

# Ovarian cancer essay



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Word Count: 4748 Of all gynecologic malignancies, continues to have the highest mortality and is the most difficult to diagnose. In the United States female population, ovarian cancer ranks fifth in absolute mortality among cancer related deaths (13, 000/yr). In most reported cases, ovarian cancer, when first diagnosed is in stages III or IV in about 60 to 70% of patients which further complicates treatment of the disease (Barber, 3).

Early detection in ovarian cancer is hampered by the lack of appropriate tumor markers and clinically, most patients fail to develop significant symptoms until they reach advanced stage disease. The characteristics of ovarian cancer have been studied in primary tumors and in established ovarian tumor cell lines which provide a reproducible source of tumor material.

Among the major clinical problems of ovarian cancer, malignant progression, rapid emergence of drug resistance, and associated cross-resistance remain unresolved. Ovarian cancer has a high frequency of metastasis yet generally remains localized within the peritoneal cavity. Tumor development has been associated with aberrant, dysfunctional expression and/or mutation of various genes. This can include oncogene overexpression, amplification or

mutation, aberrant tumor suppressor expression or mutation. Also, subversion

of host antitumor immune responses may play a role in the pathogenesis of cancer (Sharp, 77).

Ovarian clear cell adenocarcinoma was first described by Peham in 1899 as “hypernephroma of the ovary” because of its resemblance to renal cell carcinoma.

By 1939, Schiller noted a histologic similarity to mesonephric tubules and classified these tumors as “mesonephromas.” In 1944, Saphir and Lackner described

two cases of “hypernephroid carcinoma of the ovary” and proposed “clear cell”

adenocarcinoma as an alternative term. Clear cell tumors of the ovary are now

generally considered to be of müllerian and in the genital tract of müllerian origin.

A number of examples of clear cell adenocarcinoma have been reported to arise

from the epithelium of an endometriotic cyst (Yoonessi, 289). Occasionally, a renal

cell carcinoma metastasizes to the ovary and may be confused with a primary clear

cell adenocarcinoma.

Ovarian clear cell adenocarcinoma (OCCA) has been recognized as a distinct histologic entity in the World Health Organization (WHO) classification of ovarian

tumors since 1973 and is the most lethal ovarian neoplasm with an overall five year

survival of only 34% (Kennedy, 342). Clear cell adenocarcinoma, like most ovarian

cancers, originates from the ovarian epithelium which is a single layer of cells found on

the surface of the ovary. Patients with ovarian clear cell adenocarcinoma are typically

above the age of 30 with a median of 54 which is similar to that of ovarian epithelial

cancer in general. OCCA represents approximately 6% of ovarian cancers and bilateral

ovarian involvement occurs in less than 50% of patients even in advanced cases.

The association of OCCA and endometriosis is well documented (De La Cuesta,

243). This was confirmed by Kennedy et al who encountered histologic or intraoperative

evidence of endometriosis in 45% of their study patients. Transformation

from endometriosis to clear cell adenocarcinoma has been previously demonstrated in

sporadic cases but was not observed by Kennedy et al. Hypercalcemia occurs in a

significant percentage of patients with OCCA. Patients with advanced disease are more

typically affected than patients with nonmetastatic disease. Patients with OCCA are also

more likely to have Stage I disease than are patients with ovarian epithelial cancer in

general (Kennedy, 348).

Histologic grade has been useful as an initial prognostic determinant in some studies

of epithelial cancers of the ovary. The grading of ovarian clear cell adenocarcinoma has

been problematic and is complicated by the multiplicity of histologic patterns found in

the same tumor. Similar problems have been found in attempted grading of clear cell

adenocarcinoma of the endometrium (Disaia, 176). Despite these problems, tumor

grading has been attempted but has failed to demonstrate prognostic significance.

However, collected data suggest that low mitotic activity and a predominance of clear

cells may be favorable histologic features (Piver, 136).

