CHAPTER 5

COMPLIANCE WITH PERIODIC SURVEILLANCE FOR VON HIPPEL-LINDAU DISEASE


Revision submitted
ABSTRACT

Background
Von Hippel-Lindau disease (VHL) is characterized by an increased risk of developing multiple tumors at various sites and ages. To detect expression of VHL at an early stage, individuals are advised to undergo periodic surveillance. The aim of this study was to assess compliance with a periodic surveillance regimen for VHL.

Methods
In this nationwide, cross sectional study, proven carriers of a VHL mutation and those at 50% risk were invited to complete a questionnaire assessing (compliance with) advice given for periodic surveillance. Medical record data on compliance of recommended radiological surveillance examinations were also collected.

Results
Of the 84 (77%) participants, 78 (93%) indicated having received advice to undergo periodic surveillance. Of these, 71 (91%) reported being fully compliant with that advice. In 64% of the cases, this advice was only partially consistent with published guidelines. Based on medical file data, between one-quarter and one-third of individuals did not undergo surveillance as recommended in the guidelines for central nervous system (CNS) lesions, and one-half for visceral lesions. Screening delay for CNS lesions was significantly higher in one hospital and in those cases where ‘the advice given’ deviated from the guidelines (p < .01).

Interpretation
The majority of the respondents reported having received advice to undergo periodic surveillance, and being fully compliant with that advice. However, in many cases, the advice given was only partially consistent with published guidelines, and screening delays were observed. Efforts should be undertaken to stimulate guideline-based surveillance advice, and to minimize screening delay.
Von Hippel-Lindau disease (VHL) is an autosomal, dominantly inherited tumor susceptibility syndrome that is characterized by an increased risk of developing multiple benign tumors and malignant neoplasms. These tumors are often multicentric or bilateral. The most prevalent tumors are hemangioblastomas of the retina, cerebellum or myelum, pheochromocytomas, renal cysts, renal clear cell carcinomas and cysts and endocrine tumors of the pancreas. Renal clear cell carcinoma metastasis and neurological damage due to central nervous system hemangioblastomas are the most common cause of death. The cause of VHL is a germline mutation in the VHL gene. At least 90% of the carriers of a VHL mutation exhibit clinical manifestations of VHL by the age of 60. Without treatment, the median expected survival of VHL patients has been estimated to be 49 years of age. The age of onset and expression of the disease varies widely (e.g., age 1 to 67 years for retinal hemangioblastomas; age 5 to 70 years for pancreatic cancers or cysts; age 16 to 67 years for renal cell carcinoma or cysts).

Currently, there are no preventive strategies available to avoid the occurrence of tumors, and no prophylactic surgery is available. However, early diagnosis and treatment, such as laser treatment for retinal hemangioblastomas at an asymptomatic stage, may affect prognosis positively. Therefore, high risk individuals are advised to undergo periodic, multidisciplinary surveillance according to published, national guidelines. These national guidelines are largely in line with international guidelines.

In the Netherlands, surveillance begins at age 5 with an annual ophthalmologic examination. Although no large empirical studies on the effectiveness of regular surveillance for VHL are available, it is generally believed that the introduction of periodic surveillance and the improvement in surgical techniques has contributed to the substantial decrease in morbidity and mortality in this population. Research is ongoing to determine the most optimal intervals between screenings. Due to the beneficial effects of regular surveillance for VHL, it is important that individuals diagnosed with, or at high risk of VHL receive and adhere to surveillance advice that is consistent with the VHL surveillance guidelines.

Only one recent study has reported on periodic surveillance for VHL. Of the 36 identified carriers, all underwent initial surveillance for VHL manifestations after receiving their genetic test result. However, after a five year follow-up, only 39% were adherent with the advised periodic surveillance program. The symptomatic carriers were more likely to be adherent than the asymptomatic carriers. It should be noted that, in this study, non-adherence with the recommended surveillance protocol was not clearly defined. Further, 10 of the 36 carriers in the study were under the age of 18. It is most likely that non-compliance of the minors...
Periodic surveillance for VHL depends on the compliance behavior of the parents. Additionally, psychosocial questionnaires were only administered to 17 adult carriers.

