

High frequency microsatellite instability has a prognostic value in endometrial endometrioid adenocarcinoma, but only in FIGO stage 1 cases

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Abstract. *Objectives:* To analyze the prognostic value of microsatellite instability (MSI) in a population-based study of FIGO stage 1–4 endometrial endometrioid adenocarcinomas.

Study design: Survival analysis in 273 patients of MSI status and clinico-pathologic features. Using a highly sensitive pentaplex polymerase chain reaction to establish MSI status, cases were divided into microsatellite stable (MSS), MSI-low (MSI-L, 1 marker positive) and MSI-high (MSI-H, 2–5 markers positive).

Results: After 61 months median follow-up (1-209), 34 (12.5%) of the patients developed metastases but only 6.4% of the FIGO 1. MSI (especially as MSI-H vs. MSS/MSI-L combined) was prognostic in FIGO 1 but not in FIGO 2–4. The 5 and 10 year recurrence-free survival rates were 98% and 95% in the MSS/MSI-L vs. 85% and 73% in the MSI-H patients ($p = 0.005$).

Conclusions: MSI-H status assessed by pentaplex polymerase chain reaction is an indicator of poor prognosis in FIGO 1, but not in FIGO 2–4 endometrial endometrioid adenocarcinomas.

Keywords: Endometrial cancer, endometrioid, FIGO stage 1, MSI, prognosis

1. Introduction

Endometrial adenocarcinoma is the most frequent gynecologic cancer. The disease-related death rate in FIGO stage 2–4 range from 20–80% and greater while in the “favorable” early stage FIGO 1, the death rate is only 5 to 10% [3,31]. The latter has been stable for decades [41]. This wide range of disease-related death

rate prompts the search for more reliable prognostic indicators both to enable more accurate triaging of patients concerning treatment modalities, and to gain better mechanistic insights into the disease.

In early FIGO stage 1 cancers, histologic type, grade and myometrium invasion depth (MI) are often used to determine individual therapy, but their prognostic accuracy and reproducibility are not always optimal [3,41,43]. Increased understanding of the molecular biology in endometrial carcinogenesis has revealed several promising prognostic and predictive biomarkers, such as microsatellite instability (MSI), a characteristic finding in cancers deficient in DNA mis-

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match repair (MMR), seen in 9–45% of sporadic endometrial cancers (Table 1) [1,4–7,10,12,16,17,19,25,26,28,29,32,33,42,44]. In contrast to Hereditary Non-

Polyposis Colorectal Cancer (HNPCC) or Lynch syndrome, which is an autosomal dominant condition involving germline MMR gene mutation, sporadic en-

Table 1
Studies cited in PubMed on MSI in endometrial cancer

Author	No. cases	Nos type I/ type 2	FIGO stages	FIGO 1 endometrioid separately analysed?	MSI markers	MSI-High(+) %	MSI impact on prognosis
Peiro et al. [32]	89	76/13	All	No information	D2S123 D5S346 Mfd15 BAT25 BAT26	11	Not prognostic
Fiumicino et al. [12]	65	?	1 and 2	No information	D2S123 D2S119 D9S171 D9S157 D10S216 BAT26	17	Unfavorable $p = 0.0004$
Wong et al. [42]	80	80/0	No information	Yes	D2S123D5 S346D17S 250 BAT25 BAT26 NR21 NR24 NR27 BAT25 BAT26	26	No information
Black et al. [7]	473	379/94	Mix	No information	D2S123 D5S346 D17S250 BAT25 BAT26	20	Favorable $p = 0.005$
An et al. [1]	93	93/0	Only 63 staged	No information	D2S123 D5S346 D17S250 BAT25 BAT26	20	No information
MacDonald et al. [25]	259	234/25	All	No information	D10S187 D18S55 D18S58 BAT26 BAT40	45	Not prognostic
Zigheboim et al. [44]	446	446/0	1–4	308 stage 1 (not analysed separately)	D2S123 D5S346 D17S250 BAT25 BAT26	33	Not prognostic
Muresua et al. [28]	86	?	1–3	No information	D2S123 D5S346 D17S250 BAT25 BAT26	32	Not prognostic

Table 1
(Continued)

