Early Cervical Neoplasia: Advances in Screening and Treatment Modalities

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Abstract: Cervical cancer is one of the most common causes of cancer in women worldwide. However, improvements in screening programs and treatment modalities have significantly reduced the morbidity and mortality of this disease. The discovery that infection with the human papillomavirus is a crucial part of the causative pathway in cervical cancer pathogenesis has revolutionized screening and prompted investigations into alternatives to traditional cytologic evaluation, which may be useful in low-resource settings. Concomitant with improved screening has been a shift towards greater detection of both preinvasive and early-stage neoplastic disease. Earlier detection not only allows for surgical management of disease, with the avoidance of chemotherapy and radiation, but also the possibility of fertility preservation. As surgical technologies advance to encompass minimally-invasive procedures, interventions for early-stage cervical cancer are becoming increasingly effective in disease eradication while permitting patients to maintain their quality of life.

Introduction

The implementation of routine screening for cervical cancer has been one of the most successful cancer surveillance programs in the United States. Since its development in 1950, cervical screening has decreased cervical cancer incidence by 75% and mortality by 70%.[1] However, cervical cancer remains one of the most common cancers in women worldwide, with approximately 490,000 new cases diagnosed each year and 275,000 related deaths.[2] Currently, 80% of newly diagnosed cervical cancers occur in developing countries, and this percentage is expected to increase over the next decade.[2] The disparity in incidence between the United States and developing countries is attributed to poor access to screening and treatment programs. Access to care is a clear factor among the 12,000 newly diagnosed cases of cervical cancer in the United States as well.[3] Of those women diagnosed in the United States, 50% are estimated to have never had cytologic testing and an additional 10% have not

been screened in the past 5 years.[4] To further reduce the incidence and mortality from this disease in the United States and abroad, the modification and simplification of cervical screening must continue. This article will review the current literature on cervical cancer screening, advances in screening techniques, as well as advances in the treatment of preinvasive disease and invasive cervical cancer.

Human Papillomavirus

To understand the current methods for cervical screening, a basic understanding of the nature of cervical abnormalities is essential. Human papillomavirus (HPV) is the critical factor for the development of preinvasive and invasive cervical lesions. HPV is a small, nonenveloped, double-stranded DNA virus predominantly transmitted through sexual intercourse. An estimated 75% of the U.S. population is infected with this virus. More than 5.5 million incident cases are reported annually, the majority of which occur in persons aged 15–24.[5] The most consistent risk factors for acquiring HPV are number of sexual partners, age of first sexual intercourse, and a partner infected with HPV.[6]

There are over 100 genotypes of HPV, of which at least 40 genotypes are known to infect the anogenital tract.[7] These subtypes are further classified into "high-risk" HPV (HR-HPV) and "low-risk" HPV (LR-HPV) depending on their oncogenic potential for cervical cancer and its precursors. LR-HPV genotypes, including HPV 6 and 11, typically cause benign anogenital warts, though they may occasionally be associated with neoplastic cervical changes.[8] Invasive lesions, on the other hand, are much more commonly caused by HR-HPV, including, in order of frequency, types 16, 18, 45, 31, 33, 52, 58, and 35.[9] Although the majority of premalignant and invasive disease can be directly attributed to types 16 or 18, HPV DNA from any genotype is detectable in greater than 99% of all cervical cancer specimens.[9,10]

Current Cervical Cytologic Methods

Pap Smear

In the United States, there are currently 2 approved methods for obtaining cervical cytology for cancer screening: conventional Pap smear or liquid-based cytology. Thus far, studies comparing the performance of the 2 methods have not identified one method as superior to the other.[11] A distinct advantage of liquid-based cytology is the ability to test the residual components for gonorrhea, chlamydia, or trichomonas, and to run reflex HPV testing in cases of atypical squamous cells of undetermined significance (ASCUS). For this reason, 90% of gynecologists in the United States now report using the liquid-based test.[12]

