Color Doppler assessment of blood flow in endometrial cancer

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Summary

Objective: To determine the location and intensity of angiogenesis as well as selected flow parameters by transvaginal color Doppler (TVCD) and to evaluate the relation of myometrial invasion, histological grading, lymph nodes, and omental and adnexal metastasis on blood flow characteristics in endometrial cancer.

Methods: Transvaginal colour Doppler and pulsed Doppler ultrasound were performed on 90 women with endometrial cancer. The degree of invasion as well as adnexal, omental, and pelvic lymph node metastasis was evaluated. Location of the blood vessels (peripheral, central, mixed) and vascular density as well as selected Doppler blood flow indices: PSV, RI of neoplastic infiltration was assessed.

Results: The median age of the 90 women was 63.3 ± 12.3 years (range 32 to 86 years); of these 92.2% were postmenopausal. Cancer concerned only the endometrium (E), with superficial (S) and deep infiltration (D) established in 14.4%, 45.6% and 40%, respectively. The histological maturity was as follows: G_1-17.6%, G_2-66.7%, G_3-16.6% of cases. Adnexal, omental and lymph node metastasis was found in 12.2%, 3.3% and 16.6%, respectively. Abnormal low impedance and high velocity flow (mean RI 0.38 ± 0.09, PSV 20.45 ± 9.6 cm/sec) were found in 88.9% of cases. In types E, S, D in 61.5%, 92.7% and 94.4%, respectively ($p = 0.003$). Differences in RI and PSV between groups with high and low vascular density were statistically significant ($p = 0.005$ and 0.001, respectively). In all cases peripheral and mixed vascularity were found more frequently ($p < 0.05$). A positive significant correlation between vascular density increase and surgicopathological stage of cancer was found more frequently ($p < 0.005$). There were significant differences in vascular density, Doppler blood flow indices and vascular location in each type of histological malignancy ($p < 0.05$). No significant differences in each flow parameter in hematogenous-adnexal/omental metastatic and non metastatic cases were found, whereas pelvic lymph node involvement and vascular density were shown to be statistically significant ($p < 0.02$). There were significant differences in vascular density in lymph-node positive cases whereas the remaining flow parameters did not differ.

Conclusions: These results suggest that TVCD evaluation of endometrial cancer is a reliable method for assessing endometrial angiogenesis. Our results indicate that blood flow rates correspond with increased angiogenesis in endometrial cancers, and might potentially be used as a good prediction factor for tumor progression and metastasis in affected women. Preoperative ultrasound examination should be seen as an important tool in the establishment of individualized treatment programs for women with endometrial cancer.

Key words: Doppler velocimetry; Endometrial cancer.

Introduction

Cancer of the endometrium is the fourth most common gynecologic malignancy and accounts for 6% of all cancers in women. It is a highly curable tumor. The 5-year survival rate is related to myometrial invasion, histological grading and lymph node or distant metastasis. Therefore these have an important impact on the natural history and treatment selection of this disease. Aditionally endometrial cancer has a relatively good prognosis, in part because hematogenous spread is rare and generally lymphatic metastasis occurs, but in only 15% of patients.

Angiogenesis is the growth of new blood vessels toward and within a tumor, and it has been shown that tumors do not grow beyond a size of 2 to 3 mm^3 unless they are able to recruit the growth of new capillaries from the existing vascular network [1]. It has been shown that angiogenesis may play an essential role in initial growth and invasion, and may be an important prognostic factor in several aggressive malignant tumors. However it needs to be determined if it regulates tumor behavior or is only an indicator of the growth and metastatic potential of a tumor [2].

Clinical studies have shown that the intensity of angiogenesis, expressed as microvessel density, predicts the probability of metastasis and survival in several malignancies like breast and prostate carcinoma [3].

Endometrial angiogenesis is likely to be involved in the pathogenesis of many diseases of the female reproductive tract from hence growth of endometrial cancer necessitates the dynamic remodeling of the vascular supply. It is considered to depend on prognostic factors, e.g. depth of invasion, histological grading or metastasis.