The current study was undertaken to assess compliance with periodic surveillance for VHL. The main aims of this study were to investigate: 1) the surveillance advice given to high risk family members; 2) the concordance between the advice given and the national VHL surveillance guidelines; 3) the degree of compliance; and 4) variables associated significantly with non-compliance.

**Table 1:** Dutch VHL guidelines for regular surveillance

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Age</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmologic examination</td>
<td>From 5 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Anamnesis</td>
<td>From 10 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Physical examination, blood pressure</td>
<td>From 10 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Biochemical blood tests</td>
<td>From 10 years</td>
<td>Annually</td>
</tr>
<tr>
<td>24 hour urine test</td>
<td>From 10 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Upper abdominal ultrasound</td>
<td>From 10 years</td>
<td>Annually</td>
</tr>
<tr>
<td>MRI cerebellum and myelum</td>
<td>From 15 years</td>
<td>Biannually</td>
</tr>
<tr>
<td>MRI upper abdomen</td>
<td>When indicated</td>
<td></td>
</tr>
<tr>
<td>MRI inner ear</td>
<td>When indicated</td>
<td></td>
</tr>
<tr>
<td>Audiogram</td>
<td>When indicated</td>
<td></td>
</tr>
<tr>
<td>Neurological examination</td>
<td>When indicated</td>
<td></td>
</tr>
</tbody>
</table>

**METHODS**

**Study sample and procedures**
As part of a larger, ongoing nationwide cross-sectional study, 48 families with a known VHL germline mutation were identified. Five of these families were excluded from the current study because all of the family members registered at the family cancer clinics were either deceased, had emigrated, or were under the age of 16 years. In total, 109 family members with a clinical and/or molecular genetic diagnosis of VHL, or at 50% risk of VHL were invited to participate in the study. Individuals were recruited between August, 2006 and February, 2008.

Those eligible received a letter of invitation from their clinical geneticist, along with an information leaflet about the study, a consent form, a questionnaire and a prepaid return envelope. Eligible individuals who were not registered at a clinical genetics center were invited via a registered family member. Adult carriers were requested to invite their children aged 16 to 18 years to participate in the study.
Chapter 5

Measures

Advice for periodic surveillance

A self-report questionnaire was used to assess advice given for periodic surveillance. Respondents indicated what type of advice, if any, for periodic surveillance they had received on a given list with possible surveillance methods and interval options (based on the national guidelines). This allowed us to compare self-reported advice with the surveillance program as recommended in the national guidelines (see table 1).

Compliance with periodic surveillance

Compliance with periodic surveillance was assessed in two ways. First, respondents were asked to report the extent to which they had adhered to the (self-reported) advice that they had received for regular surveillance. Self-reported compliers were those high risk family members who indicated that they had followed the surveillance advice “as advised” or “more frequently than advised.” Self-reported non-compliers were those individuals who reported not having followed the surveillance advice that they indicated they had received, or did so less frequently than advised. Additionally, reasons for non-compliance were asked, including: ‘the discomfort of the surveillance method(s)’, because it was ‘too time consuming’, because of ‘difficulties in planning the examinations’, because of ‘absence of symptoms’, and/or because they believed that the probability of something being detected was very small.

Second, medical records data were used to determine objective compliance (surveillance performed in accordance with the guidelines) with the radiological surveillance examinations, including MRI of the central nervous system (CNS) and ultrasound of the upper abdomen. We focused on these two screening methods because manifestations detected by radiological examinations (e.g., CNS lesions and renal cell carcinoma (RCC)) have the most severe consequences, and these data could most reliably be collected from the medical records. Specifically, data on the number of radiological surveillance procedures and intervals between two concurrent surveillance sessions were retrieved from the medical records for the period January, 2004 to December, 2008.

Based on the national guidelines for periodic surveillance, decision rules for classifying objective compliance were developed and formulated as follows: 1) for the MRI of the cerebellum and myelum, a minimum of two examinations per 5-year period are required, and an interval of > 27 months between two consecutive examinations is considered unacceptable; and 2) for compliance with the imaging surveillance methods of the upper abdomen (ultrasound or other imaging techniques), a minimum of four examinations is required, and an interval between two consecutive examinations of > 15 months is considered unacceptable. Based on these criteria, respondents were classified either as
Periodic surveillance for VHL

compliant (surveillance as advised in the national surveillance guidelines) or under-compliant (too few examinations, or too lengthy a delay between examinations).

