Testicular Seminoma: Oncologic Rationale and Role of Surgery in Treatment

Nitin K. Yerram, MD, Hans C. Arora, MD, Abhinav Khanna, MD, Kyle Ericson, MD, Andrew Y. Sun, MD, Paurush Babbar, MD, Naveen Nandanan, MD, and Andrew J. Stephenson, MD

The authors are affiliated with the Department of Urology of the Cleveland Clinic in Cleveland, Ohio. Dr Yerram is a resident surgeon in urologic surgery, Dr Arora is a resident surgeon, Dr Khanna a resident surgeon, Dr Ericson is a resident surgeon, Dr Sun is a resident surgeon, Dr Babbar is a resident surgeon, Dr Nandanan is a resident surgeon, and Dr Stephenson is Director for the Center of Urologic Oncology at Cleveland Clinic’s Glickman Urological and Kidney Institute. Dr Stephenson is also an associate professor of surgery at Case Western Reserve University School of Medicine in Cleveland, Ohio.

Corresponding author:
Nitin K. Yerram, MD
Cleveland Clinic
9500 Euclid Ave, Q-10
Cleveland, OH 44195
E-mail: yerramn@ccf.org

Abstract: Seminomas account for approximately 50% of all cases of testicular cancer. Testicular cancer is a highly curable disease that can be broadly classified as either seminomatous or nonseminomatous; the management and treatment of the 2 forms vary widely. Although surgery plays a large role in the management of nonseminoma, its role in the management of seminoma is much more limited. Most clinicians in the United States choose orchiectomy followed by surveillance for patients with stage I seminomatous disease, and chemotherapy or radiation—followed by surgery for the management of residual masses—for patients with disease that is stage II and higher. Recently, clinicians have proposed a larger role for surgery in stage II seminoma to avoid the long-term toxic effects of chemotherapy and radiation therapy. In this review, we discuss the oncologic rationale for the treatment of seminoma, the role of surgery, and the use of minimally invasive operative techniques for retroperitoneal lymph node dissection.

Introduction

Germ cell tumors (GCTs) account for the vast majority (95%) of testicular cancers. They are the most common tumors in men 20 to 40 years of age.1 GCTs can be classified as seminomatous or nonseminomatous, with several important distinctions between the 2 forms. Seminomas, which account for 50% of all GCTs, tend to be less aggressive than nonseminomas and follow a relatively predictable course. Approximately 80% of patients who have seminomatous GCTs present with stage I disease.2 In contrast, 66% of patients who have nonseminomatous GCTs present with stage II or III disease.2 Seminomas are exquisitely sensitive to radiation and chemotherapy. Visceral metastases are uncommon; when spread occurs, it is most often to the retroperitoneal lymph nodes. Unlike nonseminomas, seminomas do not have an International Germ Cell Cancer Collaborative Group (IGCCCG) poor-risk classification. The survival rates of patients with seminoma remain high even in those who have the most advanced stages of the disease, with overall 5-year survival rates of approximately 79%.3

Historically, stage I seminomas were treated with radiation.
for stage IIA/IIB disease, postchemotherapy surgery, and the management of seminoma, with a focus on RPLND testicular seminoma and examines the role of surgery in nonseminomatous GCT.

stage seminoma, given its established efficacy in low-stage RPLND back into the discussion of treatment for low-risk.5-7 Efforts to reduce treatment toxicity have brought morbidity, secondary malignancy, and pulmonary toxicities.5-7 Efforts to reduce treatment toxicity have brought RPLND back into the discussion of treatment for low-stage seminoma, given its established efficacy in low-stage nonseminomatous GCT.

This review discusses the treatment rationale for testicular seminoma and examines the role of surgery in the management of seminoma, with a focus on RPLND for stage IIA/IIB disease, postchemotherapy surgery, and minimally invasive operative techniques.

