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Systematic immunohistochemical screening for Lynch syndrome in colorectal cancer: a single centre experience of 486 patients

Valentin Zumstein[a], Fabrizio Vinzens[a], Andreas Zettl[b], Karl Heinimann[c], Dieter Koeberle[d], Markus von Flüe[a], Martin Bolli[a]

[a] Department of Surgery, St. Claraspital, Basel, Switzerland

[b] Department of Pathology, Viollier AG, Allschwil, Switzerland

[c] Department of Medical Genetics, University Hospital Basel, Switzerland

[d] Departments of Internal Medicine and Oncology, St. Claraspital, Basel, Switzerland

Summary

BACKGROUND: Germline mutations in DNA mismatch repair (MMR) genes *MLH1, MSH2, MSH6* and *PMS2* cause autosomal dominantly inherited Lynch syndrome. Lynch syndrome patients and their families benefit from life-saving intensive cancer surveillance. Approximately one in 30 colorectal cancers arises in the setting of Lynch syndrome.

OBJECTIVE: The aim of this study was to assess the detection rate of Lynch syndrome at our institution after introduction of systematic immunohistochemical screening for MMR deficiency in colorectal cancers from 2011 to 2015.

DESIGN: Following the recommendations by the Evaluation of Genomic Applications in Practice and Prevention working group all colorectal cancers were immunohistochemically stained for the presence of MMR proteins *MLH1, PMS2, MSH2* and *MSH6*, independent of clinical criteria. In the case of loss of *MLH1*, the somatic BRAF mutation V600E was assessed with molecular testing and/or immunohistochemistry. Clinical follow-up of potential Lynch syndrome carriers (patients with tumours showing loss of *MLH1* expression with absence of BRAFV600E, loss of *PMS2*, *MSH2* or *MSH6*) was evaluated.

RESULTS: Of all patients (n = 486), loss of MMR protein expression was found in 73 (15.0%) tumours. Twenty-eight (6.0%) were classified as potential Lynch syndrome carriers. Of the genetically tested potential Lynch syndrome carriers (10 out of 28 patients), 40% were first diagnosed with Lynch syndrome.

CONCLUSIONS: Implementation of systematic immunohistochemistry screening for Lynch syndrome showed that 6% of colorectal cancers were potentially Lynch-syndrome related. Tumour board protocols should systematically contain information on MMR status of all colorectal cancers and, in MMR deficient cases, include clear recommendations for genetic counselling for all potential Lynch syndrome patients.

Key words: *Lynch syndrome; colorectal cancer; systematical screening; immunohistochemistry; universal screening*

Introduction

Colorectal cancer represents the third most common cancer worldwide and the second leading cause of cancer-related deaths after lung cancer [1].

Lynch syndrome, as the most common hereditary colorectal cancer syndrome, is responsible for up to 3% of all cases of colorectal cancer [2], caused by germline mutations in DNA mismatch repair (MMR) genes *MLH1, MSH2, MSH6* and *PMS2*. Lynch syndrome is characterised by development of colorectal, endometrial and various other cancers. Identification of these patients is important since Lynch syndrome patients and their families benefit from life-saving intensive cancer surveillance.

Several strategies have been developed to identify patients with Lynch syndrome. Since clinical criteria such as the Bethesda Guidelines or the Amsterdam Criteria are difficult to implement in daily clinical practice [2, 3] and studies showed poor sensitivity and/or specificity [4, 5], in 2009 the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) recommended screening all newly diagnosed patients with colorectal cancer for Lynch syndrome [6]. Meanwhile, this approach has been strongly endorsed by, for example, European [7] and US experts (2015 guideline issued by the American Gastroenterological Association Institute as well as 2014 guidelines issued by the US Multi-Society Task Force on Colorectal Cancer) [8, 9].

In general, Lynch syndrome is often underdiagnosed [9]. Recent studies pointed out that, although universal screening of patients with colorectal cancer is conceptually possible, the implementation of systematic screening is demanding, requiring awareness of the importance of Lynch syndrome screening and close cooperation and effective communication across multiple disciplines [10, 11].

