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Original Research

Increased incidence of advanced stage endometrial cancer: a retrospective analysis of different clinical approaches and tumour biology

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Summary

Introduction: An increasing percentage of advanced FIGO Stage has been observed among endometrial cancer patients referred to this department within the last five years. During the same time period, the diagnostic method used changed from D&C to office hysteroscopy (HSC) with a prolongation of waiting times for biopsy and surgery. The authors analyzed potential reasons for increased percentage of advanced stage disease. *Materials and Methods:* 499 consecutive new endometrial cancer patients were included from 2005 to 2015. The authors analyzed characteristics of the, diagnostic method, waiting times for biopsy and surgery, occurrence, duration of abnormal uterine bleeding (AUB), and hormonal treatment (gestagen) for AUB. A comparison between FIGO Stage I *vs.* II or more was performed. *Results:* The increase in advanced FIGO Stage disease was significant. Characteristics other than stage did not significantly change. The duration of AUB was the same. Gestagen for AUB was used almost three-fold more often during the last two years. Comparison between FIGO Stage I *vs.* II or more showed the stage was solely associated with tumor biology. *Conclusions:* The FIGO Stage of the disease was associated with more aggressive tumours whereas the diagnostic method, prolonged waiting times for biopsy and surgery, and a more conservative approach to AUB or several years of history of AUB were not associated with advanced disease.

Key words: Endometrial carcinoma; FIGO staging; Hysteroscopy; Dilatation and curettage; Time to diagnosis.

Introduction

Endometrial cancer is the most common female genital tract malignancy in developed countries with the average incidence of 30 per 100,000 [1-3]. Around 75% of patients present with localized disease, FIGO Stage I, and approximately 80% of endometrial cancers are of endometrioid histology, low tumour grade, and are estrogen-responsive. For early stage disease, prognosis is excellent with five-year survival rates of 95% [1, 2, 4].

The FIGO staging system is used routinely and worldwide for the description of the disease spread at the time of diagnosis. The FIGO stage of the disease, with the histological type, grade, and myometrial invasion, is the main known prognostic factor, with a five-year survival rates of a solid 80% for FIGO Stage III and 40% for Stage IV disease [2].

The main symptom of endometrial cancer is abnormal uterine bleeding (AUB), mostly postmenopausal bleeding, and occurring in as many as 75-90% of patients [5, 6]. The diagnosis is usually made by way of endometrial biopsy. Routinely and historically in Slovenia, Pipelle sampling of the endometrium was never used, and instead the main diagnostic tool was dilatation and curettage (D&C). At the present institution, D&C was almost completely replaced by office hysteroscopic biopsy (HSC) during the last ten to 15 years. Due to the introduction of HSC endometrial biopsy, the organization of patients' visits for HSC at the present institution led to a prolongation of waiting times for endometrial biopsy, compared to D&C.

In the years 2012, 2013, and 2014 the authors noticed a rise in FIGO stages among patients who were referred to this department for endometrial cancer treatment. Hence they decided to conduct a retrospective analysis to evaluate whether more advanced FIGO stages are associated with the biological characteristics of the tumour, changes in the method, and organization of the endometrial biopsy with prolongation of waiting times or, with a more conservative approach to AUB in the past ten years, between 2005 and 2015.

Materials and Methods

The authors retrospectively analyzed all consecutive new patients with endometrial cancer who were treated at the Department for Gynecologic and Breast Oncology at University Medical Centre Maribor from January 1st, 2005 until December 31st, 2015. From the medical records, the authors analyzed clinical and biological characteristics of the tumour (stage, grade, histological

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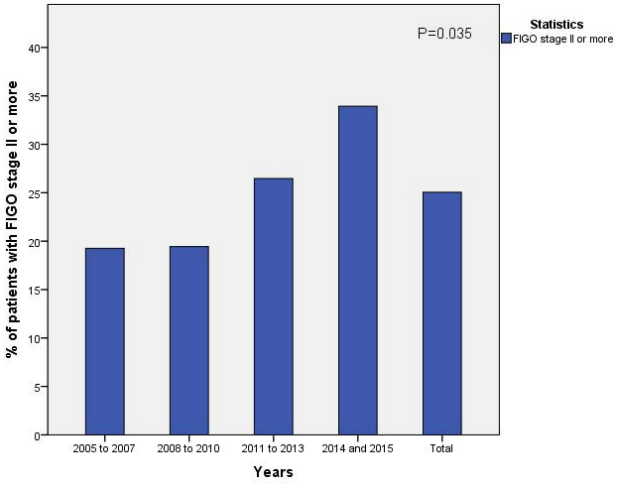

Figure 1. — FIGO Stage II or greater over the last ten years.