**Sociodemographic and clinical variables**

Participants’ age, gender, marital status, level of education, offspring, hospital, DNA-status (carrier or 50% at-risk), and disease status (affected/unaffected), were obtained from the self-report questionnaire and the medical records.

**Psychosocial data**

In order to investigate which variables were associated with ‘surveillance compliance,’ a series of questions was posed based on the central elements of two social cognition models of preventive health behavior, the Health Belief Model and the Protection Motivation Theory.

Perceived risk: Respondents were asked to report their perceived risk of developing a(nother) tumor compared to that of the ‘average person in the Dutch population’ (item adapted from Lerman et al.). Response categories ranged on a five point scale, from ‘lower’ to ‘much higher’.

Perceived benefits and barriers to periodic surveillance: Perceived benefits and barriers were assessed with an 11-item scale adapted from previous work of Champion, Kash et al., and Madalinska et al. This included 5 “pro” statements and 6 “con” statements about periodic surveillance. Response categories ranged on a five-point scale from ‘strongly disagree’ to ‘strongly agree’. Sum scores for the pro and con subscales ranged from 5 to 25, and 6 to 30, respectively. The reliability (Cronbach’s coefficient alpha) of the pro and con subscales in our study group was .83 and .53, respectively.

VHL-specific distress: VHL-specific distress was measured with the Dutch version of the ‘intrusion’ subscale of the Impact of Events Scale. This 7-item questionnaire measures intrusive thoughts and feelings about VHL during the past seven days. The IES-intrusion total score ranges between 0-35. A score of 9 or higher is considered to be clinically relevant and additional psychosocial help may be indicated. Cronbach’s alpha for the intrusion scale in this study was 0.91.

VHL-related worries: VHL-related worries were assessed with an 8-item questionnaire adapted from the Cancer Worry Scale (CWS). Scores range from 8 to 32, with higher scores indicating more frequent worries about cancer. Cronbach’s alpha in the present study was 0.89.
Data analysis

Descriptive statistics were generated to characterize the study sample in terms of sociodemographic and clinical background variables, to describe the recommended surveillance methods (self-reported advice) and to investigate the extent to which the self-reported advice on regular surveillance was in accordance with the national surveillance guidelines. In assessing concordance, the medical consultation (including an annual anamnesis and physical examination) and those examinations advised and performed ‘on indication only’ were excluded from the analysis, since these were difficult to measure reliably. Descriptive statistics were also used to assess self-reported and objectively determined compliance with surveillance, to describe reasons for self-reported non-compliance, and to identify the perceived barriers and benefits of regular surveillance for VHL.

Univariate analysis (Student’s t test, Fisher’s exact test, chi square) were used to determine which sociodemographic, clinical and psychological variables were related significantly to objective under-compliance (screening delay). The variable “hospital” was coded into four categories, one category each for the three hospitals with the largest number of participants, and the remaining category for all other hospitals. It was not possible to control for potential clustering effects (i.e., multiple family members from the same family) because multiple families had only one member who participated in the study. All analyses were conducted using the Statistical Package for the Social Sciences (version 17.0).

RESULTS

Response and sample characteristics

In total, 84 (77%) of the 109 invited high risk individuals stemming from 36 VHL families completed the questionnaire, including 68 carriers and 16 family members at 50% risk. There were no statistically significant differences between respondents and non-respondents in terms of age, gender, or actual risk status (carrier vs. 50% at risk).

Characteristics of the study participants are shown in table 2. The respondents’ ranged in age between 16 and 65 years (mean = 38.1 years; SD = 13.7 years). Gender was equally distributed. The majority of the participants were carriers, of whom most had one or more VHL manifestations.

Self-reported advice for periodic surveillance

Of the 84 participating high risk family members, six (7%) stated they had not received an advice to undergo periodic surveillance for VHL. All six family members had a 50% risk of having inherited the VHL gene mutation and had not undergone genetic testing. Four
Periodic surveillance for VHL

stemmed from the same family. All but one of these individuals belonged to families registered at the family cancer clinic of one particular hospital.

