TREATMENT RESULTS AND MICROSATELLITE INSTABILITY IN ENDOMETRIAL CANCER PATIENTS OF DIFFERENT AGE GROUPS

S.M. Kartashov, E.M. Oleshko, R.I. Musayev

Kharkiv Medical Academy of Postgraduate Education

Summary. In 342 patients aged 30 – 80 with stage I – IV endometrial cancer (EC) occurrence of microsatellite instability (MSI) in tumour tissue and blood serum was researched by means of the polymerase chain reaction method. The data obtained provide evidence of the distinct correlation between the MSI occurrence both in tumour and blood serum and the age of EC patients. MSI occurrence in tumours of EC patients is most frequent for the age period from 41 to 60. The 3-year progression-free survival is dependent on age and MSI occurrence. The recurrence rate increases proportionally to the age of patients and occurrence of microsatellite disorders.

Key words: endometrial cancer, microsatellite instability, age, survival.

Introduction

In terms of endometrial (EC) the prognosis and survival of patients depend largely on the disease stage and pathomorphological study results allowing to individualize treatment. Dismal prognosis factors significantly affecting long-term treatment results of EC patients comprise disease stage, depth of myometrial invasion, tumour differentiation and size, presence of lymphogenic metastasis, tumour emboli in the myometrial blood and lymph vessels, tumour cells in abdominal lavage [5, 8]. Achievements of genetics and molecular biology of the recent decades have provided a tremendous contribution to the understanding of EC nature and progression.

Literature data indicate that with age humans develop an increasing number of genetic disorders. Besides, the age impacts not only contraction but also the course of many illnesses, including oncologic diseases. [9]. One of the genomic

disorders revealed in endometrial carcinoma cases implies changes in the deoxyribonucleic acid (DNA) repetitive sequences, the so-called microsatellites, which is the microsatellite instability phenomenon (MSI) – the unpaired DNA bases reparation defect [3]. These disorders represent different damage of tumour suppressor genes: MSH2, MSH3, MSH6, MLH1, PMS2 [1, 2, 7].

Thus, the MSI study would contribute to clarifying EC molecular (genetic) features and progression.

Study objective – to estimate MSI frequency and progression-free survival in patients with EC of different age groups

Materials and methods

Clinical studies involved 342 patients with stage I – IV endometrial cancer (EC) with ER I - IV stages (T1a-3вN0-1M0-1). 275 of the patients had endometrioid cancer, whereas 67 had been diagnosed with non-endometrioid EC forms. The age of female patients varied from 30 to 80. The diagnosis was verified by means of pathomorphological study. In all patients occurrence of microsatellite instability (MSI) in tumour tissue and blood serum was researched by means of the polymerase chain reaction method using microsatellite sequence primers (BAT-25 and BAT-26) [4, 6]. The studies were carried out at *Virola* laboratory at Kharkiv Medical Academy of Postgraduate Education. The obtained digital study results were processed by means of conventional variation statistics methods using the χ^2 criterion.

Results and discussion thereof

In consideration of the age factor the following was established (Table 1): MSI+ tumour frequency shows a distinct pattern by increasing during perimenopausal period (55.1% of cases involving patients aged 41 – 50 and 57.1% of cases with those aged 51 – 60) and decreasing for the age periods 61 – 70 and 71 – 80, i.e. in postmenopause.

Table 1

Patients grouping by age and MSI occurrence

Age	MSI+ tumour tissue abs./ %	MSI+ blood serum abs./ %
1) 30 – 40 n=23	3 13.0±7.0%**[2,3]	-
2) 41 – 50 n=69	38 55.1±6.0%**[1,4,5]	11 15.9±4.4%**[4,5]
3) 51 – 60 n=91	52 57.1±5.2%**[1,4,5]	19 20.9±4.3%**[4,5]
4) 61 – 70 n=102	16 15.7±3.6%**[2,3]	5 4.9±2.1%**[2,3]
5) 71 – 80 n=57	6 10.5±4.1%**[2,3]	2 3.5±2.4%**[2,3]

Note. **p<0.01 difference is statistically significant between groups.

