

# Clinicopathologic Characteristics and Reproductive Outcomes of Patients with Borderline Ovarian Tumors (BOTs): A Single Institute Experience and A Review of the Literature

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**OBJECTIVES:** In borderline ovarian tumor (BOT) cases, evaluating the therapy forms, the percentage of recurrence and survival and the condition of fertility after conservative surgery, for those with a fertility wish.

**STUDY DESIGN:** The files, follow-up forms and pathological reports of 96 cases, diagnosed with BOT, at our clinic, treated between 1994-2009, have been retrospectively evaluated.

**RESULTS:** The mean age of the evaluated cases was 39.54±13.4. On the basis of histopathological data, 46 cases (47.9%) had serous and 41 cases (42.7%) had mucinous, and 9 cases (9.4%) had other histological subtypes. 88 cases were in stage I, 2 cases (2.1%) were in stage II and 6 cases (6.2%) were in stage III. 89 (92.7%) cases were operated with laparotomy, 7 (7.3%) cases were operated with laparoscopy. In 52 cases (54.1%), conservative (fertility preserving) surgery was applied (27 cases USO, 8 cases cystectomy, 17 cases USO-staging), in 44 cases (45.8%) radical surgery (in 32 cases, complete staging, TAH-BSO in 11 cases, TAH-USO in 1 case). 26% of the cases (25 cases) underwent postoperative adjuvant chemotherapy. In 39 cases with fertility wish, 8 pregnancy occurred after therapy. In the follow-up, 10 cases (10.4%) had recurrence. The rate of recurrence was 4% (2/44) after radical surgery and 15% (8/52) after conservative surgery. The general disease-free survival rate of the cases (DFS) was 89.6%, and there was no significant difference between radical and conservative surgery in view of DFS (95.45% vs 84.62%, p=0.97).

**CONCLUSION:** In cases of borderline ovarian tumor, the best therapy is surgical debulking and the post-operative recurrence rate is generally low. Although the recurrence risk in patients who underwent conservative surgery is relatively higher, disease free survival rates are no different than those who had radical surgery.

**Key Words:** Borderline ovarian tumors, Survival, Recurrence, Fertility

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## Introduction

Although ovary cancer is almost 3% of all cancer cases, after lung, breast, colorectal and pancreas cancer, the fifth

most common cause of cancer death for women. After the uterin corpus cancer, ovary cancer is the second most frequent gynecological malignancy and the most frequent cause of gynecological cancer deaths.<sup>1,2,3</sup>

Characterised by low rates of cure, there is one group among ovary cancers in which therapy is mostly successful. These are cases of Borderline or ovary tumors with low malign potential. Due to histopathological characteristics and biological reactions of the borderline ovarian tumors (BOT), provides classified between benign epithelial ovarian tumors and invasive carcinomas.<sup>4</sup> BOT are defined as a subgroup of malign ovary tumors with relatively good prognosis, making up 10-20% of ovary malignities.<sup>5,6</sup> They differ from other malign epithelial ovary tumors through being limited to the ovary for many years, being encountered mostly in premenopausal women and having a significantly better prognosis.<sup>7</sup>

Clinically, BOT patients are 15 years younger than women with malign ovary cancer. In comparison to invasive ovary tu-

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mors, BOT proceeds more slowly, with late or no recurrence, with a longer period of survival. During diagnosis, 80% of BOT patients are in stage I. In comparison to invasive ovary tumors, the rates of survival are better. Histologically, BOT displays complex structural and nuclear atyp, but no invasion is observed in the sub-stroma. The most frequent histological types are serous and mucinous.<sup>8,9,10</sup>

Currently, the therapy of choice for BOT is surgical and although its efficacy is not totally grounded, in selected cases, adjuvant chemotherapy. The surgical method should be selected in accordance with the patient's age, condition of fertility, the stage of disease and the histopathological characteristics. It is also recommended to apply a complete surgical staging.<sup>4,11</sup>

That most of the BOT patients are in a fertile age and that diagnosis is mostly possible in an early stage, makes fertility preserving surgical methods more significant while selecting the right therapy. In our study, we evaluated the clinicopathological characteristics, prognosis and fertility results of the BOT cases treated with conservative surgery.