Table 2: Characteristics of the study sample (N=84)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>38.1 ± 13.7</td>
<td></td>
</tr>
<tr>
<td>Actual risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- (a)symptomatic carriers</td>
<td>68</td>
<td>(81%)</td>
</tr>
<tr>
<td>- 50% at-risk</td>
<td>16</td>
<td>(19%)</td>
</tr>
<tr>
<td>VHL manifestation(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>66</td>
<td>(79%)</td>
</tr>
<tr>
<td>- No</td>
<td>18</td>
<td>(21%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>40</td>
<td>(48%)</td>
</tr>
<tr>
<td>- Female</td>
<td>44</td>
<td>(52%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Married/living together</td>
<td>61</td>
<td>(73%)</td>
</tr>
<tr>
<td>- Single</td>
<td>23</td>
<td>(27%)</td>
</tr>
<tr>
<td>Children (Yes)</td>
<td>48</td>
<td>(57%)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Low</td>
<td>20</td>
<td>(24%)</td>
</tr>
<tr>
<td>- Moderate</td>
<td>48</td>
<td>(57%)</td>
</tr>
<tr>
<td>- High</td>
<td>16</td>
<td>(19%)</td>
</tr>
</tbody>
</table>

Concordance between self-reported advice and the guidelines

Overall

Of the 78 respondents who reported having received advice on regular surveillance, 28 (36%) received advice that was consistent with the national VHL guidelines (see figure 1). Of those (n=50) for whom the advice received was inconsistent with the guidelines, 29 (58%) had receive advice to undergo some, but not all of the recommended screenings. The remaining 21 respondents (42%) reported having been advised to undergo all of the screening procedures found in the guidelines, but the recommended frequency of screening deviated from the guidelines for one or more of the procedures. The range of deviations from the recommended frequency in the guidelines per screening procedure is shown in table 3 (see also figure 1).

Per surveillance method

Table 3 displays the number of individuals for whom the self-reported screening advice was consistent with national guidelines, per screening method. Sixty-seven individuals (86%) indicated that they had received advice to undergo periodic radiological examinations of the upper abdomen; in 53 of these cases (79%), the frequency of this advice was consistent with the national guidelines. Additionally, 71 individuals (91%) received advice to undergo an MRI of the cerebellum and myelum; in 66 of these cases (93%) this advice was consistent with the guidelines. Of the remaining 5 individuals (7%), four reported having been advised to
undergo a MRI of the cerebellum and myelum only if they had symptoms, and one individual reporting having been advised to undergo an MRI only once every five years.

Figure 1: Periodic surveillance: advice and extent to which advice for periodic surveillance conforms to the national surveillance guidelines.

Compliance with self-reported advice

Of the 78 individuals who indicated having been advised about periodic surveillance, 71 (91%) stated they had been fully compliant with the advice given (i.e., that they had
undergone all surveillance methods as frequently or more frequently than advised). Of the 7 individuals (9%) who reported not having been compliant, 5 were symptomatic carriers and 2 were at 50% risk.

**Reasons for non-compliance with self-reported advice**
The two ‘at-risk’ non-compliers indicated that they did not undergo regular screening because they did not have any health complaints and thus considered the screening to be unnecessary. Additionally, one of these individuals reported being fearful of the MRI scan (i.e., claustrophobia) and of the possibility that a tumor would be detected. Reasons for non-compliance given by the 5 symptomatic carriers included the personal need for rest between periods of illness and/or hospitalization (n=2), fear of the MRI scan (n=2), the perceived burden of the surveillance (n=2), and fear that a tumor would be detected (n=1).

**Perceived benefits and barriers of periodic surveillance**
The most prevalent perceived benefits of surveillance were early detection of a VHL-related tumor (97%), and gaining a sense of security (73%). The most important perceived barriers to surveillance were that it would cause unnecessary worry (47%), and that it was impractical or inconvenient (e.g., in relation to work and childcare due to planning of frequent hospital visits etc.; 32%). Overall, self-reported compliers reported significantly more benefits from surveillance than non-compliers (p<.001). No significant differences were found regarding the perceived barriers of surveillance (see table 4).

