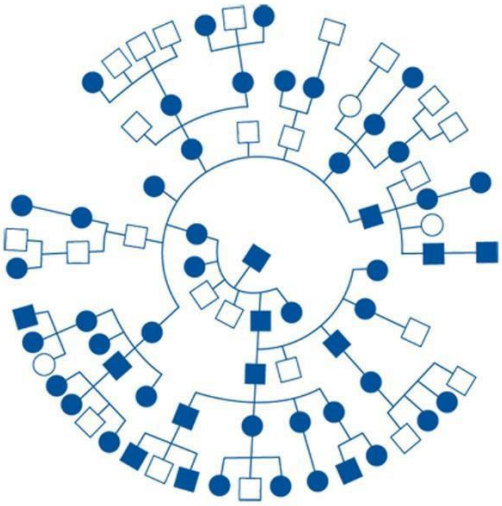
Annual Report

2018

The Netherlands Foundation for the Detection of Hereditary Tumors

Stichting Opsporing Erfelijke Tumoren (StOET)



Author: Prof. dr. H.F.A. Vasen, MD, PhD, AGAF, Medical Director

MISSION

The mission of the Foundation for the Detection of Hereditary Tumors is to prevent unnecessary death by early detection of hereditary tumors. To achieve this, the national registry offers its support in the management of patients genetically predisposed to the development of cancer. The registry helps to identify all persons within an affected family and to provide information regarding their greatly increased risk of cancer and the importance of preventive surveillance examinations. It also monitors the quality of care and adherence to the necessary lifelong surveillance. In addition, the Foundation is a port of call for patients and families. The registry promotes scientific research with the joint aims of improving screening programs and increasing our understanding of hereditary tumors. All activities described in this annual report were designed to help accomplish the above mission.

1. GENERAL ISSUES

Protection of privacy in accordance with new European legislation: AVG

The Registry keeps a record of medical data relating to patients and risk-bearing family members. The processing of such data has been subject to the General Data Protection Regulation (AVG) since May 25, 2018. The AVG sets out the conditions under which personal and medical data can be processed and also defines the rights of subjects involved. In agreement with the AVG, the STOET will only initiate registration once the person concerned has given written permission. In 2018, the Supervisory Committee for the Protection of Privacy was abolished and instead a privacy officer was appointed at the StOET, with a mandate to ensure that the rules on privacy are adhered to. If a person registered with the StOET wishes to exercise his or her rights in accordance with the AVG, this can be done by sending a message to the following email address: privacy@StOET.nl.

The European Hereditary Tumor Group

In 2006, the so-called Mallorca group was initiated by Hans Vasen and Gabriela Möslein. This group successfully developed an active network of specialists working in different fields, all of whom were involved in the prevention, diagnosis and treatment of hereditary GI tumor syndromes. The main aims of the group were (1) to conduct collaborative studies, (2) to establish guidelines and (3) to set up databases. Over the years these collaborations have led to numerous publications and guidelines, focusing mainly on Lynch syndrome and polyposis. Recently, this group (P. Møller et al.) established a prospective database of individuals with Lynch syndrome (PLSD) which is now the main resource worldwide for accurate estimates of cancer risk in Lynch syndrome patients (www.lscarisk.org). The group also initiated the "Three Country Study" (3CS) (Christoph Engel et al.), which evaluated the effectiveness of colonoscopic surveillance by collecting the results of screening from LS registries in Germany, Finland and the Netherlands (see later in this report). Ten years into its existence, a decision was taken to formalize and transform the Mallorca group into a more open group which now also addresses other GI hereditary cancers. This group was named the European Hereditary Tumor Group (Chair: Gabriela Möslein). In September 2018, the Medical Director of StOET attended the third meeting of this new group in Nice. This meeting, which drew more than 200 participants, provided an excellent overview of recent research in the field. Attendance at the annual meetings of the EHTG (www.ehtg.org) is highly recommended for all who wish to increase their knowledge of hereditary GI cancer.

