneuromas (n=8), adenomas (n=6), juvenile polyps (n=4), hyperplastic polyps (n=3), leiomyomas (n=2), lipomas (n=2), and a neurofibroma (n=1). Twenty-two patients (45\%) had both upper as well as lower gastrointestinal lesions, 14 (29\%) had only colorectal polyps, and for 13 (27\%) patients, the
location of the polyps in the gastrointestinal tract were unknown. Different mutation sites were distributed evenly among patients with and without polyps. In figure 1, the cumulative lifetime risk of developing benign gastrointestinal lesions for patients with a $PTEN$ gene mutation is shown. The risk was similar for both sexes (log rank test, $p=0.181$, figure not shown).

Four patients (2.6%) developed colorectal cancer (CRC), all above age 50. Characteristics of these patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age CRC</th>
<th>Previous GI findings</th>
<th>Other cancer</th>
<th>Other cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Male</td>
<td>57</td>
<td>&gt;100 hamartomas and adenomas whole GI tract</td>
<td>Carcinoid small intestine age 57</td>
<td>Carcinoid lung (at obduction) age 59</td>
</tr>
<tr>
<td>2 Female</td>
<td>59</td>
<td>Leiomyomas and lipomas upper GI tract</td>
<td>Melanoma, age unknown</td>
<td>DCIS* and LCIS** breast age 50</td>
</tr>
<tr>
<td>3 Female</td>
<td>53</td>
<td>-</td>
<td>Basal cell carcinoma age 62</td>
<td>Breast cancer age 50</td>
</tr>
<tr>
<td>4 Male</td>
<td>62</td>
<td>Leiomyoma and neurofibroma colon</td>
<td>Renal cancer, age unknown</td>
<td>Thyroid cancer age 53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clear cell renal carcinoma age 62</td>
</tr>
</tbody>
</table>

*DCIS: ductal carcinoma in situ ** LCIS: lobular carcinoma in situ

The patients with CRC had all a different $PTEN$ mutation site. All patients had at least one other malignant tumor at the time of diagnosis of CRC, including intestinal carcinoid, lung carcinoid, breast cancer, renal cancer, melanoma, and basal cell carcinoma. The lifetime risk of developing CRC for patients with a $PTEN$ gene mutation was 18% by the age of 60 years (Figure 2).

Thirteen patients had a missense mutation with uncertain pathogenicity. Statistical analysis without the data of these patients showed similar outcomes.
Figure 1 Cumulative lifetime risk of gastrointestinal polyps in patients with germline PTEN mutations

Figure 2 Cumulative lifetime risk of colorectal cancer (CRC) in patients with germline mutations in the PTEN gene
DISCUSSION AND CONCLUSIONS

The present study demonstrates that benign gastrointestinal lesions are common in PTEN mutation carriers and can occur at various ages. The most frequent findings were colorectal hamartomas. In this study, for patients with a PTEN gene mutation a three- to fourfold increased risk of developing colorectal cancer by the age of 60 years was observed, compared with the general population. Except for one small intestinal carcinoid, upper gastrointestinal malignancies were not observed.

Two case reports describe Cowden patients with colorectal cancer at age 28, 39 and 56, respectively.[4,6] Furthermore, two recent studies have evaluated the occurrence of colorectal neoplasms in PHTS. A study from the USA reported nine CRC cases in 127 PTEN mutation carriers (7%), leading to an adjusted standardized incidence ratio (SIR) of 224.[5] In this study, all CRC diagnoses were between ages 35 and 49 years, but an age distribution was not provided in the article. Selection of patients was based on symptomatic Cowden Syndrome, or having gastrointestinal features. Another recent study evaluated CRC cases in Cowden syndrome patients in whom diagnosis was based on clinical criteria and not confirmed by DNA testing. Most of these cases were reported in the literature, and the authors added a small new patient series.[2] Five out of 211 patients (2.4%) developed CRC, with the earliest CRC diagnosis at age 43. A lifetime risk (by the age of 70 years) of CRC of 16% was calculated. These two cohort studies, and our study evidently show a three- to four times increased risk of CRC in PHTS patients, compared with the healthy population, as for people living in industrialized countries the cumulative lifetime risk of developing CRC is about 5%.[7]

Remarkably, in our series, we observed various types of polyps, but no cancers in the upper gastrointestinal tract, except one carcinoid of the small intestine. Reviewing the literature revealed three cases of gastric carcinoma, in PHTS patients at 67, 66 and 73 years old, respectively.[5,8,9]

The mechanism of colorectal cancer development in PTEN mutation carriers remains unclear. Although hamartomas are considered as benign polyps, in the past, a hamartoma-carcinoma sequence was suggested, caused by an abnormal microenvironment due to mutations, and leading to increased risks of neoplastic transformation.[10] A case study described a patient with a germline PTEN mutation who developed two independent CRCs at age 56. She had hamartomatous and hyperplastic polyposis throughout the gastrointestinal tract and the adenocarcinomas were shown to develop from the hyperplastic polyposus lesions.[4] Of the three gastric cancers reported in the literature, two arose from a large
hyperplastic/hamartomatous polyp, but the other from an adenoma.[5,8,9] We were unable to
determine whether the CRCs in our study arose from hamartomas or other types of colorectal
polyps. A possible explanation for CRC development in PTEN mutation carriers was recently
published. Huang et al. suggested that PTEN mutations seem not to be the single driving force
for CRC development and that hMSH3 (mismatch repair) defects in nondysplastic epithelium
may explain the increased risk of neoplastic progression of colonic hamartomas in PHTS
patients.[11]

Our study comprises unique data of a large cohort of PTEN mutation carriers, and is
distinguished from the earlier cohort studies in that it is based on mutation carriers only. Due
to the retrospective design of the study, there may be a selection bias for symptomatic patients
and patients with cancer. However, the selection bias might be limited, as many submitted
patients did not even meet the Cowden syndrome diagnostic criteria.[12] On the contrary, the
calculated risks of polyps are most likely underestimations, as not all patients had full
endoscopic examinations and thus some may still have undetected polyps.

The most recent NCCN Guidelines for Cowden syndrome and other syndromes due to
PTEN mutations do not provide specific recommendations for gastrointestinal surveillance in
PHTS (0,13). Several investigators have suggested colorectal screening of PHTS patients.
Some recommended biennial screening starting at age 15,[14] others proposed performing
one baseline colonoscopy in asymptomatic patients at age 50,[15] or surveillance from the age
of 25-30 years in a study setting.[6] The authors of the most recent studies recommend
colonic surveillance starting at age 35, with follow-up examinations depending of the polyp
burden,[5] and colonic surveillance starting at age 40 with 5-year intervals,[2] respectively.
Based on our study and our review of the recent literature, for PHTS patients and patients
with demonstrated PTEN mutations, we would propose performing surveillance
colonoscopies every five years - or more frequently if polyps are discovered at baseline -,
starting at age 40, or five years before the first CRC diagnosis in the family.

In conclusion, patients with PTEN germline mutations have an increased risk of
developing CRC, which warrants colorectal surveillance. The risk of upper gastrointestinal
cancer is not increased, so gastroduodenoscopy should only be performed when clinically
indicated.
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REFERENCES