Many reports have investigated the role of transvaginal color Doppler (TVCD) in detection of tumoral neovascularization and blood flow characteristics to determine angiogenesis, which is necessary for growth and metastatic spread in endometrial cancers [4-6]. Today the sophisticated ultrasonic equipment enables large image magnification to be achieved. Moreover the application of "power Doppler" and ultrasound contrast agents considerably improve image quality. Therefore color Doppler ultrasonography permits visualization of the vasculature within the neoplastic infiltration in

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endometrial cancer, which is important in the estimation of the extensiveness of the neoplastic process [7].

The purpose of the study was to determine the location and intensity of angiogenesis as well as selected flow parameters by TVCD and to evaluate the relation of myometrial invasion, histological grading, lymph nodes, and omental and adnexal metastasis on the blood flow characteristics in endometrial cancer. Moreover, Doppler parameters were compared between cases with and without pelvic node involvement and adnexal/omental tumors.

Material and Methods

Transvaginal 2D, color Doppler and pulsed Doppler ultrasound were performed on 90 women with endometrial cancer established by histopathologic examination of the endometrial specimen acquired by D&C. The women underwent transabdominal and transvaginal ultrasonographic examination within eight days preceding curettage. The degree of invasion and uterine blood flow characteristics were evaluated preoperatively. Ultrasonographic findings were compared with the surgical staging and histopathology of the surgical specimen. The thickness of the endometrium was measured including both endometrial layers and any expansive process in the uterine cavity. Invasion of the endometrial carcinoma was assessed using Karlsson's coefficient of depth [5]. According to this, the type of infiltration was established: *type E* when cancer involved only the endometrium, i.e. when the junctional zone was preserved or there was a sharp tumor-myometrium interface with uniform thickening of the myometrium throughout the corpus; *type S* when infiltration was superficial - to half of the uterine muscle, i.e. when there was disruption of the junctional zone and faded irregular myometrial-endometrial interface; and *type D* with deep infiltration - over 50% of the uterine wall, i.e. when a heterogeneous area was visualized in the outer half of the myometrium. Additionally, neoplastic cervical involvement, adnexal and omental, as well as pelvic lymph node metastases were evaluated by TAS or TVS.

Vascularization of the uterus was visualized with the color Doppler technique and blood flow velocity waveforms were obtained by placing the Doppler gate over the colored areas and activating the pulsed Doppler function. The location of vascularity was assessed. Each Doppler examination included blood vessels situated inside the endometrium or visible endometrial tumors which were referred to as intraendometrial (central) and/or very close to the endometrial echo as subendometrial (peripheral) vascularisation. The peak systolic velocity (PSV) and the resistance index (RI) from blood flow waveforms of neoplastic infiltration were calculated. Three uniform consecutive heart beats were analyzed and the resulting values averaged. Intensity (density) of vasculature was also evaluated. Vascular density (v.ds.) was defined as "high" if ≥ 5 color vascular spaces were detectable for any given area and "low" when it was < 5.

The Siemens Sonoline Versa Pro with a 6.5-7.5 MHz linear transvaginal transducer with 50 Hz high-pass filter was used.

Final diagnosis was based on histologic examination of the hysterectomy specimen. The statistical tests used were the chi square (χ^2) test with continuity correction and Fisher's exact test. Two-tailed p values were given with 5% as the level of significance.

Results

The median age of the 90 women in the study was 63.3 ± 12.3 years (range 32 to 86 years). Of these seven (7.7%) patients were premenopausal and 83 (92.2%) postmenopausal. The median thickness of malignant endometrium was 19.5 ± 9.6 (range 7 to 54 mm). There were: 14.4% (13/90) of cases where cancer involved only the endometrium - *type E* - age 55.6 ± 13.4; 45.6% (41/90) with superficial infiltration of the uterine muscle - *type S* - age 62.2 ± 12.5; and 40% (36/90) with deep infiltration - *type D* - age 67.3 ± 10.7. In 22 cases the cervical canal was also involved, age 64.9 ± 12.7. The histological maturity (grading) of cancer was as follows: G_1 - 16.7% (15/90), G_2 - 66.7% (60/90) and G_3 - 16.6% (15/90) of cases. Histologically adnexal metastases were found in 12.2% (11/90); of these 3.3% (3/90) in the omentum. Lymph node metastases was affirmed in 16.6% (15/90) of cases.