‘Dicke Medal’ Award

During the Digestive Disease Days (DDD) organized by the Dutch Association for Gastroenterology, October 3-4, 2018 in Veldhoven, and the celebration of the 105th anniversary of the Association, the "Dicke medal" was awarded for the 12th time in its history. In 1958, the first medal was received by Prof. W.K. Dicke himself. The twelfth medal was awarded to Prof. Hans Vasen, the Medical Director of the Foundation for the Detection of Hereditary Tumors (Stichting Opsporing Erfelijke Tumoren (StOET)). As chairman of the association, Prof. Peter D. Siersema presented this prestigious award, after which he praised Prof. Vasen for his original work and his many landmark papers of fundamental importance to the field of hereditary oncological gastroenterology. Nationally and internationally, many guidelines have been based on these articles, resulting in improved care for people with a genetic predisposition to the development of gastrointestinal tumors.

Following the award, Hans Vasen gave an honorary lecture entitled "30 years of research in Lynch syndrome". His presentation opened with the family tree that Alfred Scott Warthin published in 1913 as "Family G", in which half of the 70 family members had some form of cancer, with tumors of the uterus, stomach and colon cancer in particular. Later, in 1966, Henry Lynch described two families and first coined the term HNPCC (Hereditary Non-Polyposis Colorectal Carcinoma) as a name for the condition. At the time, his firm belief in the importance of genetic factors in the development of cancer was rejected by the medical community at large. In 1987, Hans Vasen established the Dutch HNPCC working group and in 1990 he organized the first meeting of the International Working Group (ICG) HNPCC in Amsterdam. During the meeting, clinical criteria for HNPCC (the "Amsterdam Criteria") were drawn up and for many years were used worldwide for the detection of families with HNPCC. In the years that followed, the genes responsible for Lynch syndrome were discovered and evidence was provided for the genetic basis of the disorder. Professor Vasen then described one of his current activities: setting up a network for the detection of hereditary gastrointestinal tumors in the Middle East. In the course of this work he has visited many Middle Eastern countries to provide information and to raise awareness of these diseases.

Finally, he thanked the many people who have inspired him, including Mark van Blankenstein, Rob Ypma, Cees Lips, Emil van Slooten, Meera Khan, his many PhD students, all employees of the Stichting Opsporing Erfelijke Tumoren and, of course, his family. To conclude his lecture, Professor Vasen referred to the word of thanks from Professor Dicke published in the Leidsch Dagblad in April 28, 1958, in which he expressed his doubts “… whether his work was not overly appreciated. In addition to that doubt, there is the certainty that this work has only been a grain in the sand pile of human knowledge." According to Vasen, his life's work must be viewed in the same light.

Retirement of Hans Vasen and appointment of Monique van Leerdam as the new Medical Director

As of January 1, 2019, Hans Vasen retired as medical director. He is very happy that his successor is Monique van Leerdam MD, PhD, and gastroenterologist. She has a long record of excellent research in Lynch syndrome and polyposis syndromes, in particular Peutz-Jeghers syndrome. Dr van Leerdam is currently head of the Department of GI-Oncology at the National Cancer Institute (Antoni van Leeuwenhoekhuis) in Amsterdam. In addition to her appointment as Medical Director of the registry, she will also become the head of the Family Cancer Clinic at Leiden University Medical Center. A final word from Professor Vasen: “I would like to take this opportunity to thank all the people who supported the work of registry over the years”.

2. REGISTRATION

2.1 Registration of new family members

The number of subjects referred for registration has been stable for many years. Table 1 shows the current numbers of registered individuals, listed according to hereditary cancer syndrome.

Table 1. Number of individuals registered at the StOET as of December 31, 2018

Syndrome	Number of individuals registered 31-12-2018
Lynch syndrome	3658
Familial Adenomatous Polyposis	3076
Familial Atypical Multiple Mole Melanoma	4627
Hereditary prostate cancer	1332
Peutz-Jeghers syndrome	50

2.2. Automated reminder system

The StOET has an operational automated reminder system, with the aim of guaranteeing the progress of lifelong screening investigations. In practice this entails the sending of a message from the STOET to the treating specialist in which it is made clear that a certain patient is (again) eligible for screening examinations. The specialist then sends the result of the examination to the registry (or a copy of the letter to the general practitioner) and informs the StOET regarding scheduling of the next screening round.