Author	No. cases	Nos type I/ type 2	FIGO stages	FIGO 1 endometrioid separately analysed?	MSI markers	MSI-High(+) %	MSI impact on prognosis
Honore et al. [17]	218	218/0	No information	No information	BAT26	16	No information
Hirasawa et al. [16]	43	?	1–4	30 stage 1 and 2	D2S123 D5S346 D17S250 BAT26 BAT25 MSH3 MSH6 TGF RII BAX MBD4A10 MBD4A6	28	No information
Ju et al. [19]	50	50/0	1–4	30 stage 1 (not analysed separately)	D5S346 D17S250 D2S123 BAT25 BAT26	24	No information
Maxwell et al. [26]	131	131/0	All	81 stage 1, 2 and 3a analysed in one group	D14S65 D14S297 BAT26	22	Favorable $p = 0.03$
Ørbo et al. [29]	105	Mix	All	No information	D2S123 D5S346 BAT25 BAT26 TGF RII p53-1	20	Not prognostic
Baldinu et al. [4]	116	97/19	I to 3	No	D2S123 D5S346 D17S250 BAT25 BAT26	34	Not prognostic
Caduff et al. [10]	109	86/23	All	No	D2S123 D5S107 HUMCA1126 D10S197 D11S904 D13S175 D17S13223 D18S34	9	Unfavorable $p = 0.0005$
Pijnenborg et al. [33]	88	88/0	I	Yes	BAT25 BAT26	14–16	Not prognostic
Basil et al. [5]	229	173/56	All	No	D2S123 D5S346 D17S250	31	Not prognostic

Table 1
(Continued)

Author	No. cases	Nos type I/ type 2	FIGO stages	FIGO 1 endometrioid separately analysed?	MSI markers	MSI-High(+) %	MSI impact on prognosis
Bilbao et al. [6]	93	93/0	All	Stage 1 and 2 separately analysed	BAT25 BAT26 NR21 NR24 NR27 BAT25 BAT26	22	Unfavorable $p = 0.048$
Current study	224	224/0	I	Yes	NR21 NR24 NR27 BAT25 BAT26	16	Unfavorable, but only as MSS + MSI-low versus MSI-high, $p = 0.005$

ometrial cancers arise from epigenetic changes involving primarily hMLH1 promoter methylation resulting in gene inactivation. There are two pathways of genomic instability, chromosomal instability (CI) and microsatellite instability (MSI). CI is characterized by frequent loss of heterozygosity (LOH) with aneuploidy, is associated with p53 mutation and is typical of non-endometrioid (type II) endometrial cancers. The other MSI pathway involves defective MMR resulting in abnormalities at the nucleotide level, preserved near-diploidy, is often associated with PTEN and K-ras mutations, and typically occurs in endometrioid (type I) endometrial cancers.

In many MSI studies, a mix of early and late FIGO stage cancers of all histologic types has been analyzed; therefore the results of these studies can not be directly extrapolated to early stage cancers of the endometrioid type (which are by far the most common) as the type II endometrial cancers follow a different molecular development pathway [15]. Mixing types I and II endometrial cancers in fact may seriously blur the analysis. Not surprisingly, the results of different studies published thus far on MSI vary greatly. A large multicenter study consisting of 446 endometrioid (type I) endometrial cancers only and found that MSI has no prognostic value [44]. However, in spite of the large numbers of patients, it also mixed all stages which may have seriously biased the conclusions for FIGO stage 1 type I cancers. Another shortcoming was that the MSI markers used were less sensitive than the recently described ones assessed by the pentaplex polymerase chain reaction assay [8,9,42]. Another recent study of

interest investigated early stage radiation-treated endometrioid tumors only with the same MSI markers as ours, and concluded on a negative prognostic value for MSI-H patients [6].

In the present study we investigated whether MSI assessed with the pentaplex polymerase chain reaction assay containing five sensitive mononucleotide repeats has prognostic value in a population-based study of consecutive endometrioid endometrial cancer patients.

2. Materials and methods

The current MSI study is part of a project on endometrial carcinogenesis, approved prior to the initiation of the study by the Regional Ethics Committee and Norwegian Data Inspection.