## Material and Method

96 cases, diagnosed with BOT, at our clinic, treated between 1994-2009, were included in the study. Data has been collected on the basis of archival files, patient follow-up forms and pathological reports, and evaluated in accordance with the parameters researched. The study was designed as a retrospective cohort study.

The investigation was based on the age, the obstetric history and fertility wish, histopathological characteristics, disease stage, the therapy applied, conditions of recurrence and fertility and the survival analysis of the patients.

For statistical analysis, SPSS 12.0 for Windows statistical package programme was used. Evaluating data, definitional methods such as taking mean and standart deviation, and t-test for comparing quantitative data for two independant samples, was used. For evaluating qualitative data, the Chi-square test was applied. Kaplan Meier analysis was mad efor the disease free survival (DFS) analysis, and for comparing DFS rates between different groups, the Log rank test was used. The results were evaluated in the 95% reliability range and the value of statistical significance was set to be  $p < 0.05$ .

## Results

The youngest patient in our group of study was 15, the oldest being 73, and the mean age is calculated to be  $39.54 \pm 13.4$  (15-73). The highest frequency of disease was among the ages of 30 and 40, with a percentage of 33.3% (32 cases). 56% (54/96) cases were under 40.

Looking at histological subtypes: serous BOT comprised of 47.9% of the cases (46), the rate of mucinous BOT was detected to be 42.7% (41), endometrioid BOT made up 4.2% (4) and mixed type BOT was detected to be 1%.(1)

Looking at surgical stages of the cases: Stage I cases made up of 91.6% (88); (61 patients (63.5%) in stage Ia, 12 cases (12.5%) stage Ib, 15 cases (15.6%) stage Ic). stage II cases comprised of 2.1% (2 cases, both in stage IIc). The percentage of stage III cases was 6.2% (6) (3 cases in stage IIIb, 3 cases in stage IIIc). Putting the stage and the histological diagnosis in relation, we find 41 of the 46 patients of the serous type (89%) in stage I, 39 of 41 patients (95%) of the mucinous type in stage I, 3 of 4 patients (75%) of the endometrioid type in stage I and all 5 patients (5/100) with mixed type in stage I. Stage I is hereby the most frequently encountered stage of disease.

Observing the surgical treatments: 89 cases (92.7%) had laparotomy, 7 cases (7.3%) were operated with laparoscopic surgery, making laparotomy the mostly preferred treatment. In 52 of the cases (54.1%) conservative fertility preserving surgery was applied (27 cases USO, 8 cases cyctectomy, 17 cases USO-staging). 44 (45.8%) cases underwent radical surgery (32 cases complete staging, 11 cases TAH-BSO, 1 case TAH-USO).

26% of the cases (25 cases) had adjuvant chemotherapy. Adjuvant CT endications remained unclear due to unsufficient archival records and little access to patient's information, but seems to be stage Ic disease and stage Ia/Ib disease with tumor rupture.

In 39 cases who underwent conservative surgery and had a wish of fertility preservation, 8 became pregnant after therapy. In 6 of those cases 1, in 2 cases 2 pregnancies developed. All the pregnancies developed spontanously. One of the pregnancy cases had adjuvant CT and became pregnant after treatment. The mean period between BOT diagnosis and pregnancy onset was 29 months (7months-72 months). All of our pregnancy cases had stage I (6 in Ia, 2 in Ic) disease. All the pregnancy cases were under age 40. The clinicopathological characteristics of the subjects are summarized in Table 1.

In the follow-up, recurrence was detected in 10 cases (10.4%). 9 of the recurrence cases had serous BOT and 1 had mucinous BOT. 4 cases were in stage Ia, 1 case in stage Ib, 3 cases in stage Ic an done case each in IIIb and in stage IIIc. Grouped according to primary surgical therapy, 2 of cases with recurrence had complete staging surgery, 3 had USO staging surgery, 3 had USO amd 2 had cystectomy surgery. So, recurrence after cystectomy was 25%, 6% after complete staging, 11% after only USO and 17% after USO staging. In 4% (2/44) of the cases, recurrence emerged after radical surgery, and in 15% (8/52) of the cases recurrence was detected after conservative surgery. The mean period between diagno-

sis and recurrence was 24.3 months (1-69 months). According to the data, 3.1% (3 cases) of the patients with recurrence had the event in the first year after operation, 4.2% (4 cases) between the first and second year, 1% (1 case) between the second and third year and 2.1% (2 cases) five years after. In all of the recurrences, the diagnosis was borderline, and none had invasive recurrence. The age distribution of the patients with recurrence was: 1 case <age 20, 3 cases age 20 - 30, 4 cases age 30-40, 2 cases age 40-50. In the group under the age 40, the patients who underwent fertility preserving conservative surgery had higher rates of recurrence.