HPV Testing

In 1989, Tidy and colleagues suggested a clinical role for HPV testing after using polymerase chain reaction to detect HPV-16.[13] Several studies in the 1990s investigated the utility of HPV testing for women with ASCUS Pap smears. To date, the largest trial to investigate the importance of HPV testing is the ASCUS-low-grade squamous intraepithelial lesions (LSIL) Triage Study (ALTS).[14] Women with ASCUS interpretation on Pap smears were either referred directly to colposcopy, had HPV testing, or had repeat cytology with triage to colposcopy as needed. The authors concluded that reflex HPV testing is as sensitive for detecting cervical intraepithelial neoplasia (CIN) as immediate colposcopy, and should be the preferred approach for patients with ASCUS cytologies. This differed for patients with LSIL, the vast majority of whom (83%) were found to have HR-HPV.[15] Reflex HPV testing was not cost-effective in this group in determining patient triage to colposcopy, and therefore it is not recommended for the initial management of women with LSIL.[15] Wright and coauthors also investigated the use of HPV testing for women with LSIL and began using reflex HPV testing as the newer liquid-based cytology test became available.[16] This study again confirmed the utility of HPV testing in ASCUS, but showed limited use for Pap smears with LSIL due to their low specificity.

Current Recommendations for Surveillance

Several agencies publish guidelines for cervical screening, including the American Cancer Society (ACS),[17] the U.S. Preventive Services Task Force (USPSTF),[18] and the American College of Obstetricians and Gynecologists (ACOG).[19] Table 1 outlines the compiled screening recommendations.

New Techniques for Screening

The majority of women diagnosed with cervical cancer in the United States and abroad will not undergo routine cytologic testing prior to diagnosis. Increasing the accessibility of cervical cancer screening is essential in the United States to continue reducing incidence and mortality from this disease. From a global health perspective, cervical cancer screening techniques should be inexpensive, easy to use, and easy to interpret. Though such obstacles are easier to overcome in developed countries, they can be problematic in those with health care systems that are unable to support screening efforts. For this reason, sub-

Table 1. Current Cervical Cancer Surveillance Guidelines

	ACS	ACOG	UPSTF
Last Updated	October 2009	December 2009	January 2003
Commencement	Age 21 or 3 years after onset of sexual activity	Age 21	Age 21 or 3 years after onset of sexual activity
Interval			
– Conventional	Annual until age 30, then every 2–3 years if negative cytology	Biennial for ages 21–29, then every 3 years after age 30 if 3 consecutive negative cytology results	At least every 3 years
– Liquid-based	Biennial until age 30, then every 2–3 years if negative cytology	Same as for conventional screening	Insufficient evidence to recommend use
– HPV testing	Every 3 years if HPV and cytology negative	For women 30 years or older, every 3 years if HPV and cytology negative	Insufficient evidence to recommend use
Age of discontinuation	Age 70 with no abnormal results over past 10 years	Between ages 65–70 with 3 or more negative cytology tests results and no abnormal results in the past 10 years	Age 65 if not otherwise at high risk for cervical cancer
Post-hysterectomy	Discontinue if for benign reasons and no history of CIN II/III	Discontinue if for benign reasons and no history of CIN II/III	Discontinue if for benign reasons

ACOG=American College of Obstetricians and Gynecologists; ACS=American Cancer Society; CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus; UPSTF=US Preventative Services Task Force.

stantial research efforts have been undertaken to identify screening practices that are feasible in economically disadvantaged areas.

Primary HPV Testing

Persistent infection with HR-HPV is necessary for the development of cervical cancer. Given this key principle, investigators are currently evaluating the feasibility of cervical HPV testing as the primary test to replace cytologic screening. Several meta-analyses have shown HPV DNA testing to be more sensitive for high-grade lesions than cytology, although less specific. In 2007, Mayrand and associates published the results of a large trial that randomized women to either conventional cytology or HPV testing as primary screening.[20] Over 10,000 women participated in the study, which revealed that HPV testing had greater sensitivity than conventional Pap smear (94.6% vs 55.4%). Cuzick and coworkers later reported that a negative HPV test predicted a significantly longer interval free of CIN when compared with negative cytology (6 vs 3 years).[21] Subsequent studies have also shown that after an HPV-negative result on routine screening, the likelihood of developing CIN of grade 2 (CIN II) or greater was between 0.01 and 0.42%.[22]