<table>
<thead>
<tr>
<th>Benefits of surveillance</th>
<th>Total (n=78)</th>
<th>Adherent (n=71)</th>
<th>Not (fully) adherent (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Reduces the chance of a tumor being detected in an advanced stage</td>
<td>97%</td>
<td>100%*</td>
<td>71% *</td>
</tr>
<tr>
<td>- Reduces my fear of developing a tumor</td>
<td>36%</td>
<td>39% *</td>
<td>0% *</td>
</tr>
<tr>
<td>- Provides me with a feeling of control</td>
<td>35%</td>
<td>37%</td>
<td>14%</td>
</tr>
<tr>
<td>- Gives me a sense of security</td>
<td>73%</td>
<td>80%*</td>
<td>0% *</td>
</tr>
<tr>
<td>- Is a good way to detect a tumor early</td>
<td>97%</td>
<td>99%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Total score benefits (mean ± sd) 18.6 (3.2) 19.1 ± 3.0* 14.1 ± 2.1*

<table>
<thead>
<tr>
<th>Barriers to surveillance</th>
<th>Total (n=78)</th>
<th>Adherent (n=71)</th>
<th>Not (fully) adherent (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Can have a negative effect on my home mortgage and/or life and health insurance</td>
<td>27%</td>
<td>73%</td>
<td>71% *</td>
</tr>
<tr>
<td>- Can cause unnecessary worry</td>
<td>47%</td>
<td>46%</td>
<td>57%</td>
</tr>
<tr>
<td>- Causes inconvenience in my life</td>
<td>32%</td>
<td>31%</td>
<td>43%</td>
</tr>
<tr>
<td>- Screening is not important, if I am diagnosed with a tumor it will be too late</td>
<td>3%</td>
<td>1%</td>
<td>14%</td>
</tr>
<tr>
<td>- Is painful</td>
<td>6%</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>- Is uncomfortable/embarrassing</td>
<td>24%</td>
<td>22%</td>
<td>43%</td>
</tr>
</tbody>
</table>

Total score barriers (mean ± sd) 14.1 (3.6) 13.9 ± 3.5 16.1 ± 5.0

*one case missing in analysis; * significant difference p ≤ .05
# Table 3

Regular surveillance: advice and extent to which advice for regular surveillance conforms to the national surveillance guidelines per surveillance method (n=78)

| Examination advised | Advice conform guidelines | Advice not conform guidelines | Range ‘too low frequency’
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical consultation&lt;sup&gt;0&lt;/sup&gt;</td>
<td>65 (83%)</td>
<td>59 (91%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Ophthalmologic examination</td>
<td>74 (95%)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>58 (78%)</td>
<td>16 (22%)</td>
</tr>
<tr>
<td>Biochemical blood tests</td>
<td>65 (83%)</td>
<td>55 (85%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>24 hour urine test</td>
<td>64 (82%)</td>
<td>53 (83%)</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>Upper abdominal ultrasound&lt;sup&gt;1&lt;/sup&gt;</td>
<td>67 (86%)</td>
<td>53 (79%)</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>MRI cerebellum and myelum</td>
<td>71 (91%)</td>
<td>66 (93%)</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>

<sup>0</sup> Includes annual anamnesis and physical examination

<sup>1</sup> or other radiological examination of the upper abdomen

<sup>2</sup> One high risk individual underwent a bilateral enucleation of the eyes, and therefore no ophthalmologic examination was advised.

<sup>3</sup> The range of deviations from the recommended frequency in the guidelines.
Objective compliance with radiological examinations

Objective compliance data (i.e., surveillance performed in accordance with the guidelines) were obtained from the medical records. Of those individuals who indicated not having received advice for periodic surveillance (n=6), indeed no radiological data were found in the medical files of the participating academic medical centers. Medical record data on periodic radiological surveillance were available for 67 of the 78 individuals (86%) who reported having received surveillance advice for CNS lesions. Data on surveillance of the upper abdomen were available for 64 individuals (82%).

Based on the decision rules for determining objective compliance with the radiological examinations, as described in the methods, 24% (n=16) and 34% (n=23), respectively, did not undergo surveillance in accordance with the guidelines for lesions in the cerebellum or myelum (table 5). Of the 16 who were under-compliant with the radiological examinations of the cerebellum, 12 (75%) underwent fewer than two MRI's in the previous 5 year period. Additionally, for 4 individuals (25%), the interval between two consecutive MRI scans was too long (> 27 months). Of the 23 under-compliers with the radiological examinations of the myelum, 21 (91%) underwent fewer than two MRI's during the previous 5 year period, and for the remaining 2 (9%) individuals the interval between two consecutive surveillance data was too long. Among the delayers, the mean deviating time interval outside the recommended range between two consecutive MRI's of the cerebellum or myelum was, 31.8 (sd 3.9; range 28-36) and 31.5 (sd 3.5; 29-34)) months, respectively.