2.1. Cases

The cohort used in this study was population-based from Rogaland-south, a county in South West Norway covering approximately 350,000 inhabitants. From January 1, 1989 through December 31, 2004, 363 cases of endometrial cancer were diagnosed at the Stavanger University Hospital, the only hospital in the region. From this group the following cases were excluded: lack of follow-up (7 cases), no adequate histologic material available for additional studies (39 cases) or no diagnostic evidence of invasive adenocarcinoma on histologic material reviewed by two gynecologic pathologists (EG, JB) (13 cases), leaving 304 patients

in the study. In agreement with other large studies, none of the patients in our series received preoperative hormonal or chemotherapy. Surgery was performed shortly after the pathology diagnosis was rendered. Patients with FIGO stage 1A, 1B or 1C, well and moderately differentiated cancers, received only surgical treatment consisting of total abdominal hysterectomy with bilateral salpingo-oophorectomy. Adjuvant post-operative radiotherapy (RT) was administered to all patients with FIGO stage 1C poorly differentiated cancers, and all patients with FIGO stage 2 cancers. Patients with FIGO stages 3 and 4 cancers were treated post-operatively with radiation or chemotherapy or both. All patients were followed at 3-monthly intervals. Standard surveillance included physical examination and cytologic smears for at least 2 years after initial treatment. Assessments with additional cytologic and imaging studies or directed biopsies were performed as clinically indicated at the discretion of the treating physician. Recurrent disease was histologically confirmed.

The sampling and tissue processing procedures were standardized as follows. Tissue slices of approximately 4 mm in thickness were routinely fixed in 4% buffered formaldehyde, dehydrated, paraffin embedded, sections cut at 4- μ m and haematoxylin-eosin-saffran (HES) stained. Histologic grade and type, cervical involvement and myometrium invasion of all cases were re-reviewed by two of us (EG, JB) and histologic grade and type of the FIGO 1 cases was re-reviewed by one more independent gynecologic pathologist (AM, EG, JB) using the WHO 2003 criteria. Staging was performed according to the original FIGO staging system [23]. In the few cases where there was disagreement between the reviewing pathologists whether a case was type 1, type 2, neuroendocrine cancer or sarcoma, additional immunohistochemical studies including p16, p53, chromogranin, synaptophysin, pan-CK, ER, E-cadherin and desmin were performed to clarify the diagnosis. After the review the 304 cases were distributed as follows: FIGO stage 1, 248 cases (82%); FIGO stage 2, 28 cases (9%); FIGO stage 3, 18 cases (6%) and FIGO stage 4, 10 cases (3%) (similar distribution to the one seen in other studies). There were 30 non-endometrioid endometrial cancers. One more case was excluded because the sections and blocks were not available at the time of review by one of us (AM), leaving 273 endometrioid endometrial cancers and 224 FIGO 1 cancers for analysis. 62 cases were excluded from MSI analysis (too little material/bad quality material, can-

cer tissue cut through, $n = 45 + 17$) leaving 211 cases for MSI analysis.

2.2. Microsatellite analysis

Microsatellite analysis was performed on DNA isolated from archived, paraffin-embedded tissue blocks using tissue from the invasive front of each tumor (avoiding areas with extensive necrosis or normal tissue), using the QIAamp DNA Mini Kit (QiagenTM, Hilden, Germany) following the manufacturer's protocol for DNA-isolation. MSI analysis was performed using five microsatellite markers (BAT26, BAT25, NR21, NR24, NR27) known to be quasimonomorphic, with low risk for polymorphisms in the Caucasian population, as previously described [8,9,37,40]. The difference in MSI markers used by us, and in the large endometrioid endometrial cancer study by Zigelboim et al. [44] was considerable: only BAT25 and BAT26 were the same. Markers NR21, NR24 and NR27 are sensitive for MSI detection as described elsewhere [8, 9,40]. The selected markers showed a high sensitivity for MSI detection without the need for matching with patient's normal DNA. The primer sequences are listed in Table 2 and primers were labelled with either FAM or HEX fluorescent dyes. PCR-amplification was performed under standard conditions. The reactions were incubated at 95°C for five minutes followed by 35 cycles of 95°C, 56°C and 72°C for one minute each. The product length was analysed using a sequencer (GeneAnalyzerTM 3130XL, Applied Biosystems) with the GeneMapTM software. MSI in any marker was visualized as changes in the product length (Fig. 1). Instability in $\geq 40\%$ (≥ 2 of 5) of the markers was classified as high-frequency microsatellite instability (MSI-H), in 1 of 5 markers as low-frequency (MSI-L), and in no markers as microsatellite stable (MSS). In line with other studies, MSI-L were grouped together with MSS cases for most analyses.