Although primary HPV testing does afford some advantages, it poses several dilemmas with regard to management. HPV infections are very common, and may clear spontaneously, especially in adolescents and young adults. Detection of HPV in young, immunocompetent women may result in increased numbers of women triaged to colposcopy. Such a trend would not only increase medical costs for patients, but also increase rates of unnecessary excisional procedures, which may adversely affect fertility potential.[23]

Self-collected Sampling for HPV Testing

Over the last 10 years, researchers have evaluated the accuracy of detecting HPV DNA on self-collected vaginal samples, and more recently on urine samples. A meta-analysis published in 2005 evaluating the diagnostic accuracy of self-collected vaginal samples for the detection of HPV DNA noted that the combined sensitivity of HPV detection was 74%, with 88% specificity.[24] In addition, both sensitivity and specificity remained constant regardless of whether women were recruited at dysplasia referral clinics or primary care clinics.[24] This method may also be preferred for women victimized by abuse or women with cultural concerns.

Visual Inspection With Acetic Acid

Despite advances in the methods to detect cervical abnormalities in the United States, rates of cervical cancer

detection continue to be poor in the developing world due to lack of access or ineffective screening practices. Recognizing this, substantial research efforts have been initiated by the international community to identify screening modalities that are effective and feasible in economically disadvantaged areas. One such modality is visual inspection of the cervix with acetic acid (VIA). Acetic acid turns dysplastic lesions white, thus making them visible. In 2009, Sankaranarayanan and associates reported on a cluster-randomized trial performed in rural India, which assigned women either to screening by HPV testing, cytologic testing, or VIA.[25] Women in the VIA group had cervical biopsies taken if lesions were visualized at the time of exam. Although HPV testing proved to be the optimal screening procedure, cumulative incidence and mortality from cervical cancer was similar between conventional cytology and VIA. These results are encouraging, and suggest that in regions where poor laboratory infrastructure precludes adequate cytologic processing and HPV testing, an inexpensive and effective method of screening is available.

Surgical Approaches to Cervical Neoplasia

Preinvasive Cervical Neoplasia

Once a diagnosis of CIN has been made by cervical biopsy, patients are triaged to observation or surgical excision. Because the majority of CIN I (>88%) will not progress to more advanced dysplasia, the preferred management for these lesions is simple observation with follow-up cytology and/or HPV testing.[26,27] In the event that the abnormality persists for longer than 2 years, definitive treatment with either an ablative or excisional procedure is recommended.[27] When cervical biopsy reveals a more advanced intraepithelial lesion, such as CIN II or III, excision should be performed because risk of progression to invasive cancer is much more substantial than for low-grade dysplastic lesions. In fact, risk of progression to invasive disease in untreated, high-grade, preinvasive disease is estimated to be approximately 5% for CIN II, and 12–31% for CIN III.[28,29] The exception to this is in women younger than 21 years, in whom spontaneous regression of advanced dysplasia has been clearly demonstrated (60%).[27,30]

Two techniques are employed to perform excisional biopsies for cervical dysplasia: the loop electrosurgical excision procedure (LEEP) and cold knife conization (CKC). LEEP uses a semicircular wire on an insulated handle through which electricity is passed to both cut and coagulate the cervix. It is generally performed in an outpatient setting using only local anesthesia, and is a good option for women desiring fertility preservation because it removes less cervical stroma than conization. There is a small risk of post-excision bleeding, but, in general, such bleeding is easily controlled with topical hemostatic agents such as Monsell's solution or silver nitrate. One notable disadvantage of LEEP is that the wire loop may cause thermal damage to the specimen, thus obscuring pathologic assessment of margin status.[31]

CKC is an operative procedure that uses a scalpel to remove the entire transformation zone and the suspicious lesion at the same time. Indications for CKC include a cervical biopsy of adenocarcinoma in situ, the need to rule out an invasive cancer, and suspected endocervical lesions.[31] Additionally, if cytologic testing repeatedly suggests a high-grade lesion but colposcopic-directed biopsies reveal negative or low-grade dysplasia, excision is required. The advantage of CKC is that it is both a diagnostic and therapeutic procedure. However, it is more costly than LEEP, must be done in an operative suite, and may not be ideal for women with significant medical comorbidities who are at high-risk for anesthetic complications. CKC has also been associated with greater risk of preterm labor and cervical incompetence in pregnancies conceived after the procedure. In one study, 11% of subjects delivered prior to 34 weeks and 25% of subjects delivered prior to 37 weeks.[32] Ultimately, because both LEEP and CKC have demonstrated equivalent efficacy in excising cervical abnormalities,[33] the decision to proceed with one procedure over the other is made at the discretion of each patient's gynecologist.