**Stage I Seminoma**

**Current Oncologic Rationale**

At the time of diagnosis, 70% to 80% of patients with seminoma have only localized (clinical stage I) disease, and fewer than 5% have distant metastasis at presentation. The cure rate for clinical stage I seminoma is 85% to 90% with radical inguinal orchectomy alone.8-10

After orchectomy, the current National Comprehensive Cancer Network (NCCN) guidelines recommend abdominal and pelvic computed tomography (CT) and chest radiography. In addition, testing for the tumor markers β-human chorionic gonadotropin, lactate dehydrogenase, and α-fetoprotein should be repeated because the post-orchectomy levels are used to determine stage, prognosis, and further treatment. If the findings on the chest x-ray film are abnormal or abdominal/pelvic imaging raises a suspicion of metastatic disease, chest CT is recommended. Magnetic resonance imaging of the brain may be indicated if neurologic signs or symptoms are present. Sperm banking to preserve future fertility should be discussed before further treatment is undertaken.11

When demonstrable metastatic disease is absent and the tumor marker levels are within normal ranges, pure seminoma is amenable to surveillance, chemotherapy, or external beam radiation. The natural history of seminoma is significantly more favorable than that of nonseminomatous GCT, with a lower risk for metastatic disease at presentation and a lower risk for relapse, and with a high degree of sensitivity to both radiotherapy and cisplatin-based chemotherapy.2 Surgery is not a generally recommended treatment option for orchectomy-confirmed stage I seminoma, and to date, there is minimal literature comparing the efficacy and outcomes of RPLND vs chemotherapy or radiation.

Primary radiotherapy was the predominant treatment of choice for stage I pure seminoma during most of the last half century. However, the use of external beam radiation in the treatment of stage I pure seminoma has declined significantly in the modern era. Up to 74.7% to 83.9% of patients were being treated with radiotherapy at the turn of the 21st century, but more recently the percentage has decreased to 24.0% to 37.7%, with a concomitant rise in the use of both chemotherapy and active surveillance.12-14 The radiation field typically includes the para-aortic lymph nodes, and the dose consists of 20 to 30 Gy divided over 10 to 15 fractions.15 In-field recurrence occurs in fewer than 1% of patients and out-of-field recurrence in fewer than 2% of patients, and chemotherapy is completely curative in nearly all cases. However, radiation therapy is associated with several late toxicities, including chronic gastrointestinal upset (up to 5%) and persistent oligospermia (8%).15 The more concerning long-term complications of radiation are delayed cardiac toxicity and risk for secondary malignancy. The latter may occur in as many as 18% of patients with seminoma at 25 years, and there is a 2.64% risk for death due to secondary malignancy.15

Chemotherapy with carboplatin has been used increasingly in clinical stage I pure seminoma. Single-agent carboplatin (1-2 cycles) is the treatment of choice on the basis of early data showing a cure rate of up to 90% and decreased nephrotoxicity, neurotoxicity, and ototoxicity in comparison with cisplatin. Relapse-free survival rates are close to 100% at 3 to 5 years.15 In a prospective trial of 1477 patients randomly assigned to a single cycle of carboplatin vs 20 to 30 Gy of adjuvant radiotherapy, similar relapse-free survival rates (96% vs 95%) were observed at 3 years, indicating nearly equivalent therapeutic benefit but with significant differences in toxicities and potential complications. These included a decrease in the risk for a de novo GCT in the contralateral testis in the carboplatin group.13 Acute toxicities of carboplatin can range from fatigue and nausea/vomiting to thrombocytopenia and neutropenia.16 Late toxicities have not been confirmed, given the lack of long-term follow-up in patients treated with carboplatin.17 Regardless, treatment with
single-agent carboplatin remains an acceptable alternative to radiation therapy for stage I seminoma.

Surveillance after orchiectomy is a reasonable option for patients who prefer not to undergo further therapy at the time, are willing to continue regular close follow-up, and can be relied on to do so. Surveillance also avoids the potential late toxicity of infra-diaphragmatic radiation, and in North America, it is the preferred option for stage I seminoma. In a recent study of high-risk patients (primary tumor ≥6 cm), the rate of recurrence was 32% for those who underwent surveillance vs 2.8% for those who underwent adjuvant radiation therapy, but the 10-year overall survival rates were essentially equivalent in the 2 groups.18 In a meta-analysis of 13 trials encompassing 12,075 patients with stage I pure seminoma, relapse rates were on average 14.8% for those undergoing surveillance vs 3.9% for those treated with adjuvant radiotherapy.14 In the vast majority of cases managed with surveillance, recurrence develops within 3 years, with the most common site of metastasis being the retroperitoneum.18,19 Even in cases of relapse in patients initially managed with surveillance, disease-specific survival at 15 years was still as high as 99.3%.14 A review of tumor characteristics from 638 patients at 4 institutions determined a 5-year relapse-free rate of 82.3%, and a multivariate analysis found that large tumor size (>4 cm) and rete testis invasion were independent predictors of relapse.19 In an observational study of 897 patients, the rate of relapse was 15.5% among those who underwent surveillance vs 9.3% among those who received adjuvant single-dose carboplatin. In the absence of large tumor size or rete testis invasion, relapse rates were as low as 3.0% and 2.2%, respectively.18 Although both radiation therapy and chemotherapy reduce the risk for relapse in stage I pure seminoma, there is essentially no improvement in overall survival or disease-specific survival.14