2.3. Statistical analysis

The quality of the database input data was controlled by checking descriptive statistics and cross tables for all patients, to trace unlikely values or combinations. We analyzed the following endpoints: alive with local or distant recurrence ($n = 6$), and dead of endometrial cancer ($n = 28$). As recurrence and dead of endometrial cancer gave the same results, the recurrence cases and dead of endometrial cancer cases were grouped together and further described. Patients with death from other non-endometrial cancer related

Table 2
Primers used for microsatellite analysis

Marker	Gene	Primer sequence	Gene bank number	Average PCR product size (bp)
BAT26	<i>hMSH2</i>	F: 5'- TGA CTA CTT TTG ACT TCA GCC -'3 R: 5'- AAC CAT TCA ACA TTT TTA ACC C -'3	U41210	120
BAT25	<i>c-kit</i>	F: 5'- TCG CCT CCA AGA ATG TAA GT -'3 R: 5'- TCT GCA TTT TAA CTA TGG CTC -'3	L04143	124
NR21	<i>SLC7A8</i>	F: 5'- GAG TCG CTG GCA CAG TTC TA -'3 R: 5'- CTG GTC ACT CGC GTT TAC AA -'3	NM_012244	109
NR24	<i>Zink-finger 2 (ZNF-2)</i>	F: 5'- GCT GAA TTT TAC CTC CTG AC -'3 R: 5'- ATT GTG CCA TTG CAT TCC AA -'3	X60152	131
NR27	<i>Inhibitor of apoptosis Protein-1 (MIHC)</i>	F: 5'- AAC CAT GCT TGC AAA CCA CT -'3 R: 5'- CGA TAA TAC TAG CAA TGA CC -'3	AF070674	87

Notes: *F* denotes forward primer sequence; *R* denotes reverse primer sequence. The fluorescent markers used were FAM for BAT26, NR24 and NR27, and HEX for BAT25 and NR21.

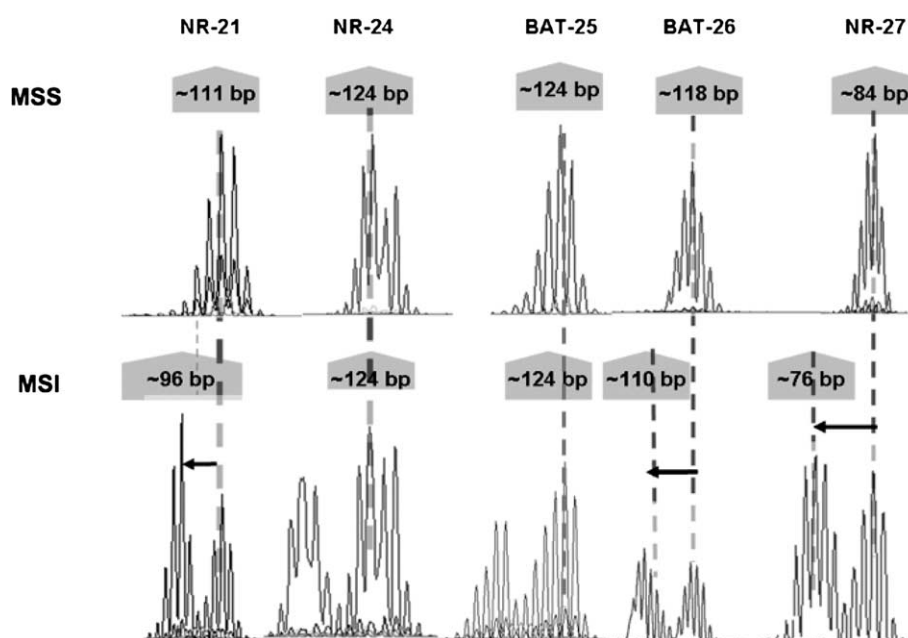


Fig. 1. MSI analysis electropherogram of the 5 markers used. Typical allelic profiles for the different markers. Top line shows microsatellite stable (MSS) tumors; bottom line shows tumors with microsatellite instability (MSI) displaying changes in product size (two peaks) with a shift, typically of about 10 bp length (bp denotes base pairs).