In 2018, all specialists caring for persons registered at the StOET were informed in this way. If it emerged that a particular individual had withdrawn from screening, action was taken. First, the patient received a reminder to attend the examination from the specialist. In case of no response, the general practitioner was then asked to remind the patient of the importance of periodic examinations. This approach helps prevent the loss of patients from screening who might later present with complaints that in many cases are due to a carcinoma.

3. EVALUATION OF SURVEILLANCE

As stated in our mission, the registry promotes scientific research with the aim of improving screening programs. Below you will find studies related to surveillance conducted or published in 2018.

3.1. Lynch syndrome

3.1.1. Carriers of pathogenic MLH1, MSH2, and MSH6 germline variants show differences in adenoma and colorectal cancer development and molecular tumor characteristics (C. Engel et al)

Lynch syndrome (LS) is caused by inherited pathogenic variants in mismatch repair (MMR) genes and is primarily associated with an increased risk of colorectal cancer (CRC). Recent studies suggest that LS-CRC can develop through different pathways. We assessed MMR gene-specific patterns of adenoma and CRC risk, as well as frequencies of somatic APC and CTNNB1 mutations characterizing different CRC development pathways. A total of 2,747 LS patients with pathogenic germline variants in MLH1, MSH2, or MSH6 gene were followed prospectively regarding adenoma and CRC development. Somatic mutation data from 48 CRCs were re-evaluated by grouping tumor characteristics by the affected MMR gene. Advanced adenoma risk was higher in MSH2 vs. MLH1 carriers, as was the frequency of somatic APC mutations in MSH2- vs. MLH1-associated CRCs. In

contrast, MLH1-associated CRCs presented more frequently with somatic CTNNB1 mutations compared to MSH2-associated CRCs. Both MLH1 and MSH2 carriers showed higher frequencies of incident cancer than MSH6 carriers. Of the three MSH6-associated CRCs none carried a somatic CTNNB1 mutation, but all three samples presented with a somatic APC mutation.
Conclusion: Adenoma and CRC development in patients with distinct pathogenic MMR gene variants are attributable to different molecular pathways, potentially explaining the variation in the efficacy of colonoscopy. These differences indicate that LS screening and management guidelines should be revisited and tailored to the MMR gene affected.

3.1.2 Effect of chromoendoscopy in the proximal colon on colorectal neoplasia detection in Lynch syndrome: a multicenter randomized controlled trial (J. Haanstra et al)
Patients with Lynch syndrome (LS) undergo regular surveillance by colonoscopy because of an increased risk of colorectal neoplasia, particularly in the proximal colon. Chromoendoscopy (CE) has been reported to improve neoplasia detection compared with conventional white-light endoscopy (WLE) but evidence is limited. Our aim was to investigate the effect of CE in the proximal colon on detection of neoplastic lesions during surveillance in LS. A multicenter prospective randomized controlled trial of 246 LS patients who were randomly assigned (1:1) to conventional WLE or colonoscopy with CE in the proximal colon, stratified for previous colorectal adenomas, and enrolling center. Two years after baseline colonoscopy, patients underwent colonoscopy with CE in the proximal colon. The primary outcome was the proportion of patients with at least one neoplastic lesion at baseline and after 2 years. Neoplasia detection rates at baseline colonoscopy were 27% for WLE versus 30% for CE. In the proximal colon, neoplasia detection rates were 16% for WLE versus 24% for CE. Total procedure time was 9 minutes longer in the CE group. At follow-up after 2 years, neoplasia detection rates were similar in both groups: 26% for the original WLE group versus 28% for the CE group.