Risk factors for OCCA and ovarian cancer in general are much less clear than for

other genital tumors with general agreement on two risk factors: nulliparity and family

history. There is a higher frequency of carcinoma in unmarried women and in married

women with low parity. Gonadal dysgenesis in children is associated with a higher risk

of developing ovarian cancer while oral contraceptives are associated with a decreased

risk. Genetic and candidate host genes may be altered in susceptible families. Among

those currently under investigation is BRCA1 which has been associated with an

increased susceptibility to breast cancer. Approximately 30% of ovarian adenocarcinomas

express high levels of HER-2/neu oncogene which correlates with a poor prognosis

(Altcheck, 375-376). Mutations in host tumor suppresser gene p53 are found in 50% of

ovarian carcinomas. There also appears to be a racial predilection, as the vast majority

of cases are seen in Caucasians (Yoonessi, 295).

Considerable variation exists in the gross appearance of ovarian clear cell adenocarcinomas and they are generally indistinguishable from other epithelial ovarian

carcinomas. They could be cystic, solid, soft, or rubbery, and may also contain

hemorrhagic and mucinous areas (O'Donnell, 250). Microscopically, clear cell

carcinomas are characterized by the presence of variable proportions of clear and hobnail

cells. The former contain abundant clear cytoplasm with often centrally located nuclei,

while the latter show clear or pink cytoplasm and bizarre basal nuclei with atypical

cytoplasmic intraluminal projections. The cellular arrangement may be tubulo acinar,

papillary, or solid, with the great majority displaying a mixture of these patterns. The

hobnail and clear cells predominate with tubular and solid forms, respectively (Barber,

214).

Clear cell adenocarcinoma tissue fixed with alcohol shows a high cytoplasmic glycogen content which can be shown by means of special staining techniques.

Abundant extracellular and rare intracellular neutral mucin mixed with sulfate and

carboxyl group is usually present. The clear cells are recognized histochemically and



ultrastructurally (short and blunt microvilli, intercellular tight junctions and desmosomes,

free ribosomes, and lamellar endoplasmic reticulum). The ultrastructure of hobnail and

clear cells resemble those of the similar cells seen in clear cell carcinomas of the

remainder of the female genital tract (O'Brien, 254). A variation in patterns of histology

is seen among these tumors and frequently within the same one.

Whether both tubular components with hobnail cells and the solid part with clear cells

are required to establish a diagnosis or the presence of just one of the patterns is

sufficient has not been clearly established. Fortunately, most tumors exhibit a mixture of

these components. Benign and borderline counterparts of clear cell ovarian

adenocarcinomas are theoretical possibilities. Yoonessi et al reported that nodal

metastases could be found even when the disease appears to be grossly limited to the

pelvis (Yoonessi, 296). Examination of retroperitoneal nodes is essential to allow for

more factual staging and carefully planned adjuvant therapy.

Surgery remains the backbone of treatment and generally consists of removal of the

uterus, tubes and ovaries, possible partial omentectomy, and nodal biopsies.

The

effectiveness and value of adjuvant radiotherapy and chemotherapy has not been clearly

demonstrated. Therefore, in patients with unilateral encapsulated lesions and

histologically proven uninvolved of the contralateral ovary, omentum, and biopsied

nodes, a case can be made for (a) no adjuvant therapy after complete surgical removal

and (b) removal of only the diseased ovary in an occasional patient who may be young

and desirous of preserving her reproductive capacity (Altchek, 97). In the more adv-

anced stages, removal of the uterus, ovaries, omentum, and as much tumor as possible

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followed by pelvic radiotherapy (if residual disease is limited to the pelvis) or chemotherapy must be considered. The chemotherapeutic regimens generally involve

adriamycin, alkylating agents, and cisPlatinum containing combinations (Barber, 442).

OCCA is of epithelial origin and often contains mixtures of other epithelial tumors

such as serous, mucinous, and endometrioid. Clear cell adenocarcinoma is characterized

by large epithelial cells with abundant cytoplasm. Because these tumors sometimes

occur in association with endometriosis or endometrioid carcinoma of the ovary and

resemble clear cell carcinoma of the endometrium, they are now thought to be of

mullerian duct origin and variants of endometrioid adenocarcinoma. Clear cell tumors of

the ovary can be predominantly solid or cystic. In the solid neoplasm, the clear cells are

arranged in sheets or tubules. In the cystic form, the neoplastic cells line the spaces.