In 80 of 90 patients (88.9%) with endometrial cancer, abnormal flow with low impedance and high velocity levels (mean RI 0.38 ± 0.09 and PSV 20.45 ± 9.6 cm/sec) was found within the endometrial echo or very close to it: in types E, S, D in 8/13 (61.5%), 38/41 (92.7%) and 34/36 (94.4%), respectively (rycl enzyme). Differences between E-S and E-D were statistically significant ($p = 0.003$), whereas between S and D they were not. No vascularity was stated in 5/13 (38.5%), 3/41 (7.3%) and 2/36 (5.6%) in types E, S and D, respectively ($p < 0.005$). Among 22 cases with neoplastic cervical canal involvement vascularity was seen in 21/22 (95.5% of cases); in 15/21 (71.4%) of high and in 6/21 (28.6%) of low vascular density (Table 3).

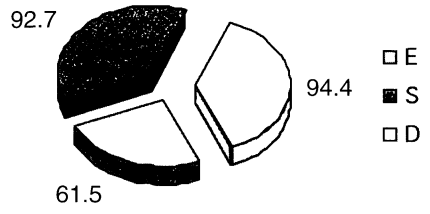

Figure 1. — **rycl** blood flow detected in each type of infiltration.

All cases with low vascular density had peripheral blood flow with a mean RI 0.43 ± 0.09, mean PSV 10.8 ± 5.61 cm/sec. However cases with high vascular density dominated mixed and peripheral types - 31/58 (53.4%) and 19/58 (32.8%), respectively, whereas a central location was established in 8/58 (13.8%) ($p < 0.05$). Indexes of flow were as follows: RI 0.38 ± 0.07, PSV 24.3 ± 10.31 cm/sec. Differences in values of RI and PSV between groups with high and low vascular density were statistically significant, p - 0.005 and 0.001, respectively. Central angiogenesis (inside endometrium) was found in 8/80 (10%), peripheral and mixed in 41/80 (51.3%) and 31/80 (38.8%), respectively. Statistically more frequently peripheral and mixed vascularisation were found ($p < 0.05$). High and low vascular density were seen in 58/80 (72.5%) and 22/80 (27.5%), respectively ($p = 0.0002$). No angiogenesis was found in 10/90 (11.1%) (Tables 1 and 2).

Table 1. — *Flow parameters with relation to vascular density.*

Blood flow indexes	Vascular density High n = 58	Low n = 22	p value
RI (mean ± SD)	0.38 ± 0.07	0.43 ± 0.09	0.005
PSV cm/sec. (mean ± SD)	24.26 ± 10.31	10.8 ± 5.61	0.001

Table 2. — *Vascular location with relation to its density in separate types of infiltration.*

Vascular density and location		E (n = 8) n %	S (n = 38) n %	D (n = 34) n %	Total n %
High (n = 58)	M	1 12.5%	15 39.5%	15 44.1%	31 53.4%
	C	–	3 7.9%	5 14.7%	8 13.8%
	P	2 25.0%	8 21.1%	9 26.5%	19 32.8%
Low (n = 22)	M	–	–	–	–
	C	–	–	–	–
	P	5 62.5%	12 31.6%	5 14.7%	22 100%

C: central; P: peripheral; M: mixed, i.e central & peripheral.

In type *E* a peripheral vascular location was found in seven (87.5%) and mixed in only one case (12.5%) - $p < 0.05$. In type *S* in 39.5% of cases it was mixed whereas in 52.7% peripheral type - NS. In type *D* mixed vasculature was seen in 44.1%, peripheral in 41.2% and central in 14.7% - (dominated mixed and peripheral vascularisation in equal proportions - NS).

In cases with high *v.ds.* mixed type was the majority - 31 (53.4%) while peripheral in 19 (32.8%) of cases - $p < 0.05$; In low *v.ds.* all cases showed only peripheral locations and there was no mixed nor central type.

Values for the resistance index and peak systolic velocity in malignant endometrium in each type of infiltration are shown in Table 3.