Here we report our experience after 4 years of prospectively testing all colorectal cancers by immunohistochemistry following the publication of the EGAPP recommendations.

Materials and methods

Setting

Our clinic is a reference centre in Switzerland specialising in colorectal surgery and performing over 400 colorectal resection procedures per year. Colorectal surgeons, gastroenterologists, oncologists, geneticists and pathologists closely collaborate, and every case of colorectal cancer is pre- and postoperatively discussed at an interdisciplinary tumour board. The surgeon-of-record is supposed to give information from the pathology report to the patient and referring clinician, and if necessary to suggest further genetic counselling and testing. The study was performed under ethics approval number EK: 258/05 and meets the current laws of Switzerland.

Screening

Following the publication of the EGAPP recommendations, a universal Lynch syndrome screening system was implemented at our clinic in spring 2011. All diagnosed colorectal cancers, independent of clinical criteria, were prospectively tested using immunohistochemistry for the expression of the four MMR proteins MLH1, PMS2, MSH2 and MSH6. Leica Bond Max III staining automats were used for immunohistochemistry. From paraffin blocks 1-µm sections were cut, mounted on superfrost glass slides and stained for MLH1 (clone G168-15, BD Pharmingen; dilution 1:25), MSH2 (clone G219-1129, BD Pharmingen; 1:200), MSH6 (clone 44, Diagnostic Biosystems; 1:25) and PMS2 (clone A16-4; BD Pharmingen; 1:200). In the event of loss of MLH1, BRAFV600E mutational status was assessed by molecular testing using an allele-specific polymerase chain-reaction (PCR)-based strip detection system (KRAS-BRAF StripAssay®; Vienna Labs) and/or immunohisochemistry (clone VE1, Spring Bioscience; 1:100), as recently published [12]. Cases with complete nuclear loss of expression in invasive tumour cells with retained expression in inflammatory cells and/or adjacent normal tissue as positive controls were considered MMR deficient (fig. 1).

In patients suspected to be Lynch syndrome carriers (i.e. tumours showing loss of *MLH1* expression combined with absence of BRAFV600E mutation, or loss of *PMS2, MSH2* or *MSH6*), clinical follow-up was evaluated (tumour board recommendations, frequency of referral for genetic counselling and testing). In patients referred for genetic testing, assessment of MLH1 promoter methylation status and testing for the BRAF V600E mutation was used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1 [13–16].

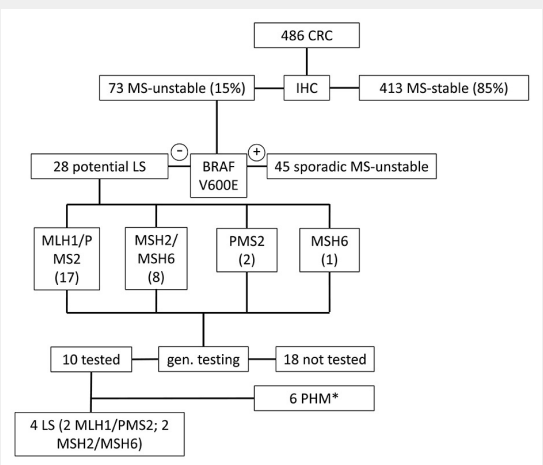

Figure 1

Study schema for universal screening for LS of all newly diagnosed CRC patients. Of all patients (n = 486), loss of MMR protein expression was found in 73 (15.0%) tumours. 28 (6.0%) were classified as potential LS carriers. Of the genetically tested potential LS carriers (10 out of 28 patients), 40% were first diagnosed with LS.

* Promoter hypermethylation

CRC = colorectal cancer; IHC = immunohistochemistry; LS = Lynch syndrome; MMR = DNA mismatch repair; MS = microsatellite

Statistics

Statistical data analysis was performed using SPSS version 14.0 (SPSS Inc., Chicago, IL). Fisher's exact and χ^2-tests were used to compare groups – microsatellite (MS)-stable, MS-unstable, Lynch syndrome (LS)-suspicious and LS – regarding the clinicopathological parameters listed in table 1. A p-value <0.05 was considered significant.