Conclusion: CE in the proximal colon for LS surveillance was not superior to WLE with respect to the initial detection of neoplasia, and not associated with reduced neoplasia detection rates after 2 years. The value of CE remains to be established.

3.2. Hereditary Melanoma and Pancreatic cancer
3.2.1. Dilatation of the main pancreatic duct as first manifestation of small pancreatic ductal adenocarcinomas detected in a hereditary pancreatic cancer surveillance program (H. Vasen et al)
MRI surveillance in a cohort of CDKN2A-p16-Leiden mutation carriers with a 20% lifetime risk of PDAC led to increased resection rates and improved survival. Patients with screen-detected PDAC were evaluated for main pancreatic duct (MPD) abnormalities in this retrospective review. Since 2000 annual MRI and optional EUS was performed in mutation carriers. Data of patients with screen-detected PDAC was collected including gender, age at diagnosis, site of tumor, size, outcome of surgery, pathology findings and survival. All MRIs were re-evaluated for MPD abnormalities. 23 PDAC were detected in 22 (10%) of 217 mutation carriers, 10 (45%) males and 12 (55%) females. The mean age at diagnosis was 59.8 years (range 39.2-74.3 years). Revision of the MRI/MRCP revealed a lesion and dilatation of the MPD in 8 of the 22 patients. In 5 of 7 patients with PDAC detected during follow-up, the previous MRI showed MPD dilatation without evidence of tumor. The mean size of PDAC was 12.3 mm (range 5-19 mm). All tumors were resectable. Conclusion: MPD dilation is common in patients with screen-detected PDAC. Abnormalities on MRI during surveillance of high-risk individuals requires intense follow-up or prompt treatment, as early treatment results in a better prognosis.

3.2.2. Surveillance for familial melanoma: recommendations from a national centre of expertise. (A. Halk et al)

The department of Dermatology at the Leiden University Medical Center, is a national center of expertise for the management of individuals with familial and hereditary melanoma. In collaboration with the department of Clinical Genetics and Gastroentrology & Hepatology, they published the current surveillance recommendations for the various syndromes in the British Journal of Dermatology.

3.2.3. Incidental findings in pancreas screening programs for high-risk individuals: results from three European expert centers (I.Ibrahim et al)

Widespread abdominal imaging has led to a substantial increase in the detection of incidentaloma. Currently, an increasing number of centers offer surveillance of the pancreas, to individuals at high risk (IAR) of pancreatic cancer (PDAC). The aims of this study were to evaluate the frequency and type of incidental findings in an MRI-based surveillance program for high-risk individuals for PDAC, and to discuss the benefit of detecting these lesions.

The outcome of MRI screening was reviewed in 568 individuals from three long-term pancreas surveillance programs conducted in three large European expert centers. All MRIs were studied in detail for the presence of incidental lesions.

The most common lesions were liver cysts, renal cysts and liver hemangioma, which together comprised 75% of all lesions. Only five (0.9%) patients underwent surgery for a benign lesion. Cancer was detected in eleven patients (2.0%),and early detection of tumors was beneficial in at least five cases.

Conclusion: The present study demonstrates that extrapancreatic incidentaloma is a common finding in IAR for PDAC, but rarely requires additional treatment. CDKN2A-p16-Leiden mutation carriers were the only patient group found to harbor a substantial number of cancers, and detection resulted in benefit in several cases.

3.3. Hereditary prostate cancer

3.3.1. Prostate-specific antigen velocity in a prospective prostate cancer screening study of men with genetic predisposition. (C. Mikropoulos et al)