Five-year survival is approximately 50% when these tumors are confined to the ovaries,

but these tumors tend to be aggressive and spread beyond the ovary which tends to make

5-year survival highly unlikely (Altchek, 416).

Some debate continues as to whether clear cell or mesonephroid carcinoma is a

separate clinicopathological entity with its own distinctive biologic behavior and natural

history or a histologic variant of endometrioid carcinoma. In an effort to characterize

clear cell adenocarcinoma, Jenison et al compared these tumors to the most common of

the epithelial malignancies, the serous adenocarcinoma (SA). Histologically determined

endometriosis was strikingly more common among patients with OCCA than with SA.

Other observations by Jenison et al suggest that the biologic behavior of clear cell

adenocarcinoma differs from that of SA. They found Stage I tumors in 50% of the

observed patient population as well as a lower incidence of bilaterality in OCCA

(Jenison, 67-69). Additionally, it appears that OCCA is characteristically larger than

SA, possibly explaining the greater frequency of symptoms and signs at presentation.

### Risk Factors

There is controversy regarding talc use causing ovarian cancer. Until recently, most

talc powders were contaminated with asbestos. Conceptually, talcum powder on the

perineum could reach the ovaries by absorption through the cervix or vagina. Since

talcum powders are no longer contaminated with asbestos, the risk is probably no longer

important (Barber, 200). The high fat content of whole milk, butter, and meat products

has been implicated with an increased risk for ovarian cancer in general.

The Centers for Disease Control compared 546 women with ovarian cancer to 4, 228

controls and reported that for women 20 to 54 years of age, the use of oral contraceptives reduced the risk of ovarian cancer by 40% and the risk of ovarian cancer

decreased as the duration of oral contraceptive use increased. Even the use of oral

contraceptives for three months decreased the risk. The protective effect of oral

contraceptives is to reduce the relative risk to 0.6 or to decrease the incidence of disease

by 40%. There is a decreased risk as high as 40% for women who have had four or

more children as compared to nulliparous women. There is an increase in the incidence

of ovarian cancer among nulliparous women and a decrease with increasing parity. The

“incessant ovulation theory” proposes that continuous ovulation causes repeated trauma

to the ovary leading to the development of ovarian cancer. Incidentally, having two or

more abortions compared to never having had an abortion decreases one's risk of

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developing ovarian cancer by 30% (Coppleson, 25-28).

## Etiology

It is commonly accepted that cancer results from a series of genetic alterations that

disrupt normal cellular growth and differentiation. It has been proposed that genetic

changes causing cancer occur in two categories of normal cellular genes, proto-

oncogenes and tumor suppressor genes. Genetic changes in proto-oncogenes facilitate

the transformation of a normal cell to a malignant cell by production of an altered or

overexpressed gene product. Such genetic changes include mutation, translocation, or

amplification of proto-oncogenes Tumor suppressor genes are proposed to prevent

cancer. Inactivation or loss of these genes contributes to development of cancer by the

lack of a functional gene product. This may require mutations in both alleles of a tumor

suppressor gene. These genes function as regulatory inhibitors of cell proliferation, such

as a DNA transcription factor, or a cell adhesion molecule. Loss of these functions

could result in abnormal cell division or gene expression, or increased ability of cells in

tissues to detach. Cancer such as OCCA most likely results from the dynamic interaction

of several genetically altered proto-oncogenes and tumor suppressor genes (Piver, 64-

67).

Until recently, there was little evidence that the origin of ovarian was genetic. Before

1970, familial ovarian cancer had been reported in only five families. A familial cancer

registry was established at Roswell Park Cancer Institute in 1981 to document the

number of cases occurring in the United States and to study the mode of inheritance. If

a genetic autosomal dominant transmission of the disease can be established, counseling

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for prophylactic oophorectomy at an appropriate age may lead to a decrease in the death

rate from ovarian cancer in such families.