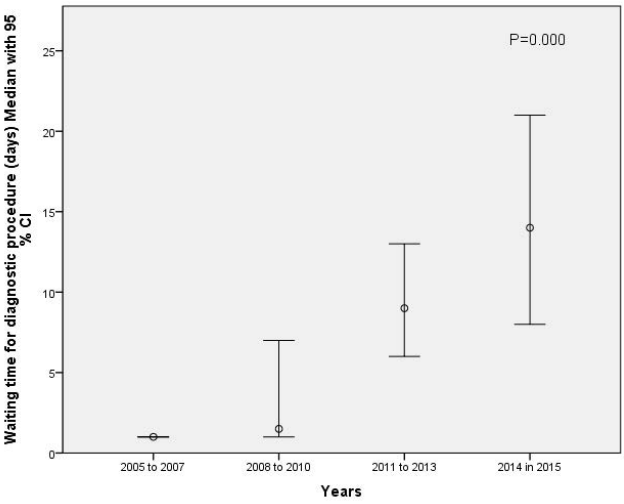

Figure 2. — Changes in waiting times for diagnostic procedure over the last ten years (median value with 95 % CI).

Table 1. — *Distribution of histologic type, tumour grade, myometrial invasion, and LVI over the last ten years.*

	Years				
	2005-2007	2008-2010	2011-2013	2014 and 2015	*p* value
Non-endometrioid type	17/109 (15.6 %)	23/108 (21.3%)	27/170 (15.9 %)	18/112 (16.1%)	0.619
Grade 3	18/109 (16.5%)	19/107 (17.8 %)	32/168 (19.0 %)	23/110 (20.9 %)	0.856
Deep myometrial invasion	46/109 (42.2 %)	30/103 (29.1%)	60/161 (37.7 %)	46/107 (43.0 %)	0.143
LVI	20/108 (18.5 %)	16/103 (15.5 %)	26/162 (16.0 %)	30/108 (27.8 %)	0.069

LVSI: lymphovascular space invasion.

Table 2. — *Occurrence and duration of abnormal uterine bleeding over the last ten years.*

		Years				
		2005-2007	2008-2010	2011-2013	2014-2015	*p*
Abnormal uterine bleeding	No symptoms	22/109 (20.2%)	18/108 (16.7%)	45/170 (26.5%)	25/111 (22.5%)	0.260
	Up to 1 month	53/109 (48.6%)	48/108 (44.4%)	52/170 (30.6%)	46/111 (41.4%)	
	Up to 6 months	20/109 (18.3%)	24/108 (22.2%)	48/170 (28.2%)	26/111 (23.4%)	
	Up to 1 year	7/109 (6.4 %)	9/108 (8.3%)	9/170 (5.3%)	5/111 (4.5%)	
	More than 1 year	7/109 (6.4%)	9/108 (8.3%)	16/170 (9.4%)	9/111 (8.1%)	

type, myometrial invasion, lymphovascular space invasion: LVSI), occurrence and duration of AUB, gestagen therapy performed, diagnostic procedures used and waiting times for the diagnosis and the surgical treatment. A comparison was made over time and between patients with FIGO Stage I *vs.* II and more. All FIGO stages were converted to the last FIGO version for endometrial cancer from 2010.

There were missing data for not more than 5% for each variable, except for the time from referral to biopsy for patients who were not diagnosed at this institution (15% of missing data among 79 patients).

The comparison of categorical variables was performed with a chi-square test and for continuous variables with non-parametric tests, except for the age of the patients, where *t*-test was used. The authors present the results as fractions and percentages. The multinominal regression model was performed to find the association of different variables with more advanced FIGO Stage II or more disease.

All the patients that were treated at this department signed the institutional form allowing the authors to retrospectively analyze their anonymous clinical data. SPSS 20.0 was used and a p value of < 0.05 was set as statistically significant.