Prostate-specific antigen (PSA) and PSA-velocity (PSAV) have been used to identify men at risk of prostate cancer (PrCa). The IMPACT study is evaluating PSA screening in men with a known genetic predisposition to PrCa due to BRCA1/2 mutations. This analysis evaluates the utility of PSA and PSAV for identifying PrCa and high-grade disease in this cohort. PSAV was calculated using logistic regression to determine if PSA or PSAV predicted the result of prostate biopsy (PB) in men with elevated PSA values. Cox regression was used to determine whether PSA or PSAV predicted PSA elevation in men with low PSAs. Interaction terms were included in the models to determine whether BRCA status influenced the predictiveness of PSA or PSAV. 1634 participants had $\geqslant$3 PSA readings of whom 174 underwent PB and 45 PrCas diagnosed. In men with PSA >3.0 $ng\,ml^{-1}$, PSAV was not significantly associated with presence of cancer or high-grade disease. PSAV did not add to PSA for predicting time to an elevated PSA. When comparing BRCA1/2 carriers to non-carriers, we found a significant interaction between BRCA status and last PSA before biopsy (P=0.031) and BRCA2 status and PSAV (P=0.024). However, PSAV was not predictive of biopsy outcome in BRCA2 carriers. Conclusions*:* PSA is more strongly predictive of PrCa in BRCA carriers than non-carriers. We did not find evidence that PSAV aids decision-making for BRCA carriers over absolute PSA value alone.

4. EDUCATION, PUBLICATIONS AND PATIENT INFORMATION

In the course of 2018, several presentations were given on various hereditary forms of cancer. In addition, many articles were published with the aim of increasing knowledge regarding hereditary cancer (see below). The leaflets produced by the StOET on various hereditary forms of cancer were updated where necessary. The StOET website is updated annually by Magdalena van Heck. In May 2018, the biannual Familial Cancer Conference was organized by the European Society of Oncology in Madrid, Spain, and attracted more than 200 participants. In 2018, we also organized a patient information day for patients participating in a pancreatic cancer screening program. You will find more information on these two meetings below.

4.1. 8th ESO-CNIO Conference on Familial Cancer: 17-18th May, 2018, Madrid, Spain

Chairs: R. Eeles, UK - W. Foulkes, CA - M. Robledo, ES - H. Vasen, NL

The ESO and CNIO Conference on Familial Cancer aims to present the advances in this field from a multidisciplinary point of view. Due to its implications not only at individual but also at the familial and social level, familial cancer has become an important challenge for oncologists, geneticists, molecular biologists and other professionals. Along the last years, new approaches have allowed to increase our knowledge about the genes responsible for familial cancer as well as their biological functions – factors that are essential in identifying the appropriate treatment in each case. The next generation sequencing is extensively used in the search of causal mutations but it represents a new challenge regarding the interpretation of variants, many of which must be classified as of unknown significance. Biannually the Conference brings together leading basic and translational researchers and clinicians involved in the diagnosis, treatment and follow-up of patients with familial cancer. These meetings help to establish connections among professionals that in turn promote progress in the understanding and treatment of these diseases. Besides the lectures from international experts, young scientists can present their work as short lectures and posters. This format aims to facilitate extensive discussion of current issues and stimulate new ideas. See for the programma: www.eso.net

4.2 Patient information day: "Screening for pancreatic cancer". December 1, 2018 (Organizer: H. Vasen)

Many patients had recently expressed an interest in a gathering at which information could be provided on all aspects of pancreas screening. To meet this need we organized a patient information day on December 1, 2018. All patients known to the Department of Gastroenterology & Hepatology with an interest in pancreas screening were invited to this meeting. We were delighted that around 220 people attended the meeting. A summary of the lectures held on the "patient information day" can be found at www.StOET.nl (News Section).

5. OTHER STUDIES

5.1 Lynch syndrome and CMMRD

5.1.1. Cancer Risks for PMS2-Associated Lynch Syndrome (S. ten Broeke et al)

Lynch syndrome due to pathogenic variants in the DNA mismatch repair genes MLH1, MSH2, and MSH6 is predominantly associated with colorectal and endometrial cancer, although extracolonic cancers have been described within the Lynch tumor spectrum. However, the age-specific cumulative risk (penetrance) of these cancers is still poorly defined for PMS2-associated Lynch syndrome. Using a large data set from a worldwide collaboration, our aim was to determine accurate penetrance measures of cancers for carriers of heterozygous pathogenic PMS2 variants. A modified segregation analysis was conducted that incorporated both genotyped and nongenotyped relatives, with conditioning for ascertainment to estimates corrected for bias. Hazard ratios (HRs) and corresponding 95% CIs were estimated for each cancer site for mutation carriers compared with the