In the absence of an appropriate response to chemotherapy or radiation, a high index of suspicion must be maintained for the transformation of seminoma into nonseminomatous GCT, which may occur in as many as 10% to 15% of patients in whom recurrence with metastatic disease develops. In a study of 154 patients who were treated for testicular GCTs, postmortem autopsy revealed evidence of nonseminomatous elements at metastatic sites in 44% of patients who originally had pure seminoma.20

Stage II Seminoma

Current Oncologic Rationale

Although the management of patients with stage II seminoma poses significant challenges, a minority of all testicular seminomas are stage II at diagnosis. Studies have shown that only 15% to 20% of all patients who have a diagnosis of seminoma present with stage II or higher disease.21 Furthermore, of these patients, close to 70% have clinical stage IIA or IIB disease.21 To understand the role of surgery in seminoma treatment, it is important to understand the initial approach to the treatment of stage II and higher disease.

The most frequently used initial treatment for patients with stage IIA or IIB disease is chemotherapy or radiation. For the treatment of nonbulky disease, radiation continues to be an option.21,22 Radiation dosages and treatment templates differ, but most centers administer 25 to 30 Gy to the retroperitoneum and pelvis, with a boost of 5 to 10 Gy given to the specific areas of disease. With this protocol, recurrence rates have been low, with rates in the literature reported to be between 0% and 8% for stage IIA disease and between 10% and 13% for stage IIB disease.23,25 Furthermore, relapse rates with systemic chemotherapy have been recorded in the single digits, with almost all cases cured.21 Recently, chemotherapy has supplanted radiation therapy as the most frequently used option for patients with stage IIA/IIB disease.4 In a recent study, Garcia-del-Muro and colleagues reported on the efficacy of either 4 cycles of etoposide/cisplatin (EP) or 3 cycles of bleomycin/etoposide/cisplatin (BEP) for the treatment of low-risk stage II disease.26 They reported that men with stage IIA disease had an estimated 5-year progression-free survival rate of 100%, whereas men with stage IIB disease had a 5-year progression-free survival rate of 87%. Although the debate continues regarding the use of chemotherapy vs radiation for the initial treatment of stage IIA/IIB seminoma, given the long-term toxicities of both regimens, emerging evidence indicates that surgery may play a role in the treatment of patients with low-risk stage II disease.

The burden of retroperitoneal disease is the main prognostic factor in stage IIC seminoma and the driving factor for treatment. Traditionally, for disease that is stage IIC or higher, chemotherapy has been regarded as the first-line treatment, given its superior relapse-free rate.27 Radiation does not play a role in the treatment of advanced-stage seminoma. Standard chemotherapy for patients considered to have “good-risk” disease consists of a cisplatin-based therapy, either 4 cycles of EP or 3 cycles of BEP.21 Studies have shown a significantly decreased survival rate in men treated with carboplatin, and therefore, patients should always receive treatment with a cisplatin-based regimen when possible.28
success of primary RPLND in nonseminomatous GCT, a few small studies have sought to evaluate the role of RPLND in low-stage seminoma. One such study was a retrospective review of 161 patients with stage I or II seminoma treated between 1975 and 1991 at the University Hospital Magdeburg in Magdeburg, Germany. In this series, 98 patients received radiation therapy and 63 underwent RPLND. Early on, RPLND was the preferred treatment for low-stage seminoma, but after 1985, radiation became the predominant therapy. The in-field relapse rate was 9.5% after RPLND vs 2% after radiotherapy, although this difference was not significant. The out-of-field relapse rate was 4.8% for RPLND vs 7.1% for radiotherapy. The recurrence rate after primary RPLND was 7% in stage I disease, whereas none of the patients with stage IIA disease showed evidence of relapse at a median follow-up interval of 6.6 years after initial diagnosis. Another study, of 14 patients with clinical stage I or IIA pure seminoma treated prospectively with primary nerve-sparing RPLND between 1997 and 2002, found evidence of lymph node metastasis in 3 of 10 clinical stage I cases and in all 4 cases of stage IIA disease. After a median follow-up of 56 months, all patients were free of retroperitoneal or distant metastases. A more recent retrospective study, of 4 patients with pure seminoma (3 of whom had T1/T2 N1 clinical stage I disease) who underwent modified template nerve-sparing RPLND between 2010 to 2014, sought to build upon previous investigations. One patient had T0 (burned-out testicular primary) N3 disease, which was classified as IIA after RPLND.