With regard to the radiological examinations for visceral lesions, 48% (n=31) did not undergo surveillance as recommended. Of these 31 individuals, 16 (52%) underwent too few examinations, and for 15 individuals (48%) the intervals between one or more consecutive surveillance data were too long (> 15 months). Among those who delayed, the mean deviating time interval outside the recommended range between two consecutive radiological examinations of the upper abdomen was 18.9 months (sd 3.0; range 16-25).

Variables associated with under-compliance

Under-compliance (screening delay) with radiological examinations for CNS lesions (i.e., too few examinations or too long an interval between examinations) was associated significantly with having received (based on self-report) advice for periodic surveillance that deviated from the guidelines (p < .01). Additionally, under-compliance was significantly higher in one hospital (p < .01). Compliance with surveillance for CNS lesions was not associated significantly with perceived risk, benefits or barriers of surveillance, or levels of psychosocial distress or worries (table 6).

None of the variables investigated were found to be associated significantly with compliance with radiological examinations of the upper abdomen to detect visceral lesions. However,
unchanged individuals ($p_{trend} = .08$), and those with lower levels of distress ($p_{trend} = .08$) and worries ($p_{trend} = .07$) tended to be less compliant (table 6).

**DISCUSSION**

For individuals diagnosed with or at high risk of VHL, periodic surveillance is important to ensure early diagnosis and treatment. To our knowledge, this study is the first to investigate the advice given about periodic surveillance for VHL, the extent to which that advice is followed, the extent to which that advice is consistent with published surveillance guidelines, and factors associated significantly with under-compliance.

On the basis of self-report data, we found that all participants clinically and/or molecular genetically diagnosed with VHL, and the majority of those at 50% risk, received advice to undergo periodic surveillance for VHL. The vast majority reported being fully compliant with the advice given. Reported reasons for not complying with the surveillance advice were fear of the MRI scan, fear that surveillance would uncover a tumor, absence of symptoms, and the personal need for rest between periods of illness and/or hospitalization.

For the majority of respondents, the self-reported advice was only partially consistent with published guidelines. Approximately half were advised to undergo all major surveillance procedures, but with a frequency that deviated from the guidelines. For the remaining 50%, one or more of the major surveillance procedures was not advised, with a median of 1 out of 5 missing examinations per individual (e.g., MRI of the cerebellum).

Radiological surveillance data from the medical records indicated that a substantial percentage of individuals did not undergo surveillance as recommended by the national guidelines: between approximately one-quarter and one-third for screening for central nervous system (CNS) lesions, and nearly 50% for screening for visceral lesions. Of those not appropriately screened for CNS lesions, the large majority underwent too few examinations ($< 2$) in a five year period. For the radiological examinations of the upper abdomen this was approximately 50%. For the remaining under-compliers, the time interval between two consecutive surveillance procedures was too long.

Under-compliance (i.e., too few examinations or too lengthy time intervals) with radiological examinations for CNS lesions was associated significantly with (having reported) receiving advice that deviated from the national guidelines, and with the hospital responsible for the surveillance.
**Periodic surveillance for VHL**

### Table 5: Objective screening compliance with radiological examinations in high risk VHL family members

<table>
<thead>
<tr>
<th>Examination</th>
<th>Compliant</th>
<th>Not compliant</th>
<th>Reason for non-compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>Limited number of exams (%)</td>
</tr>
<tr>
<td>MRI cerebellum (n=67)</td>
<td>51 (76%)</td>
<td>16 (24%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>MRI myelum (n=67)</td>
<td>44 (66%)</td>
<td>23 (34%)</td>
<td>21 (91%)</td>
</tr>
<tr>
<td>Ultrasound upper abdomen³ (n=64)</td>
<td>33 (52%)</td>
<td>31 (48%)</td>
<td>16 (52%)</td>
</tr>
</tbody>
</table>

³For a minority of individuals we were unable to collect objective compliance data since they did not undergo periodic surveillance in one of the academic medical centres, but were likely to undergo periodic surveillance in a regional non-academic hospital.