causes, or patients lost to follow-up were censored at the last known follow-up date as alive, no evidence of disease (ANED). Analyses were performed by SPSS version 15 (SPSS, Chicago, IL, USA). For age (a continuous variable) we used the median, tertiles and quartiles as thresholds, or the threshold with the objectively best sensitivity and specificity assessed by Receiver Operating Curve (ROC) analysis (MedCalc Software, Mariakerke, Belgium), for details of the ROC technique [22]. The two methods always pointed to the

same threshold which was used in further analyzes. The chi-square test was used to determine the relationship between MSI-status and the clinico-pathological risk factors. Univariate analysis was performed using the Kaplan–Meier method, and differences in survival were estimated by the Breslow and log-rank tests. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated for each feature. Multivariate survival analysis (Cox model) was used to assess the independent prognostic value of the different features.

3. Results

In the 273 FIGO stage 1–4 cases of endometrioid endometrial adenocarcinoma studied, the median age was 66 (range 32–94) years. With median follow-up of 61 months (range 1–209), 34 (12.5%) patients developed metastases.

Table 3 shows the correlation between MSI and the other variables. MSI-H is associated with high grade (grades 2 and 3), whereas grade 1 cancers more often are MSS or MSI-L.

Table 4 summarizes the univariate prognostic value of the features analysed for all FIGO stages. Age (≤ 68 vs. > 68), FIGO stage and grade had a prognostic value but MSI did not. For the FIGO stage 1 patients, grade (as grade 1 vs. grades 2 + 3) was not significant, neither were FIGO 1A, 1B or 1C, nor myometrium inva-

sion. MSS and MSI-L cancers (84% of all cases) had a good prognosis, whereas MSI-H cancers (16%) were associated with a worse survival, as shown by the survival curve (Fig. 2). The 5- and 10-year recurrence-free survival rates were 98% and 95%, respectively, in the MSS/MSI-L vs. 85% and 73%, respectively, in the MSI-H cancer patients. In the multivariate analysis, MSI had a prognostic value only in FIGO stage 1 cancers.

4. Discussion

In this population-based endometrioid endometrial cancer study MSI showed a prognostic value but only for FIGO stage 1 cancers. MSI is an objective marker and many studies found MSI to be a valuable and promising prognostic indicator in other types of cancer, especially gastric and colonic cancer. For endometrial cancer the results have been conflicting with as many studies showing prognostic value as not. A large multicenter study found that MSI-L/MSS vs. MSI-H was not of prognostic value [44]. We could confirm this for all FIGO stages analysed together. However, in the 2007 study no subgroup analysis on FIGO stage 1 cases was performed.

Another recent study of interest analysed early stage endometrioid cancers with the same panel of markers as we did (these markers have been proven to be more reliable than the ones used in other series [8,9,42]). The study concluded on a negative prognostic value of MSI-H cases, but in contrast to our study all of their cases were radiation-treated [6]. MSI-L and MSI-H were found in 11% and 16% of the cancers analyzed (totalling 27%). Of 17 previous studies on MSI in endometrial cancer, the prevalence of MSI widely varied from 9% to 45% [1,4,5,7,10,12,16,17,19,25,26,28,29,32,33,42,44] (Table 1). The table also illustrates the enormous variation in the numbers of patients, stages, histotypes and molecular techniques used in the different studies. MSI is also found in atypical hyperplasia [18], indicating that MSI is an early event in a subset of endometrial cancer. Late stage endometrial cancers are more likely to have accumulated many genetic changes, this is supported by our findings of an increasing MSI-H rate in FIGO 2 cancers of 27% and in FIGO 3 cancers 33%. For FIGO 4 there were lacking data for 4 out of 10 cases, and only 1 case were MSI-H (Table 3). It is understandable that the value of MSI (an early stage prognostic marker) is limited in late stage cancers. The use by other studies of both

Table 3

Associations between MSI and parameters analysed in endometrial endometrioid cancer. MSS and MSI-L were classified as MSI-negative (MSI-), MSI-H as MSI-positive (MSI+)