For right-sided tumors, the boundaries of dissection were as follows:

- lateral: right ureter;
- medial superior: inferior mesenteric artery to the left ureter;
- medial inferior: inferior mesenteric artery to the anterior abdominal aorta;
- superior: renal vessels; and
- inferior: bifurcation of the right common iliac artery.

For left-sided tumors, the boundaries of dissection were as follows:

- lateral: left ureter;
- medial superior: inferior mesenteric artery to the anterior inferior vena cava;
- medial inferior: inferior mesenteric artery to the anterior abdominal aorta;
- superior: renal vessels; and
- inferior: bifurcation of the left common iliac artery.

At a mean follow-up of 25 months, no disease relapse or mortality was evident, and there were no long-term complications. Given the lack of high-quality studies, the same group has initiated a prospective phase II clinical trial that is currently enrolling patients with stage I/IIA testicular seminoma (isolated retroperitoneal disease) to undergo primary RPLND. The study will assess recurrence-free survival at 5 years, along with short-term (at 12 months) and long-term (at 5 years) complications. The investigators will also attempt to assess how frequently patients can avoid adjuvant chemotherapy or radiation. The study is estimated to reach completion in August 2019.

**Advanced Seminoma After Chemotherapy**

**Current Oncologic Rationale**

Surgical resection plays an important part in the treatment algorithm for residual masses detected after first-line chemotherapy. After first-line chemotherapy, between 58% and 80% of patients have residual masses. Although surgical resection remains the accepted standard for the treatment of masses after chemotherapy in nonseminomatous GCT, the management of such masses in seminoma remains hotly debated for a number of reasons. First, although there is a 5% to 15% chance that masses after chemotherapy in nonseminomatous GCT are viable cancers and a 30% to 50% chance that they are teratomas, the chance that residual masses in seminoma are viable cancers is only 10% to 20%, and they are rarely teratomas. Secondly, these patients have received chemotherapy, and surgery is quite difficult because of the desmoplastic reaction associated with seminoma tissue following chemotherapy. Lastly, regression of postchemotherapy residual masses in patients with seminoma is reported in 50% to 60% of cases, with the median time to resolution being 13 to 18 months. Despite these findings, certain patients have been found to benefit from surgery following chemotherapy. Evidence in the literature has shown that the chance of residual masses larger than 3 cm harboring cancer is 27% to 38%, 20,31,32 The likelihood that masses 3 cm or smaller in size contain cancer has been shown to be very low. In light of these data, the recent IGCCCG and NCCN guidelines recommend that all patients with residual masses larger than 3 cm in the postchemotherapy setting undergo further workup.

With the advent of fluorodeoxyglucose positron emission tomography (FDG-PET), clinicians can further characterize residual masses. Initially, published data on the use of FDG-PET in detecting viable cancer indicated that the specificity and sensitivity of the test were 100% and 80%, respectively. However, these data have come under
Surgical Resection