In cases of recurrent or persistent high-grade cervical dysplasia, a second excisional procedure or simple hysterectomy is recommended.[27] Simple hysterectomy involves removal of the uterine corpus and the cervix. Ligation of the uterine vessels occurs immediately adjacent to the lateral aspect of the uterus. Hysterectomy is not indicated as a primary surgical treatment for CIN until invasive cancer has been ruled out, and in general it is reserved for women with concurrent gynecologic morbidities, including uterine fibroids or abnormal bleeding.[27] The approach used for hysterectomy may be vaginal, abdominal, laparoscopic, or robotic, and is dependent upon surgeon preference, available facilities, and the patient's preoperative medical condition. Abdominal hysterectomy is associated with longer post-operative in-hospital recovery times, but overall, the rates of major complications are similar between modalities.[34-36] Minimally invasive surgery has become much more widely used in gynecology, as reports on the safety and feasibility of laparoscopic, and more recently robotic, surgery have been published.[37-40] Advantages of robotic surgery include decreased blood loss, shorter hospital stays, and quicker return of bowel function and to activities of daily life.[41]

Early Invasive Cervical Cancer (Stage IA1–IB1)

Table 2 demonstrates the revised staging for cervical cancer published by the International Federation of Gynecology and Obstetrics in 2009.[42] Stage IA1 cervical cancer has long been treated conservatively, with acceptable surgical options including CKC or simple hysterectomy, similar to the treatment of cervical dysplasia noted above. Of course, care should be taken to guarantee that all margins are negative in the case of a cone biopsy to ensure more advanced invasive disease is not present and to reduce the risk of recurrent disease.[43] Furthermore, a modified radical hysterectomy should be considered in patients with stage IA1 disease in the presence of lymphovascular space invasion.[44]

Conversely, the traditional standard of care for treatment of stage IA2–1B1 cervical cancer involves radical surgery or radiotherapy. Given that the response and survival rates are equivalent between these 2 treatment options,[45] the modality is often chosen based on other factors including side effects and patient or physician preference. In the case of surgical management, treatment consists of a radical hysterectomy and pelvic lymphadenectomy. The key difference between a radical hysterectomy and the simple hysterectomy described above is the removal of the lymph nodes from along the pelvic vasculature, removal of the parametrial tissue lateral to the cervix, identification and ligation of the uterine vessels at their origin, and removal of 2 centimeters of the upper vagina.[46]

Prior to 1989, abdominal entry was the primary approach for the performance of a radical hysterectomy. However, as the field of minimally invasive surgery expanded and instrumentation improved, gynecologic oncologists began to explore radical surgery through alternative routes. Nezhat and coauthors and Canis and colleagues were the first to describe the technique of radical hysterectomy performed laparoscopically.[47,48] This procedure was quickly shown to be equivalent to the traditional approach in regard to clinical outcomes such as recurrence and overall survival.[37,49-51] Furthermore, when directly compared to the abdominal approach, the laparoscopic technique has been demonstrated to have a shorter length of stay in the hospital[52-54] and decreased estimated blood loss.[37,52,53] Although operating time is longer in the patients undergoing laparoscopic radical hysterectomy,[52] the studies have demonstrated that the rate of major complications is equivalent between the 2 groups.[52,53]

Laparoscopy is not without its disadvantages, including rigid instrumentation with no ability for articulation, 2-dimensional views, and high occurrence of operator fatigue and tremor. Therefore, when the DaVinci robotic platform (Intuitive Surgical, Inc, Sunnyvale, California) became available, gynecologic oncologists were quick to utilize it for the treatment of early cervical cancer. The robotic system offers wrist-like motion, improved optics, and reduction in the natural tremor of the surgeon.[55] Use of the robotic system to perform radical hysterectomy was described in 2006,[56] and since that time has been compared to both the abdominal and laparoscopic approaches in a retrospective fashion.