Results

Clinical data

The median age of all patients at the time of surgery was 71 years. Detailed clinicopathological information for all groups is shown in table 1.

A total of 413 (85%) colon cancer specimens showed retained expression of *MLH1, MSH2, MSH6* and *PMS2* in tumour cells. Loss of expression in at least one of the four MMR genes occurred in 73 of 486 patients (15%). Forty-five patients showed loss of *MLH1/PMS2* and positivity for BRAFV600E, the remaining 28 cases were considered to require genetic counselling for Lynch syndrome. The distribution of loss of expression of the MMR genes in this group was as following: combined *MLH1/PMS2* loss and negativity for BRAFV600E: 17; combined *MSH2/MSH6* loss: 8; isolated *PMS2* loss: 2; isolated *MSH6*: 1 (table 2). These 28 patients were recommended to undergo genetic counselling and testing, but 18 of the 28 were not further counselled and tested: lost to follow-up 14 patients, 2 of whom moved to another country (Hungary, Great Britain), or refused for personal reasons (4 patients). Ten patients were genetically tested, with four being confirmed as newly diagnosed Lynch syndrome germline mutation carriers (fig. 1). Genetic counselling revealed, in total, 52 Lynch syndrome-affected relatives (44 of them healthy at the time of genetic counselling). Detailed information regarding the newly diagnosed Lynch syndrome and affected relatives is found in table 3. Projected to the group that was not tested as recommended, this corresponds to an overall Lynch syndrome rate of 2.3%.

Correlation with clinicopathological parameters

Tumours found to be MMR deficient were significantly associated with female gender (p = 0.0022), right sided (p <0.00001), and mucinous (p <0.00001) or medullary (p <0.00001) histology. Regarding the stage of disease, pN0 nodal status was significantly more frequent in MS-unstable cases (p = 0.0024), as well as V0 (p = 0.0056) and Pn0 (p = 0.0203).

Discussion

Recent guidelines strongly recommend universal Lynch syndrome screening for all patients with colorectal cancer, regardless of clinicopathological features or family history. Universal screening is cost effective and feasible [4, 6, 17–20].

The identification of patients with Lynch syndrome and their families is important since they benefit from life-sav-

Table 1: Detailed clinicopathological data of all patients.

	Total		MS-stable		MS-unstable		LS-suspicious		LS	
	n	%	n	%	n	%	n	%	n	%
Total no. of cases	486	100.0	413	85.0	73	15.0	28	6.0	4	0.8
Age, y										
Median (IQR)	71 (15.0)		70 (15.0)		73 (15.0)		69 (13.3)		43 (39.75)	
>70	267	54.9	219	53.0	48	65.8	12	42.9	1	25.0
<70	219	45.1	194	47.0	25	34.2	16	57.1	3	75.0
Sex										
Male	254	52.3	228	55.2	26	35.6	13	46.4	2	60.0
Female	232	47.7	185	44.8	47	64.4	15	53.6	2	40.0
Tumour site										
Left colon	293	60.3	281	68.0	12	16.4	9	32.1	1	25.0
Right colon	193	39.7	132	32.0	61	83.6	19	67.9	3	75.0
Histological type										
Adenocarcinoma	408	84.0	374	90.6	34	46.6	17	60.7	4	100.0
Mucinous carcinoma	67	13.8	39	9.4	28	38.4	9	32.1	0	0.0
Medullary carcinoma	11	2.2	0	0.0	11	15.0	2	7.2	0	0.0
Tumour stage										
I	48	9.9	43	10.4	5	6.8	4	14.3	1	25.0
II	78	16.0	70	16.9	8	11.0	4	14.3	1	25.0
III	279	57.4	227	55.0	52	71.2	16	57.1	1	25.0
IV	81	16.7	73	17.7	8	11.0	4	14.3	1	25.0
Nodal status										
pN0	286	58.8	229	55.4	57	78.1	22	78.6	3	75.0
pN1a	63	13.0	60	14.5	3	4.1	0	0.0	0	0.0
pN1b	47	9.7	45	10.9	2	2.7	1	3.6	0	0.0
pN1c	8	1.6	8	1.9	0	0.0	0	0.0	0	0.0
pN2a	43	8.8	35	8.5	8	11.0	2	7.1	0	0.0
pN2b	39	8.0	36	8.7	3	4.1	3	10.7	1	25.0
Lymphatic invasion										
Negative	333	68.5	281	68.0	52	71.2	21	75.0	3	75.0
Positive	153	31.5	132	32.0	21	28.8	7	25.0	1	25.0
Venous invasion										
V0	376	77.4	309	74.8	67	91.8	25	89.3	4	100.0
V1	103	21.2	97	23.5	6	8.2	3	10.7	0	0.0
V2	7	1.4	7	1.7	0	0.0	0	0.0	0	0.0
Perineural invasion										
Pn0	426	87.7	356	86.2	70	95.9	28	100.0	4	100.0
Pn1	60	12.3	57	13.8	3	4.1	0	0.0	0	0.0
Grading (WHO)										
G1	3	0.6	2	0.5	1	1.4	1	3.6	0	0.0
G2	402	82.7	341	82.6	61	83.6	22	78.6	4	100.0
G3	81	16.7	70	16.9	11	15	5	17.8	0	0.0