Table 3. — *Doppler parameters of flow with relation to the depth of invasion (surgicopathological stage).*

Flow parameter	E (n = 8)	S (n = 38)	D (n = 34)	p value
High v.ds.	3 37.5%	26 68.4%	29 85.3%	.009
Low v.ds.	5 62.5%	12 31.6%	5 14.7%	.002
RI (*mean* ± SD)	0.43 ± 0.11	0.39 ± 0.09	0.36 ± 0.07	.01
PSV cm/sec. (*mean* ± SD)	14.37 ± 7.92	21.28 ± 10.28	20.94 ± 9.27	.02

Table 4. — *Vascular density, Doppler parameters of flow and vascular location with relation to histological malignancy (grading).*

	G_1 n = 9	G_2 n = 56	G_3 n = 15	p value
High *v.ds.*	3 33.3%	42 *75.0%*	14 93.3%	.002
Low *v.ds.*	6 *66.7%*	14 25.0%	1 6.7%	.002
Peripheral	8 *88.9%*	27 *48.2%*	5 33.3%	.007
Central	–	5 8.90%	–	–
Mixed	1 11.1%	24 *42.9%*	10 *66.7%*	.007
RI (mean ± SD)	0.44 ± 0.05	0.38 ± 0.09	0.36 ± 0.08	.006
PSV cm/sec. (mean ± SD)	14.1 ± 8.31	20.23 ± 9.25	25.06 ± 9.55	.006

There was a positive correlation between increased vascular density and blood flow indices and surgicopathological stage ($p < 0.005$).

In G_1, G_2, G_3 vascularity was seen in 9/15 (60%), 56/60 (93.3%) and 15/15 (100%) of cases respectively, with significant differences ($p < 0.05$).

In G_1 peripheral type was more frequent whereas in G_3 mixed type was more frequent ($p < 0.05$).

No significant differences in each flow parameter in hematogenous-adnexal/omental metastatic and non metastatic cases was found.

Table 5. — *Doppler parameters of flow with relation to adnexal/omental (hematogenous) metastases.*

Flow parameter	Adnexal/omental metastases n = 11	No metastases n = 69	p value
High *v.ds.*	10* 90.9%	51 73.9%	NS
Low *v.ds.*	1** 9.1%	18 26.1%	–
RI (*mean* ± SD)	0.36 ± 0.08	0.38 ± 0.09	NS
PSV cm/sec. (*mean* ± SD)	23.0 ± 12.6	19.6 ± 9.0	NS

* mixed vasculature in 7 cases (70%); in 3 cases in type S, 4 in type D; peripheral in 3 cases (30%); in 2 cases: type S and in 2 cases type D.
** peripheral vasculature in 1 case (100%) in type S.

Table 6. — *Doppler parameters of flow with relation to lymph nodes (lymphatic) metastases.*

Flow parameter	Lymph nodes metastases n = 15	No metastases n = 65	p value
High *v.ds.*	14* 93.3%	45 69.2%	0.02
Low *v.ds.*	1** 6.7%	20 30.8%	–
RI (*mean* ± SD)	0.32 ± 0.06	0.39 ± 0.09	NS
PSV cm/sec. (mean ± SD)	23.35 ± 9.06	19.9 ± 9.6	NS

* mixed vascularization in 11 cases (78.6%); in one case type E, in three cases type S and in ten type D; peripherial vascularisation in three cases (21.4%) in D type.
** peripherial vascularisation in one case (100%) in S type.

Pelvic lymph node involvement and vascular density were shown to be statistically significant ($p < 0.02$). There were significant differences in vasculare density in lymph-node positive cases whereas remaining flow parameters did not differ.

Discussion

Angiogenesis plays a role in all neoplastic growth. In cervical intraepithelial neoplasia the punctuation and mosaicism seen at colposcopy represent angiogenesis. In inflammatory breast cancer, the rapid growth of new vessels leads to the characteristic inflamed appearance [8]. Primal microangiogenesis could be initiated even in premalignant processes. This vasculature differs from the normal larger diameter and scattered arrangement and its rapid growth permits dynamic growth of tumor. Hence this intensive vascularization (high angiogenic state) and tumor mass growth enables neoplastic cells to penetrate into the blood and lymphatic vessels and thus spread of the malignant process [9]. Moreover vascular density within the primary tumor has been reported to affect the clinical outcome of patients with a variety of gynecological malignancies such as carcinoma of the ovary, uterine corpus, etc. [10, 11]. Therefore it can be postulated that the number of pathologic microvessels and flow characteristics could be a potential predictor of more advanced disease, tumor progression and metastasis in affected women and therefore could have prognostic value in the expectation of recurrence. It has been confirmed in our study that blood flow rates correspond to increased angiogenesis in endometrial cancer.