Parameter	No. (%)		<i>p</i> -value ¹
	MSI-	MSI+	
<i>FIGO stage 1–4</i>			
Age <68 years	95 (85)	17 (15)	0.29
≥68 years	78 (79)	21 (21)	
FIGO 1	144 (84)	27 (16)	0.28
2	16 (73)	6 (27)	
3	8 (67)	4 (33)	
4	5 (83)	1 (17)	
Grade 1	84 (91)	8 (9)	0.006
2	63 (77)	19 (23)	
3	26 (70)	11 (30)	
<i>FIGO stage 1</i>			
Age <68 years	81 (86)	13 (14)	0.29
≥68 years	63 (82)	14 (18)	
FIGO stage 1			0.67
1a	22 (82)	5 (19)	
1b	93 (86)	15 (14)	
1c	29 (81)	7 (19)	
Myometrium Invasion			0.50
inner half	115 (85)	20 (15)	
outer half	29 (81)	7 (19)	
Grade 1	74 (90)	8 (10)	0.10
2	55 (80)	14 (20)	
3	15 (75)	5 (25)	
Grade 1	74 (90)	8 (10)	0.03
2 + 3	70 (79)	19 (21)	

Note: ¹*p* – probability of no difference.

Table 4
Survival data stratified for the different parameters analyzed

Parameters	Variable	Events/At risk (%)	<i>p</i> -value ¹ (log rank)	HR ²	95% CI ³
<i>FIGO stage 1–4</i>					
Age	≤68 years	10/149 (6.7)			
	>68 years	24/124 (19.4)	<0.0001	3.9	1.9–8.2
FIGO	1	14/224 (6.3)			
	2	7/27 (25.9)		6.1	2.4–15.2
	3	3/12 (25.0)		4.1	1.2–14.6
	4	10/10 (100.0)	<0.0001	67.4	27.7–170.0
FIGO grade	1	6/120 (5.0)			
	2	15/105 (14.3)			
	3	13/48 (27.1)	<0.0001	n.d. ⁴	n.d. ⁴
MSI	MSS	15/148 (10.1)			
	MSI-L	3/25 (12.0)		n.d. ⁴	n.d. ⁴
	MSI-H	7/38 (18.4)	0.16	n.d. ⁴	n.d. ⁴
MSI	MSS/MSI-L	18/173 (10.4)			
	MSI-H	7/38 (18.4)	0.06	n.d. ⁴	n.d. ⁴
<i>FIGO stage 1</i>					
Age (years)	≤68	4/126 (3.2)			
	>68	10/98 (10.2)	0.004	4.7	1.5–15.3
FIGO1	1a	1/53 (1.9)			
	1b	10/129 (7.8)		5.2	0.7–40.5
	1c	3/42 (7.1)	0.22	3.9	0.4–37.9
Myometrium invasion	inner half	11/182 (6.0)			
	outer half	3/42 (7.1)	0.94	n.d. ⁴	n.d. ⁴
FIGO grade	1	4/108 (3.7)			
	2	8/87 (9.2)			
	3	2/29 (6.9)	0.25	n.d. ⁴	n.d. ⁴
FIGO grade	1	4/108 (3.7)			
	2 + 3	10/116 (8.6)	0.09	n.d. ⁴	n.d. ⁴
MSI ⁵	MSS	6/125 (4.8)			
	MSI-L	0/19 (0)		n.d. ⁴	n.d. ⁴
	MSI-H	4/27 (14.8)	0.02	4.6	1.3–16.7
MSI ⁵	MSS/MSI-L	6/144 (4.2)			
	MSI-H	4/27 (14.8)	0.005	5.2	1.5–18.8

Notes: ¹*p* – probability of no difference; ²HR – hazard ratio; ³CI – confidence interval; ⁴n.d. – not done, not significant or divided by zero error; ⁵MSI – microsatellite instability; MSS – microsatellite stable; MSI-L – microsatellite instability at low frequency; MSI-H – microsatellite instability at high frequency.

types I and II cancers which follow different pathways is likely to further blur the evaluation of the prognostic value of MSI. We conclude therefore that one must be careful when attempting to draw any conclusions from these studies for the most frequent endometrial cancer: FIGO stage 1 endometrioid endometrial cancer.