Studies comparing abdominal radical hysterectomy to robotic-assisted radical hysterectomy have clearly favored the use of the robotic system. Boggess and associates reported outcomes of 51 patients that underwent a robot-assisted type III radical hysterectomy with pelvic lymphadenectomy for early-stage cervical

Table 2. Revised Internal Federation of Gynecology and Obstetrics Staging for Cervical Cancer, 2009[42]

Stage I: the carcinoma is strictly confined to the cervix
IA: invasive carcinoma that can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≤7 mm.
- IA1: measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm.
- IA2: measured stromal invasion of >3.0 mm and ≤5.0 mm with an extension of not more than 7.0 mm.

IB: clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA.
- IB1: clinically visible lesion ≤4.0 cm in greatest dimension.
- IB2: clinically visible lesion >4.0 cm in greatest dimension.

Stage II: cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA: without parametrial invasion.
- IIA1: clinically visible lesion ≤4.0 cm in greatest dimension.
- IIA2: clinically visible lesion >4 cm in greatest dimension.

IIB: with obvious parametrial invasion.
Stage III: the tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney
IIIA: tumor involves lower third of the vagina, with no extension to the pelvic wall.
IIIB: extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.
Stage IV: the carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum
IVA: spread of the growth to adjacent organs.
IVB: spread to distant organs.

cancer.[57] This report showed a significant decrease in blood loss, operative time, hospital stay, and postoperative complications in comparison to laparotomy.[41] In 2009, Maggioni and coauthors reported similar findings of 40 patients with robotic-assisted surgery with decreased blood loss, increased number of pelvic lymph nodes removed, and a mean hospital stay of 1 day.[58] Furthermore, a multi-institutional report by Lowe and associates in 2009 had similar findings among 5 different surgeons, supporting that surgeons at various skill levels may achieve similar outcomes.[59]

The benefit of the robotic system over traditional laparoscopy for the treatment of early cervical cancer is less clear. In a study of 15 patients undergoing minimally invasive radical hysterectomy (8 laparoscopy, 7 robot-assisted), the mean operating time was shorter in the robotic group, with lower blood loss and decreased hospital stay. Furthermore, pathologic factors were equivalent, including size of the parametrium and vaginal margin, as well as lymph node count.[60] In a prospective study of 13 patients undergoing robotic-assisted radical hysterectomy compared to a historical cohort of 30 patients who underwent laparoscopic radical hysterectomy, there was no difference between the groups in regard to blood loss, hospital stay, complication rates, operative times, or pathologic factors.[39] A study comparing all 3 techniques revealed that the 2 minimally invasive techniques outperformed the abdominal approach in terms of blood loss and length of stay. The laparoscopy group was noted to have the longest mean operative time. All 3 options were equivalent in terms of complications and cancer outcome.[61]

Although these results are promising, the use of minimally invasive techniques for radical hysterectomy has yet to be evaluated in a prospective, randomized fashion. A current multi-institutional study lead by M.D. Anderson Cancer Center is comparing laparoscopic or robotic-assisted radical hysterectomy to abdominal radical hysterectomy. This study aims to determine outcomes of minimally invasive surgery to laparotomy. The study plans to enroll a total of 740 patients, with interim analysis at 100 patients for feasibility of enrollment. Endpoints include disease-free survival, as well as quality of life, short- and long-term complications, overall survival, and cost effectiveness.[62]

Conservative Treatment of Early Cervical Cancer

In the United States, cervical cancer is a disease of young women. It is the second most common cause of cancer in women aged 20–39 years, and only one quarter of cases occur in women older than 65 years.[3,4] As such, there is a significant proportion of women diagnosed with cervical cancer that wish to maintain fertility. Furthermore, the removal of the parametrium can impact bowel, bladder, and sexual function due to the autonomic nerve fibers that run within it.[63-65] As survival rates continue to improve, there has been a broadening of focus to explore the role of more conservative surgical options for early-stage cervical cancer.