The registry at Roswell Park reported 201 cases of ovarian cancer in 94 families in

1984. From 1981 through 1991, 820 families and 2946 cases had been observed.

Familial ovarian cancer is not a rare occurrence and may account for 2 to 5% of all cases

of ovarian cancer. Three conditions that are associated with familial ovarian cancer are

(1) site specific, the most common form, which is restricted to ovarian cancer, and (2)

breast/ovarian cancer with clustering of ovarian and breast cases in extended pedigrees

(Altchek, 229-230). One characteristic of inherited ovarian cancer is that it occurs at a

significantly younger age than the non-inherited form.

Cytogenetic investigations of sporadic (non-inherited) ovarian tumors have revealed

frequent alterations of chromosomes 1, 3, 6, and 11. Many proto-oncogenes have been

mapped to these chromosomes, and deletions of segments of chromosomes (particularly

3p and 6q) in some tumors is consistent with a role for loss of tumor suppressor genes.

Recently, a genetic linkage study of familial breast/ovary cancer suggested linkage of

disease susceptibility with the RH blood group locus on chromosome 1p.

Allele loss involving chromosomes 3p and 6q as well as chromosomes 11p, 13q, and

17 have been frequently observed in ovarian cancers. Besides allele loss, point mutations

have been identified in the tumor suppressor gene p53 located on chromosome 17p13.

Deletions of chromosome 17q have been reported in sporadic ovarian tumors suggesting

a general involvement of this region in ovarian tumor biology. Allelic loss of MYB and

ESR genes map on chromosome 6q near the provisional locus for FUCA2, the locus for

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a-L-fucosidase in serum. Low activity of a-L-fucosidase in serum is more prevalent in

ovarian cancer patients. This suggests that deficiency of a-L-fucosidase activity in serum

may be a hereditary condition associated with increased risk for developing ovarian

cancer. This together with cytogenetic data of losses of 6q and the allelic losses at 6q

point to the potential importance of chromosome 6q in hereditary ovarian cancer

(Altchek, 208-212).

Activation of normal proto-oncogenes by either mutation, translocation, or gene

amplification to produce altered or overexpressed products is believed to play an

important role in the development of ovarian tumors. Activation of several proto-

oncogenes (particularly K-RAS, H-RAS, c-MYC, and HER-2/neu) occurs in ovarian

tumors. However, the significance remains to be determined. It is controversial as to

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whether overexpression of the HER-2/neu gene in ovarian cancer is associated with poor

prognosis. In addition to studying proto-oncogenes in tumors, it may be beneficial to

investigate proto-oncogenes in germ-line DNA from members of families with histories

of ovarian cancer (Barber, 323-324). It is questionable whether inheritance or rare

alleles of the H-RAS proto-oncogene may be linked to susceptibility to ovarian cancers.

### Diagnosis and Treatment

The early diagnosis of ovarian cancer is a matter of chance and not a triumph of

scientific approach. In most cases, the finding of a pelvic mass is the only available

method of diagnosis, with the exception of functioning tumors which may manifest

endocrine even with minimal ovarian enlargement. Symptomatology includes vague

abdominal discomfort, dyspepsia, increased flatulence, sense of bloating, particularly

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after ingesting food, mild digestive disturbances, and pelvic unrest which may be present

for several months before diagnosis (Sharp, 161-163).

There are a great number of imaging techniques that are available.

Ultrasounds,

particularly vaginal ultrasound, has increased the rate of pick-up of early lesions,

particularly when the color Doppler method is used. Unfortunately, vaginal sonography

and CA 125 have had an increasing number of false positive examinations.

Pelvic

findings are often minimal and not helpful in making a diagnosis. However, combined

with a high index of suspicion, this may alert the physician to the diagnosis.