IQR = interquartile range; LS = Lynch syndrome; MS = microsatellite; WHO = World Health Organisation

Table 2: Distribution of loss of expression of the DNA mismatch repair (MMR) genes in MMR deficient group.

	Cases	%
MLH1/PMS2; BRAFV600E+	45	61.6
MLH1/PMS2; BRAFV600E–	17	23.3
MSH2/MSH6	8	11.0
PMS2	2	2.7
MSH6	1	1.4

ing intensive cancer surveillance [6]. The success of universal screening is highly dependent on patients and referring physicians, in particular family doctors, receiving the screening results, with pursuit of genetic counselling and genetic testing afterwards [10].

In our study loss of MMR protein expression occurred in 15% of all patients, in line with published frequencies of MMR deficiency and microsatellite instability in large colon cancer cohorts [21]. The role of microsatellite unstable tumours as a clinically relevant subgroup of colorectal cancers has been described extensively [22]. These tumours share clinical features such as predilection for the proximal colon, female sex and mucinous histology. We could reproduce these features in our study; additionally we showed an association with lower stage of disease with a significantly more frequent occurrence of pN0, V0 and Pn0 stages. In contrast, although carcinomas with microsatellite instability (MSI) tend to be less aggressive and rarely metastasise, one of the Lynch syndrome and 16 of the MSI carcinomas detected presented with lymph node metastases.

The majority of sporadic MSI cancers show BRAFV600E [23], which distinguishes them from Lynch syndrome cancers and therefore is a useful tool to differentiate these groups. In our study, 28 cases still had suspected Lynch syndrome after testing for BRAFV600E. These cases should all be recommended to undergo genetic counselling and testing [6, 8, 9].

Testing for MMR deficiency, in particular with immunohistochemistry, has become a fast routine standard test in diagnostic histopathology. With the advent of second step BRAFV600E testing, in particular with immunohistochemistry, in MLH1-deficient tumours, the differentiation of sporadic vs potentially hereditary MMR-deficient colorectal cancer cases has become a routine diagnostic element that can be performed at initial histological diagnostics of colorectal cancer. Of paramount importance, however, is the appropriate communication of the test results by pathologists to clinicians. Clinicians need to be aware of the importance of MMR deficiency in potential Lynch syndrome cases and of the steps that should follow the diagnosis. Backes et al. [24] reported poor compliance with genetic counselling referral in endometrial cancer and Lynch syndrome. Heald et al. [10] reported similar problems. The main reasons were loss to follow-up, lack of appropriate “aggressive” communication to referring physicians or refusal of genetic counselling by the patients. These findings show that it is a challenge to capture all patients in a screening programme, and highlight the importance of encouraging and educating patients and their referring physicians

In our study, unexpectedly, 18 of 28 patients (64%) did not undergo genetic counselling. We identified the surgeon-of-record and the oncologist as key players in giving this information to the referring physician and the patient. To prevent patients being lost to follow up, MSI status was subsequently integrated as chief information in all colorectal cancer cases discussed in the tumour board. Treating clinicians were re-educated on the importance of Lynch syndrome identification. Furthermore, the information was given to the patient directly after tumour board still during their stay in hospital. Since then, loss to follow-up no longer occurred.