Trachelectomy

One such option is the performance of a radical trachelectomy. This procedure includes removal of the cervix, vaginal cuff, and parametrial tissue with preservation of the uterine body.[66] In 2004, Sonoda and colleagues performed a feasibility study and found that 48% of patients under the age of 40 years with operable cervical cancer were eligible for fertility-sparing procedures in the form of a radical trachelectomy based on clear clinical and pathologic criteria.[67] Just as the radical hysterectomy may be approached in several ways, the trachelectomy may be performed abdominally, vaginally, and most recently, robotically. Overall, the literature regarding this demonstrates consistent surgical, pathologic, and oncologic outcomes to the traditional radical hysterectomy.

In general, abdominal radical trachelectomy (ART) is more commonly performed in the United States than vaginal radical trachelectomy (VRT). VRT requires a laparoscopic pelvic lymphadenectomy. Complication rates for both approaches are comparable; however, median operative times are less in the ART group, whereas median blood loss is typically less in the VRT group.[68-70] Pathologic specimens from VRT are typically smaller than ART, but no differences in cancer detection or the numbers of patients requiring adjuvant radiation or chemoradiation have been observed.[69] The overall recurrence rate for women with early-stage cervical cancer treated with VRT is approximately 4%, with rates of death from cervical cancer as low as 2.8%.[71] For ART, several studies have reported no recurrences or deaths from disease, though the numbers of patients and time to follow-up are less than that reported in the VRT literature.[68-70] Obstetric outcomes from both procedures are promising, with rates of term delivery being quoted as high as 50%.[68] Perhaps more encouraging are the results of a study on ART performed in Colombia, which mirrored these findings, thus demonstrating the feasibility and success of this technique in developing countries.[72]

Current experience with robotic-assisted radical trachelectomy is primarily found in case reports and case series. The largest series of 4 women was reported by Ramirez and coauthors in 2009, and demonstrated acceptable operative times, blood loss, and complication rates.[73] Of these women, none had residual tumor in the specimen or required adjuvant therapy. Certainly, as the

data continue to accrue, this minimally invasive approach is an option that should be discussed with any patient who desires a fertility-sparing procedure for early-stage cervical cancer.

Elimination of Parametrectomy

Overall, the rate of parametrial involvement in women with clinical stage IA2–IB1 cervical cancer is low. As the surgical treatment for early cervical cancer has evolved, the discussion has turned to the elimination of parametrectomy in a group of carefully selected women. In general, these criteria include small tumor size (<2 cm), minimal depth of invasion, lack of lymphovascular space involvement, and negative pelvic lymph node status. Retrospective studies analyzing the proportion of patients with these low-risk features have demonstrated a very reassuring 0–1% involvement of the parametrial tissue.[44,74-76] This indicates that a large number of women with early cervical cancer may be over-treated by performance of a radical procedure. Currently, different groups have explored the use of CKC, laser conization, simple trachelectomy, or simple hysterectomy in conjunction with pelvic lymph node dissection to treat early cervical cancer with low risk features.[77,78] Overall, these studies show promising results with low recurrence rates and high pregnancy rates.[79]

Again, the majority of these data come in the form of retrospective case series and small prospectively analyzed studies. Our institution is currently spear-heading a multi-center cohort study of conservative treatment for early cervical cancer. All patients with stage IA2-IB1 disease with the aforementioned low-risk features who have undergone a CKC with negative margins are offered enrollment. For patients desiring a fertility-sparing procedure, a CKC with negative margins is considered adequate surgical treatment. In those patients beyond childbearing years, a simple hysterectomy is performed. All patients must have a pelvic lymphadenectomy. Endpoints for this study include recurrence rate and quality of life.

Conclusion

Cervical cancer continues to be a global epidemic, but improved methods of detection and surveillance are helping to reduce the morbidity and mortality of this disease. Less aggressive and fertility-sparing treatments are now providing women with early-stage disease more options for family planning, while allowing them to maintain an acceptable quality of life. The goal for gynecologists now is to increase both accessibility to cervical cancer screening and the availability of definitive treatments worldwide. Although this goal is ambitious, it is an important public health initiative that has the potential to save the lives of thousands of women.

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