These pelvic signs include:

Mass in the ovarian area

Relative immobility due to fixation of adhesions

Irregularity of the tumor

Shotty consistency with increased firmness

Tumors in the cul-de-sac described as a handful of knuckles

Relative insensitivity of the mass

Increasing size under observation

Bilaterality (70% for ovarian carcinoma versus 5% for benign cases) (Barber, 136)

Tumor markers have been particularly useful in monitoring treatment, however, the

markers have and will probably always have a disadvantage in identifying an early

tumor. To date, only two, human gonadotropin (HCG) and alpha fetoprotein, are

known to be sensitive and specific. The problem with tumor markers as a means of

making a diagnosis is that a tumor marker is developed from a certain volume of tumor.

By that time it is no longer an early but rather a biologically late tumor (Altchek, 292).

Many reports have described murine monoclonal antibodies (MAbs) as potential tools

for diagnosing malignant ovarian tumors. Yamada et al attempted to develop a MAb

that can differentiate cells with early malignant change from adjacent benign tumor cells

in cases of borderline malignancy. They developed MAb 12C3 by immunizing mice with

a cell line derived from a human ovarian tumor. The antibody reacted with human

ovarian carcinomas rather than with germ cell tumors. MAb 12C3 stained 67.7% of

ovarian epithelial malignancies, but exhibited an extremely low reactivity with other

malignancies. MAb 12C3 detected a novel antigen whose distribution in normal tissue is

restricted. According to Yamada et al, MAb 12C3 will serve as a powerful new tool for

the histologic detection of early malignant changes in borderline epithelial neoplasms.

MAb 12C3 may also be useful as a targeting agent for cancer chemotherapy (Yamada,

293-294).

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Currently there are several serum markers that are available to help make a diagnosis.

These include CA 125, CEA, DNB/70K, LASA-P, and serum inhibin. Recently the

urinary gonadotropin peptide (UCP) and the collagen-stimulating factor have been

added. Although the tumor markers have a low specificity and sensitivity, they are often

used in screening for ovarian cancer. A new tumor marker CA125-2 has greater

specificity than CA125. In general, tumor markers have a very limited role in screening

for ovarian cancer.

The common epithelial cancer of the ovary is unique in killing the patient while being,

in the vast majority of the cases, enclosed in the anatomical area where it initially

developed: the peritoneal cavity. Even with early localized cancer, lymph node

metastases are not rare in the pelvic or aortic areas. In most of the cases, death is due to

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intraperitoneal proliferation, ascites, protein loss and cachexia. The concept of

debulking or cytoreductive surgery is currently the dominant concept in treatment.

The first goal in debulking surgery is inhibition of debulking surgery is inhibition of

the vicious cycle of malnutrition, nausea, vomiting, and dyspepsia commonly found in

patients with mid to advanced stage disease. Cytoreductive surgery enhances the

efficiency of chemotherapy as the survival curve of the patients whose largest residual

mass size was, after surgery, below the 1.5 cm limit is the same as the curve of the

patients whose largest metastatic lesions were below the 1.5 cm limit at the outset

(Altchek, 422-424).

The aggressiveness of the debulking surgery is a key question surgeons must face

when treating ovarian cancers. The debulking of very large metastatic masses makes no

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sense from the oncologic perspective. As for extrapelvic masses the debulking, even if

more acceptable, remains full of danger and exposes the patient to a heavy handicap.

For these reasons the extra-genital resections have to be limited to lymphadenectomy,

omentectomy, pelvic abdominal peritoneal resections and rectosigmoid junction

resection. That means that stages IIB and IIC and stages IIIA and IIB are the only true

indications for extrapelvic cytoreductive surgery. Colectomy, ileectomy, splenectomy,

segmental hepatectomy are only exceptionally indicated if they allow one to perform a

real optimal resection. The standard cytoreductive surgery is the total hysterectomy with

bilateral salpingoophorectomy. This surgery may be done with aortic and pelvic lymph

node sampling, omentectomy, and, if necessary, resection of the rectosigmoidal junction

(Barber. 182-183).

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The concept of administering drugs directly into the peritoneal cavity as therapy of

ovarian cancer was attempted more than three decades ago. However, it has only been

within the last ten years that a firm basis for this method of drug delivery has become

established. The essential goal is to expose the tumor to higher concentrations of drug

for longer periods of time than is possible with systemic drug delivery.