We newly identified four Lynch syndrome patients in our study, two of them between 2014 and 2015. Projected to the group that was not further tested, this corresponds to an overall Lynch syndrome rate of 2.3%. Regarding histology, all four Lynch syndrome carcinomas and almost 50% of MSI carcinomas detected were adenocarcinomas of no special histological subtype. This finding is important since before systematic MSI testing was introduced, pathologists relied on clinical data and special morphology (i.e. medullary or mucinous adenocarcinoma) to decide if further testing is needed. Therefore, many MSI carcinomas may have been missed in the past.

In conclusion, identification of patients with Lynch syndrome and their families is important since they benefit from life-saving intensive cancer surveillance. Implementation of universal screening for Lynch syndrome in clinical practice is challenging. Before institution of MMR deficiency screening of colorectal cancer, a standardised plan must be created where the key players (pathologists, surgeons, oncologists, geneticists and referring physicians, in particular family doctors) have their roles and responsib-

Table 3: Detailed data of the four newly diagnosed cases of Lynch syndrome.

	MMR-IHC	Age (y)	Sex	Gene mutated	Exon	Mutation	Personal history (age at diagnosis, y)	Affected relatives
Case 1	MSH2/ MSH6	74	M	MSH2	7	Genomic deletion of exon 7 c.1077-?_1276+?del	CRC 59, prostate-cancer 66, bladder-cancer 73, renal pelvis cancer 74, lung cancer 74	1 sister (endometrial cancer, 40 y; brain tumour, 49 y), 1 paternal aunt (endometrial cancer, 40 y) Healthy: 2 children, 1 nephew, 4 grandchildren
Case 2	MSH2/ MSH6	38	F	MSH2	9	c.1449_1450delAAinsT	CRC 38	Father (CRC 45 y), paternal aunt (endometrial cancer 58 y), paternal grandfather (bowel cancer 49 y) Healthy: 1 son, 1 brother, 1 paternal aunt
Case 3	MLH1/ PMS2	47	M	MLH1	18	c.2103+1G>T	CRC 46	Mother (ovarian and breast cancer, 55 y), maternal aunt (endometrial cancer 53 y, CRC 55 y), maternal grandmother (bowel cancer, age not known) Healthy: 1 sister and 3 children, 2 maternal uncles, 3 nephews/nieces
Case 4	MLH1/ PMS2	24	F	MLH1	18	c.2059C>T; p.Arg687Trp	CRC 24	No “directly” affected relatives known (except for paternal great-grandmother with CRC and breast cancer between age 60 and 70 y); Healthy: father (carrier), 3 paternal uncles, 2 siblings, 10 paternal cousins, 1 niece

CRC = colorectal cancer; IHC = immunohistochemistry; MMR = DNA mismatch repair

ilities clearly assigned. It is of utmost importance that the information given by the pathologist finds its way to the patient. Integration of MMR deficiency status into tumour board decisions can be an effective way to prevent patients from being lost to follow-up. As previous authors mentioned [10], educational material about Lynch syndrome and genetic counselling could help increasing compliance in patients suspected of having Lynch syndrome.

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Authors' contribution: Valentin Zumstein, Fabrizio Vinzens, Andreas Zettl, Karl Heinimann, Dieter Koeberle, Markus von Flüe and Martin Bolli contributed all substantially to conception and design of this study. They all contributed to acquisition, analysis and interpretation of data. Valentin Zumstein drafted the article; all authors revised it critically for important intellectual content. Before submission all authors approved the final version.