In this study, disease free survival (DFS) was calculated as the period between the primary surgery to the first diagnosis of recurrence. As all patients were alive at the last control, the overall survival has not been calculated. The mean DFS rate of the patients was 89.6% (Figure 1). The DFS rates of the patients with serous BOT was 80.4%, being 97.6% for the mucinous types. As there was no recurrence in the cases with other histological types, the DFS rates were not calculated.

Table 1: The clinicopathological characteristics of BOT-diagnosed cases

	Number of patients	Percentage
<b>Age</b>		
< 40	54	56.2%
> 40	42	43.7%
<b>Histological type</b>		
Serous	46	47.9%
Mucinous	41	42.7%
Endometrioid	4	4.2%
Mixed	5	5.2%
<b>Stage</b>		
Stage I	88	91.6%
Stage II	2	2.0%
Stage III	6	6.2%
<b>Method of surgery</b>		
Radical	44	45.8%
Conservative (fertility preserving)	52	54.1%
<b>Adjuvant Chemotherapy</b>		
Received	25	26%
Did not receive any	71	74%
<b>Fertility</b>	8	20.5%*
<b>Recurrence</b>	10	10.4%

\*: Evaluation of the 39 cases with a wish for fertility after conservative surgery

There is no statistically significant difference between the DFS rates calculated for the histological types (p=0.08). Patients with stage I had a DFS of 90.9%, in patients with stage III disease, this rate was 66.7%. None of the patients in stage II showed recurrence, so DFS was not calculated. There was no statistically significant difference between the stage of disease with regards to the DFS rates (p=0.16). The DFS rates of the patients who underwent conservative surgery was 84.6%, this rate was 95.5% for the patients who underwent radical surgery (Table 2). There was no statistically significant difference between the groups of patients who underwent different forms of surgery (p=0.07) (Figure 2).

Table 2: The correlation between histological type, stage and the method of operation

	Number of patients	Percentage	
<b>Histological type</b>			
Serous	46	47.9%	p=0.08
Mucinous	41	42.7%	
Endometrioid	4	4.2%	
Mixed	5	5.2%	
<b>Stage</b>			
Stage I	88	91.6%	p=0.16
Stage II	2	2.0%	
Stage III	6	6.2%	
<b>Method of operation</b>			
Radical	44	45.8%	P=0.07
Conservative (fertility preserving)	52	54.1%	