Results

All 499 consecutive new endometrial cancer patients from 2005 up to 2015 were analyzed. The mean age of the patients was 66.3 ± 11.2 (from 34 to 89) years. Most of the patients [374/491 (76.2 %)] had FIGO Stage I disease, of endometrioid type [414/499, (83.0 %)], grade 1 or 2 [402/494, (81.4 %)], with no LVSI [389/481, (80.9 %)]. The percentage of advanced disease (FIGO Stage II or more) increased significantly through the years (Figure 1). The distribution of histologic type, grade, myometrial invasion, and LVSI did not differ through the years (Table 1).

Table 3. — *Comparison between FIGO Stage I vs. FIGO Stage II or more disease in terms of biological characteristics, diagnostic method, waiting times, symptoms, and hormone therapy for abnormal uterine bleeding (AUB).*

	FIGO Stage I disease	FIGO Stage II or more	*p* value
Histological type	49/374	36/125	0.000
% of patients with non-endometrioid type	13.1%	28.8%	
Tumour grade	48/373	44/121	0.000
% of patients with grade 3 disease	12.9%	36.4 %	
LVSI	44/370	48/111	0.000
% of patients with LVSI	11.9 %	43.2%	
Myometrial invasion	110/369	72/111	0.000
% of patients with deep invasion	29.8%	64.9%	
Age	65.1±11.0	69.7±11.1	0.000
D&C	170/374 (45.5%)	63/125 (50.4%)	0.337
	Twice or more 8.0%	Twice or more 5.8%	0.596
HSC	217/374 (58.0%)	58/125 (46.4%)	0.024
	Twice or more 13.6%	Twice or more 6.4%	0.117
Average waiting time for the diagnostic procedure	21.6 ± 36.4 5.5 (1-242)	15.6±33.6 6.0 (1-270)	0.976
Waiting for diagnostic procedure more than 30 days	138/374 (36.9%)	36/125 (28.8%)	0.100
Average waiting time for surgery	31.5±19.7 29.5 (0-241)	28.4±17.1 30.0 (0-108)	0.341
Waiting for surgery more than 35 days	120/374 (32.1%)	51/125 (40.8%)	0.076
Gestagen for AUB	26/336 (7.7%)	8/118 (6.8%)	0.583
Symptomless	86/373 (23.1%)	24/125 (19.2%)	0.629
AUB several years	29/373 (7.8%)	12/125 (9.6%)	0.629

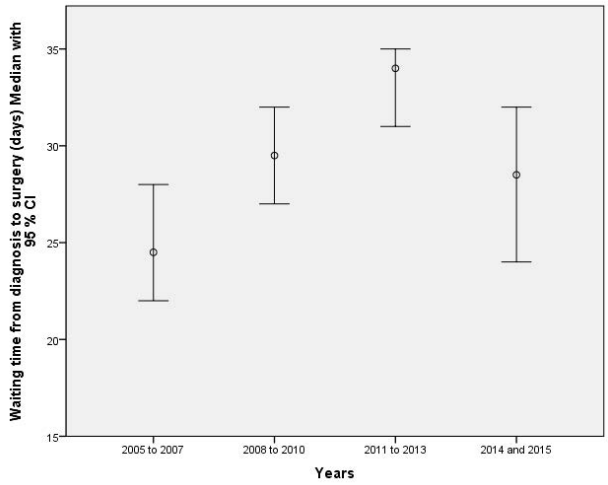

Figure 3. — Median waiting times from receiving the histologic report from endometrial biopsy to surgery with 95% CI.