¹For the MRI of the cerebellum and myelum a minimum of two examinations were required in a 5 year period (2004-2008); for the upper abdominal ultrasound a minimum of four examinations was required.

²For the MRI of the cerebellum and myelum an interval of ≤27 months between two consecutive examinations is considered acceptable; for the upper abdominal ultrasound an interval of ≤15 months:

- Mean deviation interval between two consecutive examinations
  - MRI cerebellum: mean 31.8 months (sd 3.9); Range 28-36 months
  - MRI myelum: mean 31.5 months (sd 3.3); Range 29-34 months
  - Ultrasound upper abdomen: mean 18.9 (sd 3.0); Range 16-25

³or other radiological examination of the upper abdomen
Table 6: Variables possibly associated with compliance with radiological surveillance methods at the univariate level

<table>
<thead>
<tr>
<th>Variable</th>
<th><strong>Ultrasound (n= 64)</strong></th>
<th><strong>MRI Cerebellum (n=67)</strong></th>
<th><strong>MRI Myelum (n=67)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n= 38.8) (12.5)</td>
<td>Yes (n= 38.4) (13.6)</td>
<td>Yes (n= 39.2) (13.5)</td>
</tr>
<tr>
<td></td>
<td>No (n= 39.0) (14.0)</td>
<td>No (n= 39.0) (13.5)</td>
<td>No (n= 37.4) (13.5)</td>
</tr>
</tbody>
</table>

- **Age**
  - Male
    - Yes (n= 17) (53%)
    - No (n= 16) (50%)
  - Female
    - Yes (n= 15) (47%)
    - No (n= 16) (50%)

- **Gender**
  - Male
    - Yes (n= 16) (77%)
    - No (n= 21) (62%)
  - Female
    - Yes (n= 8) (24%)
    - No (n= 13) (38%)

- **Actual risk**
  - Carrier
    - Yes (n= 31) (55%)
    - No (n= 25) (45%)
  - 50% at-risk
    - Yes (n= 2) (25%)
    - No (n= 8) (75%)

- **Disease status**
  - Affected
    - Yes (n= 16) (89%)
    - No (n= 2) (11%)
  - Unaffected
    - Yes (n= 14) (100%)
    - No (n= 4) (0%)

- **Attending hospital**
  - A
    - Yes (n= 9) (50%)
    - No (n= 10) (50%)
  - B
    - Yes (n= 10) (71%)
    - No (n= 4) (29%)
  - C
    - Yes (n= 5) (31%)
    - No (n= 11) (69%)
  - Other
    - Yes (n= 9) (56%)
    - No (n= 7) (44%)

- **Self report advice surveillance method**
  - Conform guidelines
    - Yes (n= 23) (52%)
    - No (n= 50) (48%)
  - Deviating from guidelines
    - Yes (n= 10) (21%)
    - No (n= 9) (79%)

- **Perceived benefits**
  - Conform guidelines
    - Yes (n= 18.5 (2.9))
    - No (n= 18.9 (3.6))
  - Deviating from guidelines
    - Yes (n= 14.2 (3.5))
    - No (n= 13.9 (3.6))

- **Perceived risk or developing a tumor**
  - Low
    - Yes (n= 5) (50%)
    - No (n= 5) (50%)
  - Moderate
    - Yes (n= 14) (48%)
    - No (n= 15) (52%)
  - High
    - Yes (n= 14) (58%)
    - No (n= 10) (42%)

- **VHL specific distress (IES)**
  - Yes (n= 10.0 (11.1))
  - No (n= 5.8 (6.9))

- **VHL related worries (CWS)**
  - Yes (n= 16.4 (6.1))
  - No (n= 14.0 (4.1))

<sup>a</sup> for these variables means and standard deviations (sd) are given; <sup>b</sup> or other radiological examination of the upper abdomen; <sup>✓</sup> one case missing in analysis

<sup>✓</sup> appropriately screened =screened in concordance with the national guidelines according to the decision rules based on the guidelines

<sup>✓</sup> significant difference p ≤ .05; <sup>✓</sup> borderline significant difference p ≤ .10.
Periodic surveillance for VHL

With regard to the latter association, this could reflect hospital budgetary issues (i.e., absence of insurance coverage for preventive surveillance of at-risk individuals), logistical problems (e.g., inability to schedule various screening examinations (of the various disciplines) on the same day; difficulty in scheduling examinations at least three months in advance), and individual clinician’s personal interpretation of the guidelines (e.g., use of MRI for possible CNS lesions only if the individual is symptomatic).