DFS: Disease-free Survival

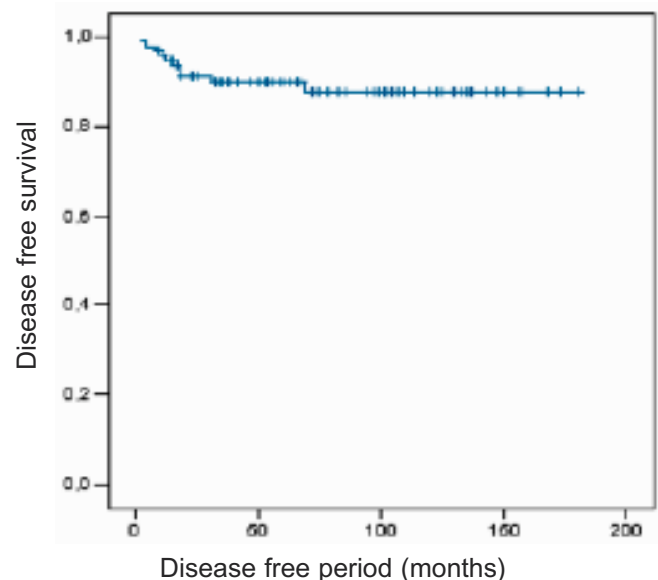


Figure 1: DFS Distribution curve

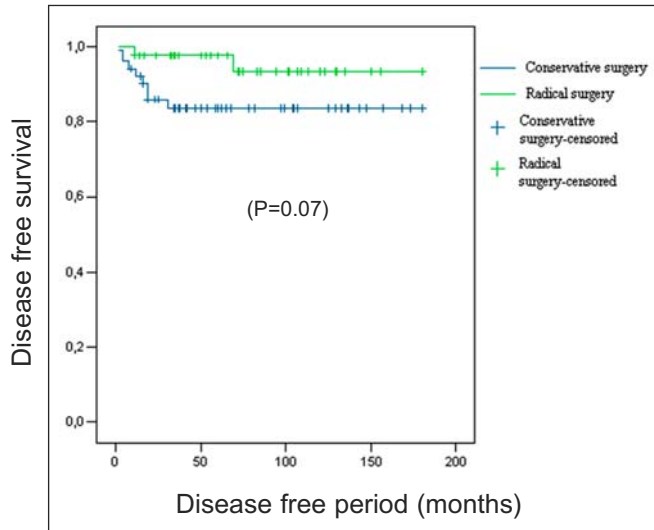


Figure 2: The effect of the method of surgery on DFS

## Discussion

Borderline ovary tumors (BOT) were first defined by Taylor in 1929, being hyperplastic ovarian tumors with semi-malign or peritoneal implants, but showing no stromal invasion.<sup>12</sup> That this entity being a stage between benign and malign processes was generally acknowledged, was only possible after the FIGO (International Federation of Gynecology and Obstetrics) and WHO (World Health Organization) included this category in their classifications. In 2003, WHO included the term “borderline ovarian malignancy” in its classification and so the currently accepted term borderline ovarian tumor (BOT) was created.<sup>13,14</sup>

BOT accounts for 10-20% of ovarian tumors.<sup>6</sup> In Turkey, the little number of studies done show that its occurrence among all malign ovary tumors is 10%.<sup>15</sup> In comparison to malign ovary tumors, the diagnosis is made in an early stage and a younger (10 years younger than malign ovary cancers) age. P. De Iaco et al. reported the mean age of the BOT patients to be 45.5 (between 14-85).<sup>16</sup> Similarly, J.Y. Park et al. reported 54% of the BOT cases to be under 40.<sup>17</sup> In our study too, the mean age of all our patients with borderline ovary tumor was found to be 39 (between 15-73). 56.3% of our cases were under the age of 40.

Looking at the histological subtypes of BOT, 50% are of serous histology, 46% of mucinous histology, the rest of 5% being of nonserous-nonmucinous (Endometrioid, Brenner, with clear cells and mixed types) histological types.<sup>18</sup> P. De Iaco et al., detected the serous histological type to make up 60% of all cases (102 cases of 168) and the mucinous type making up 23% (40 cases in 168), other types being of 15% (26 cases in 168), and reported the serous and the mucinous types as being most frequently encountered.<sup>16</sup> In our study, in

accordance with general literature, the serous and mucinous types are found to be the most frequent histological types.

There is no specific staging for BOT and the staging developed by FIGO for malign epithelial ovary cancer. The significance of surgical staging for malign ovary cancer is equally valid for tumors with a low potential of malignity. Of those BOT, emerging in a young age and having a good prognosis, 50-80% are diagnosed to be in stage I and stage III is diagnosed only in 8-35% of the cases.<sup>18</sup> Chao et al. reported the chance of diagnosing cases with borderline ovarian tumor at stage I is as high as 81.3%.<sup>19</sup> Zanette et al. did research on 339 borderline ovary cases and reported 83.4% of the patients to be in stage I, 7.9% in stage II and 8.5% in stage III.<sup>7</sup> The results in our study on the surgical stages of the cases evaluated also point to the diagnosis of this disease at an early stage.

The relation between survival and the stage of disease has already been demonstrated. Leake et al. reported the survival rates for 20 years to be 99% for stage I, 96% for stage II and 45% for stage III, and supported this correlation.<sup>20</sup> A similar relation has been detected between recurrence rates and stage of disease, being 2,1% for stage I, 7,1% for stage II and 14,4% for stages III-IV.<sup>21</sup> Romagnolo et al. showed a similar correlation between disease free survival and stage of disease. In their series, they reported disease free survival rates for 10 years to be 89.2% for stage I, 66.6% for stage II and 45% for stage III.<sup>22</sup> In our study, in accordance with former studies, the DFS rates for higher stages are lower, however there seems to be no statistically significant difference between disease stages in relation to disease free survival ( $p=0.16$ ).