Correspondence: *Valentin Zumstein, MD, St. Claraspital Basel, Kleinriehenstrasse 30, CH-4058 Basel, valentin.zumstein[at]gmail.com*

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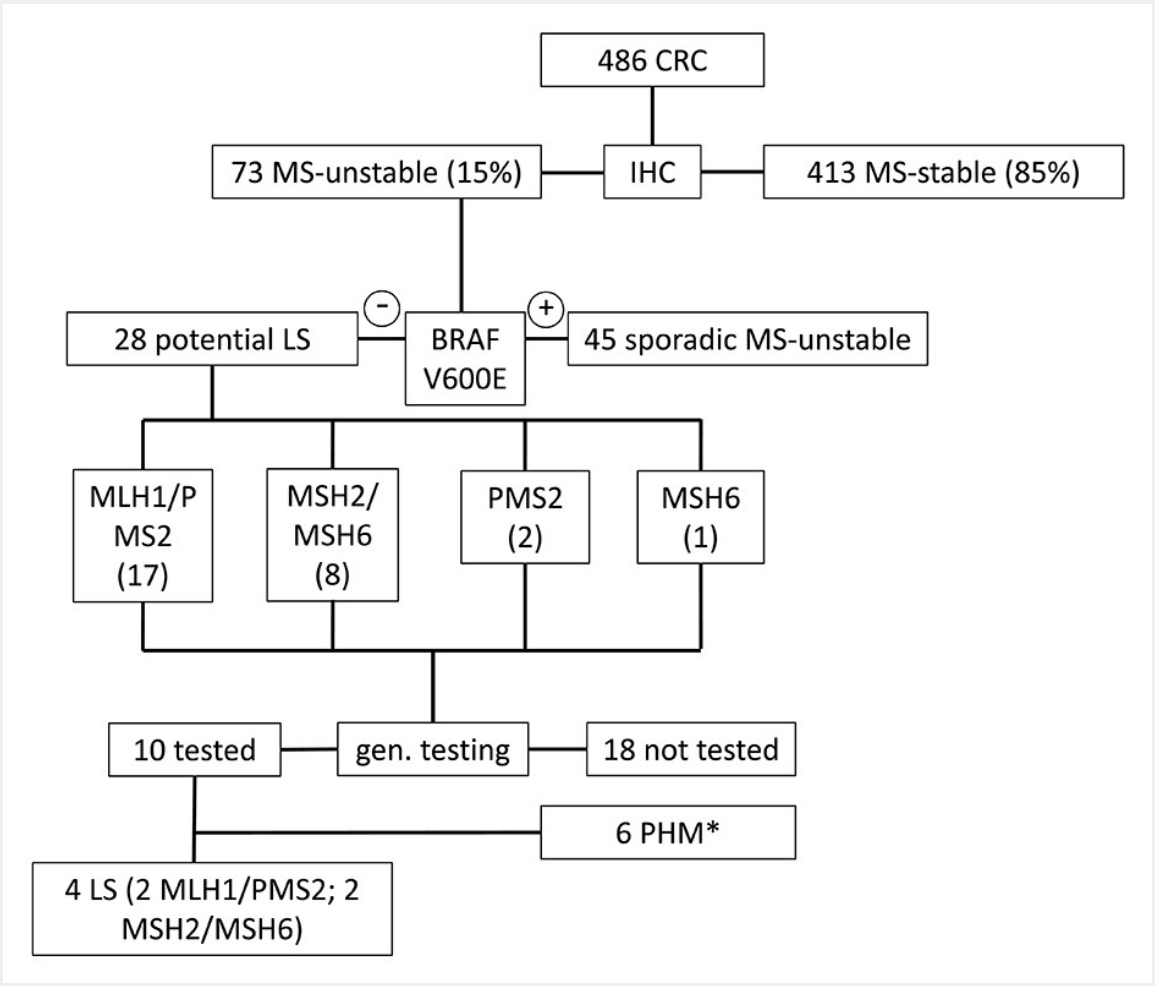
Figures (large format)



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* Promoter hypermethylation

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