Moreover, it has been shown that as vascular density increased, impedance of flow decreased while velocity of flow increased. Highly vascularized tumors displayed higher velocity blood flow with lower impedance com-

pared with those of low vascularisation (Table 1). Thanks to "mapping" the location and intensity of pathological angiogenesis can be established. Our data proved that in most cases peripheral and central vascularisation independent of type of infiltration and vascular density were seen. It also showed that typically in neoplastic infiltration, peripheral and mixed intense vascularity with a low impedance high velocity waveform is present (mean RI = 0.38 ± 0.09, PSV = 20.45 ± 9.6 cm/sec.). However it varies depending on the staging and grading of the neoplasm (Tables 1-4). Moreover, the presence of intense, scattered angiogenesis coexisted more often with lymph node metastases (Table 6).

Analysis of these characteristics enables additional information to be obtained which is helpful in specifying the diagnosis, qualification of prognosis and the choice of suitable treatment. A factor making of the foci of pathological vascularisation difficult is the relatively small volume of the tumor with respect to neoplastic lesions in other organs, eg. in the ovary. Therefore difficulties with visualization of pathologic microvessels and the heterogeneity of the tumor still remain a challenge in determining tumor vascular density.

Vascular density, impedance and flow velocity registered in endometrial cancer can indirectly characterize the type of the tumor. It appears that cells of lesions which show Doppler signaling are characterized as having greater proliferative activity and more intense growth through dynamic angiogenesis. Therefore the qualification of vascular density can be a precious prognostic indicator of neoplastic invasion with the ability of detecting metastases, among other locations, to the lymphatic nodes [12]. As our data show, patients with more neoplastic extention into the uterine muscle had significantly higher tumor vascularity (Table 3). Hence it can be judged that the ascertainment of distinct, more intense vascularisation with a low-resistance high-speed waveform inside the neoplastic lesion can be clinically significant in planning the treatment (surgery alone, radiotherapy, surgery and radiotherapy, chemotherapy) and prognosis in patients with endometrial cancer.

In his report Abulafia *et al.* [13] demonstrated that angiogenesis in endometrial cancer correlates with tumor grade and depth of invasion.

Our study shows that there were significant differences in the resistance index and velocity of flow between each type of neoplastic myometrial invasion. There was a positive correlation between increased vascular density and surgicopathological stage ($p < 0.005$).

Myometrial invasion is frequently a harbinger of lymph node involvement and distant metastases, and as our data show vascular characteristics changed significantly in association with myometrial invasion depth. Along with increased depth of invasion the number of cases with visible blood vessels also increases. Additionally as depth of neoplastic invasion and vascular density increases the location of angiogenesis changes from the peripheral to the mixed type. However cases with superficial neoplastic invasion (type E and S) and grade 1 or 3 have a low risk (5% to 9%) of nodal involvement, while patients with deep muscle invasion (type D) and high-grade tumors and/or intraperitoneal disease have a significant risk of nodal spread, with 20% to 60% to the pelvic nodes and 10% to 30% to the paraaortic nodes [14-16].

As our data showed high vascularity (vascular density, low impedance and high speed of flow) was more frequently diagnosed in the latter group of tumors.

Moreover the results reported in our study indicate that resistance levels were lower in cases of deep tumor invasion into the myometrium, where there was evidence of lymph node metastasis with presence of lymphovascular emboli in the histologic specimen.

Our data also showed that the pattern of vascularity and blood flow characteristics was modified by cancer grading and was dependent on the degree of cellular differentiation, i.e., location of vascularity depended on type of histological malignancy. There were significant differences (positive correlation) in vascular density, location of vascularization and flow parameters in neoplastic tissue between each histological grade of cancer. Grading increased in cases with visible blood vessels and also vascular density increased as the location of vascularity significantly changed from peripheral in G_1 to mixed in G_3. On the other hand resistance index values manifested a distinct decrease, and PSV a distinct increase with increasing histological malignancy of tumor.

Well-differentiated tumors which tend to limit their spread to the surface of the endometrium, showed low vascular density with relatively high impedance flow and low velocity: RI 0.44 ± 0.05 and PSV 14.1 ± 8.31 cm/sec., respectively.