The basic therapy for BOT in all stages is surgical, the standard therapy in higher stages being maximum cytoreduction. In patients with higher stages, the primary tumor and all metastatic implants should be resected like in invasive cancers. In cases with tumoral residues, the rates of recurrence and related deaths were higher. For young patients wishing to remain fertile, even in higher stages, normal-looking ovaries could be left untouched.

Although in early stages, the surgical procedure leading to cure is similar to the intervention for invasive ovary cancers, the good prognosis of BOT, its occurrence in younger ages than is the case with invasive tumors and its high frequency at patients in young age with a wish for fertility plays a role in determining the surgical method. For tumors with slow progress, showing rare recurrence and with effective recurrence therapy already developed, especially for cases in early stages, conservative or fertility preserving surgical methods are advised. Conservative surgery is defined as phase surgery, where the uterus and at least one ovary is preserved (with the application of USO or cystectomy, peritoneal washing, multiple peritoneal biopsies, omentectomy, appendectomy). In several stud-

ies, the recurrence rates after conservative surgery is found to be 0-20% after USO and 12-58% after cystectomy. In contrast, the rates of recurrence after radical surgery, during which the uterus and the bilateral ovaries are removed, is detected to be 2.5-5.7% (being significantly lower).<sup>7,23,24</sup> P. De Iaco et al. also supported this data with recurrence rates being 34% after cystectomy, 20% for the USO group and 6% for the group who underwent radical surgery.<sup>16</sup> In our study too, the data supports the literature available. In the same line, the recurrence rates are found to be higher after conservative surgery, within conservative procedures, the rates of recurrence being higher for the cystectomy group than the USO group. At stage I borderline ovarian tumors where conservative surgery is planned, first therapy of choice is USO, due to its low recurrence rates. Because of high recurrence rates, cystectomy should only be considered if there is bilateral ovarian spread or a former history of unilateral USO.

P. De Iaco et al. compared the DFS correlation with the form of operation applied, revealing the rate to be 64.2% for cystectomy, 78.4% for USO and 93.5% for radical surgery. Although the DFS rates are higher for the radical surgery group, there was no statistical significance between the two groups with conservative and radical surgery with regards to DFS rates.<sup>16</sup> J.Y. Park et al. also reported no statistically significant difference ( $p=0.65$ ) in their series between radical surgery and fertility preserving surgery.<sup>17</sup> In our study, no statistically significant difference was detected between the radical and conservative surgery groups with regards to survival rates ( $p=0.07$ ).

A correlation between risk of recurrence and the age of the patient was also reported. Kaern et al. stated that the risk of recurrence increases with higher age,<sup>25</sup> whereas P. De Iaco et al. declared that in cases under 35, there is a significantly higher rate of recurrence.<sup>16</sup> In our study, all of the 8 cases with recurrence were under the age of 40. The reason why the cases with recurrence are younger may be, that at groups with young patients who have a wish for fertility, the choices of therapy may effect the results and that more often, fertility preserving, conservative surgical methods are preferred in those patients.

In the literature, the rates of pregnancy for BOT cases is noted between 32-65%.<sup>26</sup> Yinon et al. reported the fertility rates of 62 patients who underwent conservative surgery. (40 USO and 22 cystectomy) to be 40.3% (25/62).<sup>(27)</sup> Donnez et al. reported the rate of pregnancy for patients who had conservative surgery as 63.6%, all cases developing spontaneous pregnancy.<sup>28</sup> Camatte et al. reported 17 cases of pregnancy at 14 cases from 44 borderline ovary tumor patients 15 of the pregnancies developed spontaneously, 1 occurred after clomifen citrate therapy and 1 with IVF techniques.<sup>29</sup> Fasouliotis et al. reported that in 3 of 5 borderline ovarian tumor cases, 3 pregnancies ending with birth came to hap-