Interestingly, the behaviour of endometrioid endometrial cancer according to MSI seems the opposite of that in colonic and gastric cancers, where MSI-H tumors have a better prognosis [34,36]. Chemotherapy is

widely used in these cancers, contrasting the habits in early stage endometrioid cancer. This raised the question whether MSI-H cancers may be especially sensitive for chemotherapy. If so, FIGO stage 1 endometrioid cancer patients with MSI-H may benefit from adjuvant chemotherapy. Chemotherapy data is unfortunately incomplete for our patient population.

The sharp increase of endometrial cancer incidence during the last few decades in the western world and increasingly in many young patients of childbearing

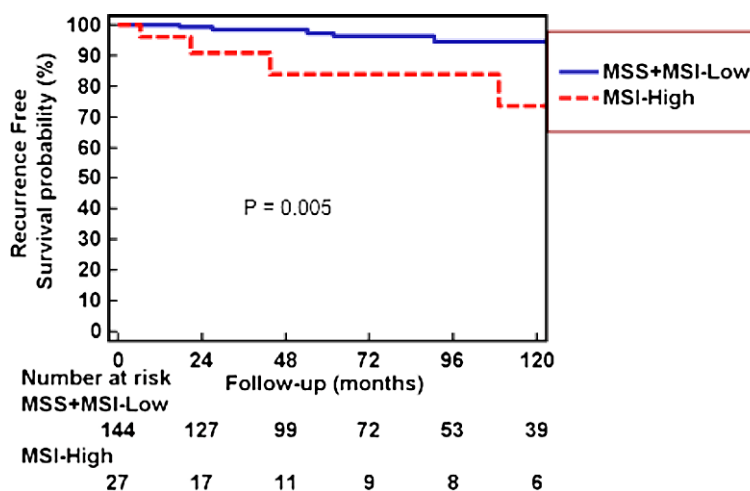


Fig. 2. Survival curve of the FIGO 1 endometrioid endometrial cancer according to MSI-status. (Colors are visible in the online version of the article; <http://dx.doi.org/10.3233/ACP-CLO-2010-0550>.)

age, raises the important point of fertility-sparing and ovary-saving surgery. Patients with obesity, diabetes or cardiovascular disease amongst others, also would benefit from less aggressive surgery such as vaginal hysterectomy and no lymphadenectomy. This of course requires reliable preoperative identification of low- and high risk patients. MSS/MSI-L status is shown here to be an adequate marker to identify endometrioid FIGO stage 1 cancers with a very low risk, while MSI-H identifies the small subgroup of aggressive cancers. This may be used to indicate radical surgery, radiotherapy and early start of postoperative adjuvant chemotherapy as suggested above.

The molecular causes and consequences of MSI in sporadic endometrial carcinomas have been less well studied. In sporadic colorectal cancers, MSI is associated with somatic hypermethylation of the promoter of the mismatch repair gene hMLH1 [11,35] as is the case in the great majority of sporadic endometrial carcinomas [14,21]. Furthermore, RASSF1A promoter is also frequently methylated in endometrial carcinoma and significantly associated with MSI [20,30]. APC promoter hypermethylation is correlated with MSI in endometrioid endometrial carcinomas [27]. Moreover, high frequency promoter methylation of P16, MGMT [13], and RARb2 [2], were found in endometrial carcinoma and lack of CDH13 promoter hypermethylation was prognostic [39].

Since promoter hypermethylation of certain genes appears to be an early and frequent event in endometrial carcinogenesis, this raises the question of what are the molecular interactions between a tendency for promoter hypermethylation and other genetic changes

in FIGO stage 1 endometrial endometrioid adenocarcinoma cases. Type I cancers often show K-ras mutations which are correlated with MSI [24]. We recently found that decreased P21 and survivin overexpression were prognostic [38]. Therefore, what is the prognostic value of combinations of promoter methylation, MSI and genetic changes in FIGO stage 1 endometrial endometrioid adenocarcinoma cases?

Our population-based endometrioid FIGO stage 1 endometrial cancer study on MSI is one of the largest with long and complete long follow up. We conclude that in FIGO stage 1 endometrial endometrioid adenocarcinoma cases, MSI assessed with highly sensitive pentaplex polymerase chain reaction has independent prognostic value.

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