Failure to comply with surveillance recommendations (screening delay) for VHL is a cause of concern. As previously mentioned, CNS lesions and renal cell carcinoma (RCC) are the main causes of morbidity and mortality in patients with VHL. In the case of RCC, to reduce the risk of metastasis, treatment is advised for tumors with a maximum diameter of 3 cm. CNS lesions are, in general, only treated if symptomatic, with surgical resection as standard treatment. However, with periodic surveillance it is possible to detect changes in tumors, based on tumor size and growth rate, in order to predict future symptoms. This can permit excision at an earlier stage, before severe neurological deficits occur. In general, it is observed that preoperative symptoms are not reversible. Additionally, one study has suggested that screening delay can increase the risk of interval tumors. For example, it has been reported that a biannual time interval between two consecutive radiological CNS examinations results in an average risk of 7% of developing an interval tumor. It is likely that longer intervals will result in increased risk.

Study limitations

Several limitations of this study should be noted. First, much of the data generated in this study was based on self-report. However, several recent studies of medical screening behavior have reported generally high levels of agreement between self-report data and medical chart audits. Second, the cross-sectional nature of the study only allows us to speak of statistical associations, rather than causal attributions. Third, for practical reasons, we were only able to assess objective compliance for the radiological examinations, and not for the ophthalmologic examination, biochemical blood tests and 24-hour urine analysis. However, we included three surveillance methods for which the data were most reliable and clinically relevant. Fourth, a minority of the high risk VHL family members may have had periodic surveillance in a local, non-academic hospital in which we were unable to collect data. It is unclear as to whether inclusion of data from these latter hospitals would affect the compliance estimates reported here and, if so, in which direction. Finally, the choice of cut-off for defining objective non-compliance can always be subject of debate.
Clinical relevance
Our results indicate that the majority of individuals diagnosed with or at high risk of VHL report having received advice to undergo regular surveillance. The vast majority indicate being fully compliant with that advice. However, for the majority of individuals, the advise they reported having received was not entirely consistent with published guidelines. Additionally, based on medical record data, delay in screening was observed for a substantial number of individuals.

Efforts should be undertaken to improve the provision of advice based on available guidelines, and to minimize screening delay. Several concrete steps could be taken in this direction. First, VHL-families may benefit from the availability of a “case manager” (e.g., a specially trained nurse practitioner) who could serve as the primary contact for VHL patients and relatives in the hospital, periodically assess the medical and psychosocial needs of the patients, coordinate multidisciplinary care, and supervise the planning of regular surveillance. Second, due to the low prevalence and complexity of VHL, it might be better to concentrate the surveillance and treatment of VHL patients to a limited number of specialized academic centers in the Netherlands. In the report ‘Quality of Cancer Care’ of the Signalling Committee Cancer of the Dutch Cancer Society, it is stated that “treatment in hospitals of sufficiently large volumes of specific patient populations, decreases the morbidity and mortality rate”33. The same may hold for complex rare hereditary cancer syndromes, such as VHL. Third, if feasible, a ‘one stop outpatient clinic’ for regular surveillance could be introduced34. Additionally, those at 50% risk need to better understand that the absence of symptoms is not a reason to delay screening. Ongoing research about geno-phenotype correlations might, in the future, lead to tailored advice for periodic surveillance depending on the VHL mutation35. However, until then, it is important that those individuals diagnosed with or at high risk of VHL undergo periodic surveillance in accordance with existing guidelines. This will facilitate early detection of VHL manifestations, and appropriate treatment that can have a salutary effect on both the clinical prognosis and the quality of life of the patient.

ACKNOWLEDGEMENTS
This study was financially supported by the Dutch Cancer Society (grant number NKI 2005-3209). We are grateful to all respondents who participated in this study. We thank Prof. dr. C.J.M Lips for his comments on an earlier draft of this paper.
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Reference List