Several agents

have been examined for their efficacy, safety and pharmacokinetic advantage when

administered via the peritoneal route.

Cisplatin has undergone the most extensive evaluation for regional delivery.

Cisplatin

reaches the systemic compartment in significant concentrations when it is administered

intraperitoneally. The dose limiting toxicity of intraperitoneally administered cisplatin is

nephrotoxicity, neurotoxicity and emesis. The depth of penetration of cisplatin into the

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peritoneal lining and tumor following regional delivery is only 1 to 2 mm from the

surface which limits its efficacy. Thus, the only patients with ovarian cancer who would

likely benefit would be those with very small residual tumor volumes.

Overall,

approximately 30 to 40% of patients with small volume residual ovarian cancer have

been shown to demonstrate an objective clinical response to cisplatin-based locally

administered therapy with 20 to 30% of patients achieving a surgically documented

complete response. As a general rule, patients whose tumors have demonstrated an

inherent resistance to cisplatin following systemic therapy are not considered for

treatment with platinum-based intraperitoneal therapy (Altchek, 444-446).

In patients with small volume residual disease at the time of second look laparotomy,

who have demonstrated inherent resistance to platinum-based regimens, alternative

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intraperitoneal treatment programs can be considered. Other agents include mitoxantrone, and recombinant alpha-interferon. Intraperitoneal mitoxantrone has been shown to have definite activity in small volume residual platinum-refractory ovarian cancer. Unfortunately, the dose limiting toxicity of the agent is abdominal pain and adhesion formation, possibly leading to bowel obstruction. Recent data suggests the local toxicity of mitoxantrone can be decreased considerably by delivering the agent in microdoses.

Ovarian tumors may have either intrinsic or acquired drug resistance. Many mechanisms of drug resistance have been described. Expression of the MDR1 gene that encodes the drug efflux protein known as p-glycoprotein, has been shown to confer the characteristic multi-drug resistance to clones of some cancers. The most widely

considered definition of platinum response is response to first-line platinum treatment

and disease free interval. Primary platinum resistance may be defined as any progression

on treatment. Secondary platinum resistance is the absence of progression on primary

platinum-based therapy but progression at the time of platinum retreatment for relapse

(Sharp, 205-207).

Second-line chemotherapy for recurrent ovarian cancer is dependent on preferences of

both the patient and physician. Retreatment with platinum therapy appears to offer

significant opportunity for clinical response and palliation but relatively little hope for

long-term cure. Paclitaxel (trade name: Taxol), a prototype of the taxanes, is cytotoxic

to ovarian cancer. Approximately 20% of platinum failures respond to standard doses of

paclitaxel. Studies are in progress of dose intensification and intraperitoneal

administration (Barber, 227-228). This class of drugs is now thought to represent an

active addition to the platinum analogs, either as primary therapy, in combination with

platinum, or as salvage therapy after failure of platinum.

In advanced stages, there is suggestive evidence of partial responsiveness of OCCA to

radiation as well as chemotherapy, adriamycin, cytoxan, and cisPlatinum-containing

combinations (Yoonessi, 295). Radiation techniques include intraperitoneal radioactive

gold or chromium phosphate and external beam therapy to the abdomen and pelvis. The

role of radiation therapy in treatment of ovarian cancer has diminished in prominence as

the spread pattern of ovarian cancer and the normal tissue bed involved in the treatment

of this neoplasm make effective radiation therapy difficult. When the residual disease

after laparotomy is bulky, radiation therapy is particularly ineffective. If postoperative

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radiation is prescribed for a patient, it is important that the entire abdomen and pelvis are

optimally treated to elicit a response from the tumor (Sharp, 278-280).

In the last few decades, the aggressive attempt to optimize the treatment of ovarian clear cell adenocarcinoma and ovarian cancer in general has seen remarkable

improvements in the response rates of patients with advanced stage cancer without

dramatically improving long-term survival. The promises of new drugs with activity

when platinum agents fail is encouraging and fosters hope that, in the decades to come,

the endeavors of surgical and pharmacological research will make ovarian cancer an

easily treatable disease.

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