The occurrence and duration of AUB did not change throughout the years (Table 2). The use of gestagen for AUB in the past increased from 5/95 (5.2%) of patients in 2005-2007 to 16/108 (14.8%) in 2014/15, $p = 0.002$ and 420/499 (84.2%) patients had the diagnostic procedure at thus institution. In total, 275 HSC and 233 D&Cs were performed, with 44 patients receiving both procedures, whereas 26/109 (23.9%) of patients had HSC as the main diagnostic procedure in the first three years analyzed (2005 until 2007) and as many as 81/112 (72.3%) had HSC in the last two years (2014 and 2015). Among patients having only HSC biopsies, 44/231 (12.1%) required more than one procedure to confirm a diagnosis, whereas 14/189 (7.4%) of those having D&C had the procedure performed twice or more. HSC was not associated with deep myometrial invasion [100/266 (37.6%) *vs.* 82/214 (38.3 %), $p = 0.871$], LVSI [51/266 (19.2% *vs.* 41/215 (19.1 %), $p = 0.977$] nor with positive abdominal cytology [46/260 (17.7%) *vs.* 40/214 (18.7 %), $p = 0.779$] when comparing patients having or not having HSC. The median times with 95% CI of waiting times for the biopsy and for the surgery are shown in Figures 2 and 3 and 25/109 (22.9%) of patients waited for a diagnostic procedure for more than 30 days in 2005-2007 *vs.* 48/112 (42.9%) in 2014/15, $p = 0.00$; the percentage increased gradually during the analyzed years; 20/109 (18.3%) patients had surgery 35 or more days after receiving the histological report of the biopsy in 2005-2007, whereas in 2014/15 the figure was 38/112 (33.9 %). The percentage dropped from 77/170 (45.3%) in 2011-2013, $p = 0.00$. Twenty patients were not surgically treated at all, for advanced disease or comorbidities.

Table 3 represents the comparison of biological characteristics, diagnostic procedures, waiting times, symptoms, and gestagen usage of the FIGO Stage I disease with the more advanced disease (FIGO Stage II or more).

According to multinominal logistic regression model the only predictive variables for not having FIGO Stage II or more disease were tumour grade 1 or 2 (OR 0.401, $P = 0.003$), no myometrial invasion (OR 0.329, $P = 0.000$), and absence of LVSI (OR 0.304, $p = 0.000$); Goodness-of-Fit (chi-square 4.379, $p = 0.957$).

Discussion

According to the present results, the main factors for advanced FIGO Stage disease remain the biological characteristics of the tumour and not the observed change of diagnostic procedure or prolongation of waiting times.

The present results show the rising incidence of endometrial cancer in the present region, as is seen in the Slovenian national cancer registry and worldwide [1, 2]. However, the authors also confirm an increasing incidence of more advanced disease, with as many as 33.9% of patients having FIGO Stage II or greater in 2014/15.

When analyzing different possible factors influencing the increase in the FIGO Stage, the authors first evaluated the distribution of biological characteristics of the tumour through the same years. As is presented in Table 1, the distribution of prognostically worse biologic characteristics did not change during the analyzed years, although there was a non-statistically significant increase in tumours with LVSI. Secondly, the authors hypothesized that perhaps a more conservative approach to AUB, with using gestagen and ultrasound follow up without endometrial biopsy, might be causing a delay in the diagnosis or treatment. The authors confirmed that approximately three-fold more gestagens were used for AUB in years 2014 and 2015 in patients who later had endometrial cancer diagnosed when compared with the first analyzed years of 2005-2007. However, as shown later, the increase of gestagen use was not associated with more advanced stages.

The occurrence and the duration of past AUB did not change during the last ten years. Approximately 20% of the present patients were without AUB in their history, and the occurrence and duration of the bleeding did not change through the years. These results are similar to those already published [5, 6].

As stated the HSC endometrial biopsy mostly replaced D&C at the present institution in the last ten years. D&C was performed in case of heavy AUB or for complete cervical stenosis or, for the patients' anxiety and pain. Since the introduction of office HSC, with more expensive equipment and the historical organization of work, the waiting times for endometrial biopsy were significantly prolonged, reaching a median value of 14 (mean 31.1) days in 2014/15 compared with a median time of one (mean 8.3) day in 2005-2007. In other words, 42.9% of patients waited for endometrial biopsy more than 30 days in 2014/15 compared to 22.9% of patients in 2005-2007. Historically, the patients having AUB were referred for D&C. There were no waiting times for D&C and the patients had the procedure usually the same day or few days after referral. After introducing HSC, the method was performed for several years by only one gynaecologist, who introduced the method. Since the high number of referrals and limited number of HSC performed, the prolongation of waiting time for diagnostic procedure occurred. The organizational scheme did not follow the improvement and changes in diagnostic procedures. However, HSC as a diagnostic tool per se was not, according to our results, associated with tumour deep myometrial invasion, LVSI or, positive cytology at the surgery (presented among results). Hence HSC should not be associated with worse prognostic factors seen with endometrial carcinoma. As was also shown in a meta-analysis of observational studies, there were no significant differences in the frequency of positive peritoneal cytology in women with endometrial cancer who had or had not undergone diagnostic HSC [7]. In addition, there is no known long-term survival detriment associated with pre-staging diagnostic HSC [8]. The present patients who had diagnostic HSC more frequently had two or more procedures done before receiving the definitive diagnosis compared with D&C, however, the difference was small (12 *vs.* 7%). The HSC was performed two or more times in 13% of FIGO Stage I patients, compared with 6% in those with more advanced disease, showing probably worse sensitivity of hysteroscopy for detecting diffuse early disease; this difference was not so evident in the D&C group, and was not statistically significant. HSC is known to improve the uterine cavity visualization and to aid the detection rate of focal lesions [9, 10]. However, one large study on 1,286 women found that the endometrial cancer was missed in 34.5% with the sensitivity of diagnostic HSC being only 65% [11].