Surgical resection for residual masses after chemotherapy in patients treated for seminoma remains a challenging undertaking. Given the desmoplastic tissue reaction that occurs with chemotherapy, the resection of masses is rarely straightforward, and evidence shows a higher rate of additional surgeries (eg, nephrectomy, vascular repair) in patients treated for advanced seminoma vs nonseminomatous GCT. \(^{11}\) Complete resection of the masses is difficult, with reported rates in the literature between 58% and 74%.\(^{35-38}\) In addition, the therapeutic benefit of complete resection is unknown. Herr and colleagues noted no difference between the overall survival rates of patients who underwent complete resection and the rates of those who underwent incomplete/no resection.\(^{35}\) However, Rice and colleagues reported on 17 patients in their cohort whose disease relapsed following RPLND or an incomplete resection.\(^{39}\) Of these 17 patients, 12 had disease that relapsed in the retroperitoneum, indicating a high rate of local failure, possibly caused by incomplete resection. Furthermore, the authors noted that salvage chemotherapy was an independent predictor of cancer-specific mortality, implying that an immediate resection of residual masses (after first-line chemotherapy) might confer a survival benefit vs delayed resection (after second-line/salvage chemotherapy). Although no definite guidelines exist for area of treatment, it is the opinion of these authors that an immediate, complete resection along with a bilateral RPLND should be attempted for patients with sizable residual masses following chemotherapy, given the possible benefit of decreased local failure rates. If a complete resection is not possible, the goal should be to remove as much residual mass as can be done safely. Because of the difficulty of resections following chemotherapy, and the increased morbidity, it is recommended that such patients be referred to a tertiary care center where a high-volume RPLND surgeon is available.\(^{40}\)

Refractory/Relapsing Seminoma

For patients with seminoma that is refractory to first-line chemotherapy, surgery is of limited benefit as a treatment option. Rice and colleagues analyzed 36 patients who were found to have pure seminoma at time of RPLND after chemotherapy for progressing cancer. The 5-year cancer-specific survival rate was extremely poor, at 54%, with only 9 patients having no evidence of disease at last follow-up. As discussed earlier, the authors noted that a sizable portion of patients had local retroperitoneal recurrence, implying the likelihood of microscopic disease in the cohort.\(^{39}\) Conversely, chemotherapy seems to provide a considerable survival advantage compared with surgery for patients who have refractory seminoma. Agarwala and colleagues reported an overall survival rate of 75% at a median follow-up of 46 months for patients who had relapsed pure seminoma treated with high-dose carboplatin and etoposide followed by peripheral blood stem cell transplant.\(^{41}\) Encouragingly, 92% of the patients (22/24) who received a high-dose chemotherapy regimen as second-line treatment achieved “no evidence of disease” status, further proving the utility of chemotherapy in this setting.

Although surgery continues to play a role for a selected cohort of patients, it is likely of benefit only for patients with anatomical factors (ie, ureteral obstruction) or those with residual masses after second-line chemotherapy. Residual masses after second-line chemotherapy have been found to be more likely to contain viable GCT,\(^{42-43}\) so it is the authors’ opinion that surgical resection should play a significant role in the management of patients with residual masses. High-level evidence regarding the management of refractory seminoma is lacking, further stressing the need for high-quality studies to assess the true utility of all treatment options.
Minimally Invasive Surgery

Laparoscopic Retroperitoneal Lymph Node Dissection
The oncologic indications for minimally invasive RPLND mirror those for open RPLND, discussed earlier. Generally, patients selected for minimally invasive approaches have limited disease without extensive involvement of nearby organs or vasculature. Most of the reports on laparoscopic and robotic RPLND are in the nonseminomatous GCT setting, although some studies do include laparoscopic or robotic RPLND following chemotherapy for pure seminoma.

High-volume laparoscopic centers began using laparoscopic approaches for RPLND in the 1990s. An initial report of 26 patients by Rassweiler and colleagues suggested safety in the primary RPLND setting, but the majority of cases of laparoscopic RPLND after chemotherapy were converted to open surgery in this early series. With continued experience, laparoscopic outcomes continued to improve. Permpongkossol and colleagues later reported 16 cases of laparoscopic RPLND after chemotherapy, of which 14 were successful. Complication rates in this series decreased as surgical experience grew, suggesting a learning curve for this technically challenging surgery.

Additional series confirmed the safety of a laparoscopic approach and began to suggest oncologic efficacy as well. Steiner and colleagues reported 188 cases of laparoscopic RPLND, with a 2.6% rate of conversion to open surgery and a disease recurrence rate of only 3% at more than 50 months of follow-up. The same group later published the outcomes of 100 cases of laparoscopic RPLND exclusively in the postchemotherapy setting, citing a 1% rate of conversion to open surgery, a mean blood loss of less than 100 mL, and a recurrence rate of 1% at more than 6 years of follow-up. Furthermore, a systematic review of more than 800 patients undergoing laparoscopic RPLND suggested relapse rates similar to those achieved with open approaches, with no cases of in-field recurrence.