In patients with poorly differentiated tumors, where myometrial invasion occurs much more frequently, the parameters were as follows in G_2 and G_3: RI 0.38 ± 0.09 and 0.36 ± 0.08, PSV 20.23 ± 9.25 and 25.06 ± 9.55 (Table 4).

Tumor cells rarely shed into the circulation in the preinvasive phase, however this process in tumors with a high angiogenic state may be enhanced by the leaky and fragmented basement of the new capillaries. Thus contact with the capillary-lymphatic space is considerably more likely [17, 18]. Metastatic spread in endometrial cancer occurs in a characteristic pattern and in several ways. Spread to the pelvic and paraaortic nodes is common whereas hematogenous (adnexal/omental) metastases are rare [19]. There were no significant differences in each flow parameter in hematogenous-adnexal/omental metastatic and non metastatic cases. It is known that adnexal/omental metastasis appears in far advanced cases where the prognosis is extremely bad. Therefore it becomes justifiable to emphasize the need for further clinical investigation of vascular density as an important criterion. Node and adnexal/omental-negative patients who showed highly vascularized tumors (in our series 69.2% and 73.9%, respectively) should benefit from more intense postoperative treatment.

As emphasized earlier the prognosis of patients with endometrial cancer is thought to be dependent on the presence or absence of pelvic lymph node metastasis.

Hence patients with positive pelvic lymph nodes are considered to be at risk for recurrence and should be treated more aggressively.

As shown above angiogenesis could be predictive of metastatic spread to the lymph nodes in endometrial cancer, however in hematogenous routes its role is not valid. Hence it may be a useful prognostic factor in endometrial cancer because vascular density correlates positively with lymphatic metastasis [20, 21].

Although angiogenesis factors do not induce growth of new lymphatic vessels for gynecologic tumors, such as endometrial cancer that spreads primarily through lymphatic channels, microvessel counting would become a clinically useful prognostic factor.

Increased vascular density with increased neoplastic extension of the uterine muscle can explain this phenomenon. In cases with deep uterine involvement neoplastic cells contact the vascular-lymphatic space, hence lymphatic spread is facilitated. Extrauterine and nodal spread of tumor is caused by involvement of the capillary-lymphatic space which is seen on histopathologic examination [22, 23].

This study provides evidence that vascular density measured by TVCD could affect the prognosis of patients with endometrial carcinoma because those with positive lymph nodes had significantly higher vascularized tumors, whereas those with negative nodes did not. Pelvic lymph node involvement and vascular density were shown to be statistically significant ($p < 0.02$). There were significant differences in vascular density in positive lymph node cases whereas remaining flow parameters did not differ (Tables 5 and 6).

Our data demonstrated that the growth and spread of endometrial cancer is angiogenesis-dependent and stress the need for clinical trials to study the influence of antiangiogenetic substances on endometrial cancer.

As pelvic lymph node metastasis and extent of angiogenesis correlate positively, qualitative analysis of tumor angiogenesis could be useful in predicting the prognosis in these patients thus contributing to the individualization of treatment. Moreover, as stressed above, it may also be helpful to select patients for future antiangiogenic therapy [24].

Conclusions

The results reported in our study indicate that blood flow rates correspond to increased angiogenesis in endometrial cancers, and might potentially be used as a good prediction factor for tumor progression and metastasis in affected women.

A correlation between tumor angiogenesis expressed as vascular density within the neoplastic infiltration and pelvic node metastasis in patients with endometrial carcinoma has been demonstrated. No correlation was seen in the group with adnexal/omental metastsis.

A correlation was seen between flow parameters, vascular density and staging (depth of tumor invasion) and grading of the neoplasm.

Lower resistance indices were reflected by higher grade and stage tumors, deeper invasion into the uterus, lymphovascular emboli, and metastasis to the lymph nodes.

These results suggest that TVCD evaluation of endometrial cancer is a reliable method for assessing endometrial angiogenesis. Uterine blood flow analysis could not predict the tumor staging and grading, however it did provide additional discriminatory information on tumor vascularization which can be used with morphology for more accurate diagnoses. Preoperative ultrasound examination should be seen as an important tool in the establishment of individualized treatment programs for women with endometrial cancer.

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