The peak age for MSI occurrence in blood serum varies from 51 to 60. With further aging of women MSI occurrence frequency decreases. The data obtained provide evidence of the distinct correlation between the MSI occurrence both in tumour and blood serum and the age of EC patients. Probably, hormonal status of women which changes with age also offers influence on the established pattern. Significant increase in the number of microsatellite disorders is observed during perimenopause period. Exactly at this age the hyperproliferative processes in the endometrium are most frequent, providing background for the development of highly- and moderately differentiated EC forms. Lower occurrence frequency of MSI in women at a young age can, in our view, be observed due to the same factors, i.e. lower number of hormonal and metabolic disorders as well as endometrial hyperplasia. In postmenopausal women MSI is rarely observed, although the overall number of genetic disorders increases with age. The data obtained suggest possible correlation between age-related and hormonal disorders, hyperplastic process and EC, since during postmenopausal period carcinoma often develops from the atrophic endometrium.

We have analyzed the 3-year progression-free survival of EC patients depending on the age period of women and MSI occurrence (Table 2).

Table 2

3-year progression-free survival frequency depending on the age of EC patients

Age	MSI+ tumour tissue	MSI- tumour tissue (comparison group)
1) 30 – 40 n=23	3 100% n=3	20 100% n=20
2) 41 – 50 n=69	33 86.8±5.5%**4,5 n=38	31 100% n=31
3) 51 – 60 n=91	42 80.8±5.5%#3 n=52	37 94.9±3.5%**5#3 n=39
4) 61 – 70 n=102	9 56.3±12.4%**2#4 n=16	74 86.0±3.7%**5#4 n=86
5) 71 – 80 n=57	3 50.0±20.4%**2 n=6	38 74.5±6.1%**3,4 n=51
6) Total n=342	90 78.3±3.8%#6 n=115	200 88.1±2.1%#6 n=227

Note. ** $p<0.01$, # $p<0.01$ difference is statistically significant between groups.

According to the data obtained, the treatment results of EC patients aged 30 – 40 were the best, whereas none of the analyzed cases implied recurrence of the disease. The fact of recurrence absence was also prompted by a small number of patients under observation in this age group, thus not allowing to draw a general conclusion as to the tumour MSI phenotype impact on treatment results of EC patients in this age group.

As regards the age period from 41 to 50, EC occurs quite frequently and, therefore, the number of patients under observation was higher. The treatment results of patients in this group correlated with microsatellite disorders. Thus, cases of recurrence involved only the patients with genotype disorders under the study, and were not observed in patients with MSI-negative tumour phenotype. It should be noted that differences in the treatment results were statistically significant (80.8 ± 5.5% and 100.0%, respectively, $p <0.01$).

A group of patients aged 51 – 60 was one of the largest, which increased reliability of the results obtained. As seen from the provided data the progression-free survival significantly depended on the MSI tumour phenotype and was higher among patients without microsatellite disorders (94.9 ± 3.5% and 80.8 ± 5.5% to the groups, $p < 0.01$).

The peak of EC occurrence can be observed at the age interval from 61 to 70. Regarding our study, this group was the largest, whereas the treatment results depended on MSI tumour phenotype. In particular, microsatellite disorders in the patients were associated with significant reduction in 3-year progression-free survival (56.3 ± 12.4%) as compared to the patients without similar genotype disorders (86.0 ± 3.7%).

The group of the most elderly patients with endometrial carcinoma in terms of our study consisted of patients aged 71 – 80. It should be noted that the number of such patients exceeded that of patients aged 31 – 40 more than twice. The survival rates of the most elderly patients also depended on the occurrence of the DNA genes reparation disorders under the study. According to our data, the 3-year progression-free survival was 1.5 times higher in the group of patients without microsatellite disorders (74.5 ± 6.1% compared to 50.0 ± 20.4%, $p = 0.168$).