general population, followed by estimation of penetrance. In total, 284 families consisting of 4,878 first- and second-degree family members were included in the analysis. PMS2 mutation carriers were at increased risk for colorectal cancer (cumulative risk to age 80 years of 13% for males and 12% for females) and endometrial cancer (13%), compared with the general population (6.6%). There was no clear evidence of an increased risk of ovarian, gastric, hepatobiliary, bladder, renal, brain, breast, prostate, or small bowel cancer.

Conclusion: Heterozygous PMS2 mutation carriers were at small increased risk for colorectal and endometrial cancer but not for any other Lynch syndrome-associated cancer. This finding justifies that PMS2-specific screening protocols could be restricted to colonoscopies. The role of risk-reducing hysterectomy and bilateral salpingo-oophorectomy for PMS2 mutation carriers needs further discussion.

5.1.2. Characteristics of Lynch syndrome associated ovarian cancer (J.Woolderink et al)

The aim of this study was to describe clinical characteristics of Lynch syndrome associated ovarian cancer and the efficacy of surveillance in the early detection of these ovarian cancers. All Lynch syndrome associated ovarian cancer cases identified in either the Dutch Lynch syndrome registry (DLSR) between 1987 and 2016, and/or the cohort at the University Medical Center Groningen (UMCG) between 1993 and 2016 were included. Clinical data on age at diagnosis, mutation type, histological type, FIGO stage, treatment, follow-up and gynecological surveillance were collected.

A total of 46/798 (6%) women in the DLSR and 7/80 (9%) in the UMCG cohort were identified as LS associated ovarian cancer patients. The median age at ovarian cancer diagnosis was 46.0 years (range 20-75 years). The most frequently reported histological type was endometrioid adenocarcinoma (40%; n = 21) and serous carcinoma (36%; n = 19). Most tumors (87%; n = 46) were detected at an early stage (FIGO I/II). Forty-one of 53 (77%) patients were diagnosed with ovarian cancer before LS was diagnosed. In the other 12/53 (23%) women, ovarian cancer developed after starting annual gynecological surveillance for LS; three ovarian cancers were screen-detected in asymptomatic women. Overall survival was 83%. Conclusions: Ovarian cancer in women with LS has a wide age-range of onset, is usually diagnosed at an early stage with predominantly endometrioid type histology and a good overall survival. The early stage at diagnosis could not be attributed to annual gynecological surveillance.

5.1.3. Constitutional mismatch repair deficiency as a differential diagnosis of neurofibromatosis type 1: consensus guidelines for testing a child without malignancy (M.Suerink)

Constitutional mismatch repair deficiency (CMMRD) is a rare childhood cancer predisposition syndrome caused by biallelic germline mutations in one of four mismatch-repair genes. Besides very high tumour risks, CMMRD phenotypes are often characterised by the presence of signs reminiscent of neurofibromatosis type 1 (NF1). Because NF1 signs may be present prior to tumour onset, CMMRD is a legitimate differential diagnosis in an otherwise healthy child suspected to have NF1/Legius syndrome without a detectable underlying NF1/SPRED1 germline mutation. However, no guidelines indicate when to counsel and test for CMMRD in this setting. Assuming that CMMRD is rare in these patients and that expected benefits of identifying CMMRD prior to tumour onset should outweigh potential harms associated with CMMRD counselling and testing in this setting, we aimed at elaborating a strategy to preselect, among children suspected to have NF1/Legius syndrome without a causative NF1/SPRED1 mutation and no overt malignancy, those children who have a higher probability of having CMMRD. At an interdisciplinary workshop, we discussed estimations of the frequency of CMMRD as a differential diagnosis of NF1 and potential benefits and harms of CMMRD counselling and testing in a healthy child with no malignancy. Preselection criteria and strategies for

counselling and testing were developed and reviewed in two rounds of critical revisions. Existing diagnostic CMMRD criteria were adapted to serve as a guideline as to when to consider CMMRD as differential diagnosis of NF1/Legius syndrome. In addition, counselling and testing strategies are suggested to minimise potential harms.