pen.<sup>30</sup> Fauvet et al. calculated the rate of pregnancies as %32,3 (21 cases from 65) after conservative therapy, we had a similar mean period between therapy and pregnancy onset, being 28,6 months.<sup>31</sup> Zanetta et al., in their study with 189 cases, reported the rate of pregnancies as 23% (44 cases).<sup>7</sup> In our study, we noted that 39 cases wished to remain fertile after surgical intervention, and determined the rate of pregnancy as 20% (8/39). The reason why the rate of pregnancies is lower than in the general literature can be interpreted in connection with the low number of patients included in the study, the lack of archival follow-up and lack of information on the patients later history after intervention. In light of this information, especially in cases under 40, having an early stage tumor and still being fertile, conservative-fertility preserving methods should be preferred. One handicap of this kind of therapy is, that the rate of recurrence is higher in comparison to radical surgery, making a close follow-up work necessary.

## Conclusion

The occurrence of BOT in early ages, the fact that its diagnosis is mostly possible in earlier stages than in malign ovary tumors, its better prognosis, its rare and late onset recurrence and long survival rates makes the conservative surgical methods the therapy of choice for women in the reproductive age. This is why factors such as the age of the patient and her wish for fertility are important factors while choosing the right therapy, besides the dimension of the spread of the tumor. In young patients with a wish for fertility, whatever the stage of the disease, conservative methods should be preferred, in spite of the high risk of recurrence, as this has no significant effect on the survival rates. In many patients treated with conservative surgery, no problems are observed with regards to fertility and successful obstetrical results are reported. Ovulation induction and IVF techniques can also be made use of in such cases.

## Borderline Over Tümörlerinin Karakteristik Özellikleri ve Fertilité Sonuçları: Tek Merkezli Deneyimlerimiz ve Literatür Taraması

**AMAÇ:** Borderline over tümörlerinde yapılan tedaviye göre rekürans ve survival oranlarını hesaplamak ayrıca fertilité koruyucu cerrahi sonrasında fertilité sonuçlarını hesaplamak.

**GEREÇ VE YÖNTEM:** Kliniğimizde 1994-2009 yılları arasında patoloji raporlarında BOT tespit edilen hastaların dosyaları ve takip formları retrospektif olarak araştırıldı.

**BULGULAR:** Ortalama yaş 39,54±13,4 idi. 46 (%47,9) hastada seröz, 41 (%42,7) hastada müsinöz, ve 9 (%9,4) hastada diğer histolojik alttipler tespit edildi. 88 (%91,7) hasta evre I, 2 (%2,1) hasta evre II ve 6 (%6,2) hasta evre III idi. 89 (%92,7) hasta laparatomik, 7 (%7,3) hasta laparoskopik olarak operasyon edildi. 52 (%54,1) hastaya konservatif cerrahi teknik (fertilité koruyucu) uygulanırken, (27 USO, 8 kistektomi, 17

USO+evreleme), 44 (%45,8) radikal cerrahi teknikle tedavi edildi (32 komplet evreleme, 11 TAH-BSO, 1 TAH-USO). Hastaların %26'sı (25 hasta) postoperatif adjuvan kemoterapi aldı. Fertilite isteği olan 39 hastanın 8'inde tedavi sonrası gebelik meydana geldi. Takipler sırasında 10 (%10,4) hastada rekürans oluştu, rekürans oranı radikal cerrahi sonrası %4 (2/44) ve konservatif cerrahi sonrasında %15 (8/52) olarak tespit edildi. Bütün hastaların ortalama hastaliksız sağ kalım oranı %89,6 idi ve hastaliksız sağ kalım oranına göre radikal ve konservatif cerrahi teknik arasında bir farklılık tespit edilmedi. (%95,45 vs %84,62, p=0,97).

**SONUÇ:** Borderline over tümörlerine en iyi yaklaşım cerrahi olarak tümörün çıkarılması ve sıfırlanmasıdır ve genel olarak post operatif rekürans oranları düşüktür. Her ne kadar konservatif cerrahi ile tedavi edilen hastalarda rekürans, oransal olarak daha yüksek ise de hastaliksız sağ kalım oranlarına bakıldığında radikal cerrahi ile arasında farklılık yoktur.

**Anahtar Kelimeler:** Borderline over tümörü, Sağ kalım oranı, Rekürans, Fertilite

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