By analyzing survival rates in general, regardless of the age of patients and taking into account only the MSI factor, it should be noted that during the 3-year observation period the recurrence rate was significantly higher in patients with MSI+ tumour phenotype.

Thus, our analysis of the 3-year progression-free survival of EC patients depending on the age period of women and MSI occurrence showed correlation with the criteria analyzed. The data obtained indicate better survival rates in younger patients. With increasing age of the EC patients the recurrence rate also increased, whereas this trend was observed regardless of microsatellite disorders present or not. However, our main objective was to study the MSI tumour phenotype effect on the treatment results. It has been established that only in young patients (aged 31 – 40) no MSI influence on survival is observed. This distinction

may be caused by both small number of patients under observation and peculiarities of the EC course in patients with DNA genes reparation disorders. Apparently, at young age other genetic factors also affecting DNA reparation are more pronounced and allow compensating microsatellite disorders in patients. After the age of 40 the survival rates of patients significantly depend on MSI tumour phenotype. In particular, this type of genetic disorders occurrence in patients is accompanied by the treatment results deterioration. At that, it should be noted that regarding age periods 41 – 50 and 51 – 60 the recurrence frequency in patients with microsatellite disorders was 1.2 times higher, whereas regarding age periods 61 – 70 and 71 – 80 it was higher by 1.5 times. Therefore, with increasing age of the patients the MSI effect on survival also increases. This may be related to reduction of the body compensation abilities and development of other genetic disorders affecting DNA reparation and, eventually, the survival of patients.

Conclusions

1. Microsatellite disorders in tumours of EC patients are most common for the age period of 41 – 60.

2. MSI+ tumour phenotype in patients after the age of 40 is accompanied by the treatment results deterioration.

3. MSI tumour status of EC patients can be used as an additional disease course prognostic factor.

References

1. *Abbaszadegan M.R., Asadzadeh Aghdayi H., Rastin F. et. al.* (2009). Microsatellite Instability in Young Women with Endometrioid type Endometrial Cancer // Iranian J. Publ. Health. V. 38. № 3. P. 24–30.

2. *Bilbao C., Ramirez R., Rodriguez G. et. al*. (2010). Double strand break repair components are frequent targets of microsatellite instability in endometrial cancer // European Journal of Cancer Prevention. V. 46. № 15. P. 2821–2827.

3. *Bischoff J., Ignatov A., Semczuk A. et al.* (2012). hMLH1 promoter hypermethylation and MSI status in human endometrial carcinomas with and without metastases // Clin. Exp. Metastasis. № 29 (8). P. 889–900.

4. *Grady William M.* (2004). Genomic instability and colon cancer // Cancer and metastasis reviews. V. 23. № 1–2. P. 11–27.

5. *Nalbandyan A.V., Kuznetsov V.V., Nechushkina V.M.* (2006). Long-term treatment results of uterine cancer patients with regional lymph node metastases // Bulletin of N.N. Blokhin Russian Cancer Research Centre. V. 17. No. 4. P. 38–41.

6. *Shia Jinru, Black Destin, Hummer Amanda J. et. al.* (2008). Routinely assessed morphological features correlate with microsatellite instability status in endometrial cancer // Human Pathology. V. 39. № 1. P. 116–125.

7. *Soliman Pamela T., Lu Karen* (2007). Endometrial cancer associated with defective DNA mismatch repair // Obstetrics and Gynecology Clinics of North America. V. 34. № 4. P. 701–715.

8. *Steinbakk A., Malpica A., Slewa A. et al.* (2011). High frequency microsatellite instability has a prognostic value in endometrial endometrioid adenocarcinoma, but only in FIGO stage 1 cases // Cell. Oncol. (Dordr.). № 34 (5). P. 457–465.

9. *Zauber N.P., Denehy T.R., Taylor R.R. et al.* (2010). Microsatellite instability and DNA methylation of endometrial tumors and clinical features in young women compared with older women // Int. J. Gynecol. Cancer. № 20 (9). P. 1549–1556.