Later studies in this systematic review trended toward lower complication rates, again suggesting that a learning curve is associated with laparoscopic RPLND.

Although reports of laparoscopic RPLND have been encouraging, this approach has been limited to technically skilled, high-volume laparoscopic surgeons, and outcomes may not apply broadly. More recently, case reports and small series of robotic RPLND have emerged. One series compared 16 robotic and 21 laparoscopic RPLND procedures by a single surgeon and reported similar operative times, amounts of blood loss, complication rates, and lymph node yields for the 2 approaches. As comfort with robotic surgery has grown among urologists, so have reports of robotic RPLND.

Robotic Retroperitoneal Lymph Node Dissection

Technique. Case reports have described the early experience of robotic RPLND following chemotherapy, including RPLND in patients with seminoma. Techniques vary based on laterality, tumor burden, and surgeon preference. Annerstedt and colleagues have described a rightsided robotic RPLND approach in which they reflect the right colon medially to expose the inferior vena cava and associated nodes. This is performed with the patient in right flank position, and port placement is similar to that for right renal surgery.

Bora and colleagues have described a bilateral template robotic RPLND in nonseminomatous GCT, with dissection carried laterally to the ureters, superiorly to the renal veins, and inferiorly to the bifurcation of the common iliac artery. These authors begin with the patient in the left-side-up position to reflect the left side of the colon medially until the anterior aorta is identified. After left-sided lymphadenectomy, the robot is undocked, the patient is repositioned in right-side-up position, and the robot is redocked for right-sided lymphadenectomy.

Stepanian and colleagues have described the evolution of their technique over the course of 20 robotic RPLND procedures. Early in their experience, the authors employed a flank approach, as described earlier, with undocking and repositioning between the left and right sides. They then transitioned to a supine approach, which allowed bilateral RPLND without repositioning. The authors used a stitch on the cut edge of the posterior peritoneum to retract it toward the anterior abdominal wall and improve exposure to the retroperitoneum without repositioning.

Outcomes. Descriptions of robotic RPLND in seminoma are few and limited to the postchemotherapy setting. The largest series of robotic RPLND procedures exclusively in the postchemotherapy setting was described by Kamel and colleagues, in which 12 patients, 25% of whom had pure seminoma, underwent robotic RPLND after chemotherapy. The procedure was successfully performed with a robotic approach in 11 of 12 men, with a mean operative time of 312 minutes, a mean estimated blood loss of 475 mL, and a mean length of hospital stay of 3.2 days. Complications developed in 3 men, and only 1 complication was major (Clavien grade III or higher). There was no disease recurrence at 31 months.

Although robotic RPLND for seminoma is largely limited to the postchemotherapy setting, robotic primary RPLND for nonseminomatous GCT has also been described. The largest such series is a multicenter study of 47 men with low-stage nonseminomatous GCT undergoing robotic primary RPLND. The median operative
time was 235 minutes, with blood loss of 50 mL and a 1-day length of hospital stay. The early postoperative complication rate was 9%, and the recurrence rate was 3% at 2-year follow-up. Although robotic primary RPLND is limited to nonseminomatous GCT, open primary RPLND for low-stage seminoma is currently being investigated, as discussed earlier.31 As this area of surgery continues to mature, it is likely that robotic approaches for the primary management of seminoma will also be explored. Nonetheless, open surgical approaches remain the mainstay of treatment for RPLND in seminoma, and indeed in all testicular cancers.

Conclusion

Seminomatous GCTs are highly curable malignancies with an exquisite sensitivity to both radiation and chemotherapy. The current treatment paradigm employs the judicious use of surveillance, chemotherapy, and radiation therapy in most stages of seminoma. The role of surgery in seminoma is classically limited to orchectomy and the postchemotherapy resection of residual masses. As the focus shifts toward limiting treatment toxicity in seminoma survivors, however, RPLND may be an attractive option for patients with lower-stage disease owing to the limited long-term morbidity with modern operative techniques. Further research in this population will help delineate which patients will benefit most from surgical intervention for low-stage disease.

Disclosures

The authors have no relevant financial disclosures.

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