With a rising incidence of endometrial cancer patients, the waiting time for the surgery was also significantly prolonged during the last ten years, with 33.9% patients that waited for surgery for 35 days or more in 2014/15 compared with 18.3 % of patients in 2005 to 2007, with the median time for surgery being 28.5 days in 2014/15 *vs.* 24.5 in 2005-2007.

After analyzing the variables during the past ten years the authors further compared all patients with early FIGO Stage I disease to those with advanced FIGO Stage II or more. The comparison shows that the only significant differences between them were the biological characteristics of the tumour, indicating that the advanced FIGO Stage was solely associated with prognostically worse non-endometrioid histologic type, grade 3 tumours, with deep myometrial invasion and presence of LVSI. The FIGO Stage II or greater patients were also significantly older, which was associated with the known fact that prognostically worse type II endometrial cancer is more prevalent among elderly patients. Patients did not differ regarding the occurrence and duration of AUB. Gestagen used in the past, the diagnostic tool used, and the waiting time for the endometrial biopsy and surgery, were all similar between the groups.

As can be seen from the present results, AUB did not occur in around 20% of patients, and the distribution of AUB and duration of AUB was not associated with FIGO

Stage. Interesting, even history of several years of AUB was not associated with more advanced disease at the time of diagnosis. Similar findings have already been published and there is no apparent association between AUB and prognosis of the disease [5, 6, 12]. In addition, despite the years-long duration of unopposed estrogen or tamoxifen use in postmenopausal women, -associated with a higher risk of endometrial cancer development - patients affected are similar in FIGO Stage distribution and histologic types to patients with no hormonal therapy and might have even less aggressive tumours [13–18]. The most common type I estrogen-responsive tumours have excellent prognosis progress slowly disease and the duration of AUB is not of clinical importance. Hence, the prolonged waiting times for a diagnostic procedure should not, and was not according to the present results, associated with more advanced disease. However, the prolonged waiting times for endometrial biopsy may be a quality indicator that should be improved. Although not necessarily associated with worse prognosis, the psychological impact of waiting for diagnosis with knowledge of possible malignant disease may represent a significant burden for the patients. That is why the British National Health System still recommends waiting times of 14 days for a diagnostic procedure when malignant disease is first suspected, a waiting time of 31 days from the decision to treat and treatment, and 62 days from first GP referral for suspected malignant disease to treatment [19]. The introduction of Pipelle endometrial sampling would present one possible solution, given the excellent results in terms of sensitivity compared to D&C, low costs, office settings, and no general or even local anesthesia [20, 21].

Conclusion

In conclusion, although there were significant changes in the diagnostic methods, prolonged waiting times for the endometrial sampling and higher use of gestagens for AUB in the last ten years, the present authors were not able to confirm that these changes attributed to the rising percentages of advanced FIGO Stage II or more disease. The main reason for the advanced disease remains the biology of the tumour, such as tumour grade, histologic type, myometrial invasion and, LVSI, as was already published [2]. The observed more advanced FIGO stage of the present endometrial cancer patients was probably associated with natural cycles and will hopefully drop in next few years.

The present analysis is retrospective and hence there were missing data present, although not for more than 5% of the patients for each variable. Future studies should be conducted especially for studying the biology of different endometrial malignancies with a focus on finding new biomarkers, clinical parameters, and precancerous lesions associated with more aggressive tumours for successful early detection or prevention of advanced disease.

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