5.1.4. Transscan studie (coordinator: Janneke Ringelberg en Hans Vasen)

As stated in previous annual reports, a large European collaborative study was started in 2014 on research into the effect of 5-ASA on polyp and cancer development in patients with Lynch syndrome. In the study, patients receive 2 different doses of 5-ASA or a placebo. The duration of treatment is 2 years. The endpoint of the research is the development of "advanced" adenomas. In 2017 permission was obtained from the medical ethics committee of the LUMC. Unfortunately, in 2018 the sponsors of the study including the Dutch Cancer Fund (KWF) decided to discontinue the study because of insufficient inclusion of study subjects.

5.2 Familial adenomatous polyposis (FAP)

5.2.1. Optimizing the timing of colorectal surgery in patients with familial adenomatous polyposis in clinical practice (H. Vasen et al)

Familial adenomatous polyposis (FAP) is characterized by the development of hundreds of colorectal adenomas in the second decade of life, and prophylactic colectomy is usually performed around age of 20. A common question is the appropriate timing of surgery and which endoscopic findings indicate surgery.

All FAP patients known at Leiden University Medical Centre from 1985 onwards were included. The patients were then subdivided into those diagnosed before or after 2000. Patient information included age at diagnosis, colonic phenotype, age at surgery, pathological findings, and the outcome of follow-up colonoscopies in whom surgery was postponed.

The 72 FAP patients identified consisted of 33 patients diagnosed before (group A) and 39 after (group B) 2000. The median age at diagnosis for patients with classical FAP was 18 in groups A and B. All patients diagnosed before 2000 underwent colorectal surgery versus 68% of those diagnosed >2000. The median age at surgery for classical FAP patients was 19 and 24 years in groups A and B, respectively. In patients with intact colon, the number of adenomas gradually increased over many years. Although most adenomas remained <5mm, the proportion of 5-15mm adenomas slowly increased. Only one patient developed a high-grade adenoma. None of the patients developed CRC.

Conclusion: Surgery today in FAP is performed less often and at a more advanced age. Our experience also suggests that surgery can be safely postponed in selected patients. The most important endoscopic indication for surgery is substantial number of large adenomas of >5-10mm.

5.3 Hereditary melanoma and pancreatic cancer

5.3.1. CM-Score: a validated scoring system to predict CDKN2A germline mutations in melanoma families from Northern Europe (Th Potjer et al)

Several factors have been reported that influence the probability of a germline CDKN2A mutation in a melanoma family. Our goal was to create a scoring system to estimate this probability, based on a set of clinical features present in the patient and his or her family. Five clinical features and their association with CDKN2A mutations were investigated in a training cohort of 1227 Dutch melanoma families (13.7% with CDKN2A mutation) using multivariate logistic regression. Predefined features included number of family members with melanoma and with multiple primary melanomas, median age at diagnosis and presence of pancreatic cancer or upper airway cancer in a family member. Based

on these five features, a scoring system (CDKN2A Mutation(CM)-Score) was developed and subsequently validated in a combined Swedish and Dutch familial melanoma cohort (n=421 families; 9.0% with CDKN2A mutation). All five features were significantly associated ($p<0.05$) with a CDKN2A mutation. At a CM-Score of 16 out of 49 possible points, the threshold of 10% mutation probability is approximated (9.9%; 95%CI 9.8 to 10.1). This probability further increased to >90% for families with ≥36 points. A CM-Score under 16 points was associated with a low mutation probability (≤4%). CM-Score performed well in both the training cohort (area under the curve (AUC) 0.89; 95%CI 0.86 to 0.92) and the external validation cohort (AUC 0.94; 95%CI 0.90 to 0.98). Conclusions: We developed a practical scoring system to predict CDKN2A mutation status among melanoma-prone families. We suggest that CDKN2A analysis should be recommended to families with a CM-Score of ≥16 points.

6. ORGANIZATION

6.1. Board

Prof. Dr. W. Bemelman, chair, surgeon, Amsterdam Medical Center, Amsterdam
Prof. Dr. R. Hofstra, Head, Department of Clinical Genetics, Erasmus Medical Center, Rotterdam
Prof. Dr. W. Bergman, Department of Dermatology, Leiden University Medical Center, Leiden
Dr. de Vos tot Nederveen Cappel, gastroenterologist, Isala Clinics, Zwolle
Prof. Dr. M. Mourits, gynaecologist, University Medical Centre Groningen, Groningen

6.2. Registry staff

Prof. dr. H.F.A. Vasen, internist, Medical Director
Mw. drs. M. van Heck, communication, organization, finances
Mw. I.S.J. van Leeuwen-Cornelisse, medical social worker
Mw. C. van der Kaa, registration Lynch syndroom
Mw. C. Meijvogel, registration Lynch syndroom
Mw. I.E.M. Voncken, registration Polyposis
Mw. drs. J. Ringelberg-Borsboom, coördinator Transscan study
Mw. H.L. van Randeraad, registration Hereditary Melanoma and Hereditary Prostate cancer

6.3 . Committee of supervision of the protection of privacy

Mr. I. de Vries, chair
Dr. F. Menko, Family Cancer Clinic, NKI, Amsterdam
Mw. A. Dietvorst, member (patient)

6.4. Research Commission

Dr. P. van Duijvendijk, surgeon, Gelren Hospital, Apeldoorn
Prof. dr. E. Dekker, gastroenterologist, AMC, Amsterdam
Dr. S. Sanduleanu, gastroenterologist, University Medical Centre Maastricht, Maastricht
Dr. R. van Doorn, dermatologist, Leiden University Medical Centre, Leiden
Dr. A. Wagner, clinical geneticist, Erasmus Medical Cente, Rotterdam

ENCLOSURES

1. Presentations

1. Leiden University Medical Centre, Department of Gastroenterology & Hepatology: Hans Vasen: Pancreas screening, February 8, 2018
2. Mashhad, Iran, April 24, 2018: Hans Vasen: Prevention of hereditary CRC in the Middle East
3. ESO Familial Cancer Conference May 17 & 18, 2018: Zeinab Ghorbanoghli: First results of surveillance of CMMRD patients
4. Dutch Digestive Disease Days, Veldhoven, October 3, 2018: Dicke medal award lecture: Hans Vasen: 30 years of research in Lynch syndrome
5. Patient Information Day, December 1, 2018: Hans Vasen: The outcome of 18 years of screening for pancreatic cancer in carriers of a CDKN2A (p16-Leiden) mutation
6. Mashhad, Iran, December 28, 2018: Hans Vasen (video presentation): Familial CRC syndromes and the importance of registries

2. Publications

1: Ghorbanoghli Z, Bastiaansen BA, Langers AM, Nagengast FM, Poley JW, Hardwick JC, Koornstra JJ, Sanduleanu S, de Vos Tot Nederveen Cappel WH, Witteman BJ, Morreau H, Dekker E, Vasen HF. Extracolonic cancer risk in Dutch patients with APC (adenomatous polyposis coli)-associated polyposis. J Med Genet. 2018 Jan;55(1):11-14.

2: Ghorbanoghli Z, Jabari C, Sweidan W, Hammoudeh W, Cortas G, Sharara AI, Abedrabbo A, Hourani I, Mahjoubi B, Majidzadeh K, Tözün N, Ziada-Bouchaar H, Hamoudi W, Diab O, Khorshid HRK, Lynch H, Vasen H. A new hereditary colorectal cancer network in the Middle East and eastern mediterranean countries to improve care for high-risk families. Fam Cancer. 2018 Apr;17(2):209-212.

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