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Research Article

THE AGE ANALYSIS OF CERVICAL CANCER IN CHINA

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ABSTRACT

Objective: To analyze the age distribution of cervical cancer in China.

To explore the correlation with other clinicopathological factors and the influence on the prognosis of cervical cancer.

Method: Based on the large database of clinical diagnosis and treatment of cervical cancer in China, clinical data of cervical cancer patients initially treated by surgery and radical chemo radiotherapy in 47 hospitals in different cities in China were collected on January 1, 2004 and December 31, 2019. In cases of surgery plus radiation and chemotherapy, surgery cases and radical radiation and chemotherapy cases analysis of cervical cancer in three layers of age in years, histological type, diameter, FIGO staging of tumor, preoperative neoadjuvant therapy, city, region, economy, marriage, birth, classifications, HPV infection situation and history of sexually transmitted diseases, postoperative complications are grouped is with high risk factors, analysis, and to explore whether age influence cervical cancer treatment and prognosis of cervical cancer oncology independent risk factors.

Result: The age of surgery and radical radiation and chemotherapy patients were analyzed, and the results show that the distribution of age and year of histology, diagnosis trend, FIGO staging, hospital type, region, city level, occupation, marital status, family status, venereal disease, preoperative neoadjuvant or not relevant, but age is the independent risk factors influencing the prognosis of cervical cancer.

By analyzing the surgical treatment of the patient's age, the results show that the distribution of age and year of histology, diagnosis trend, FIGO staging, hospital type, region, city level, occupation, marital status, family status, venereal disease, preoperative neoadjuvant or not relevant, but age is the independent risk factors influencing the prognosis of cervical cancer.

The age of the in patients undergoing radical radiation and chemotherapy were analyzed, and the results show that the distribution of age and year of histology, diagnosis trend, FIGO staging, hospital type, region, city level, occupation, marital status, family status, venereal disease, preoperative neoadjuvant or not relevant, but age is the independent risk factors influencing the prognosis of cervical cancer oncology.

Conclusions: To sum up, by analyzing the age of cervical cancer receiving surgery and radical chemo radiotherapy from multiple perspectives and at multiple levels, it was found that the age of cervical cancer was correlated with multiple clinicopathological factors and was an independent risk factor affecting the prognosis of cervical cancer.

Keywords: Cervical cancer; Age; China

INTRODUCTION

Cervical cancer has become the second most common female malignant tumor with the highest mortality worldwide. More than 85% of cervical cancer patients occur in developing countries, making it the most common gynecological malignant tumor among women in developing countries [1, 2]. At the same time, it is also one of the major malignant tumors that seriously endanger the health of Chinese women. In recent years, its incidence has increased and tends to be younger [3, 4].

The occurrence and development of cervical cancer is a biological process of multiple factors. From HPV infection to the development and incidence of cervical cancer is a slow and gradual process [5], is a process from quantitative change to qualitative change, gradual change to mutation, CIN1 takes about 10 to 15 years to develop into invasive cancer, namely from high-risk type HPV infection to the development of cervical cancer interval of about 15 years, carcinoma in situ to invasive cancer takes about 3-4 years [6], the HPV infection is the main factor [7].

Human papillomavirus (HPV) is a double-stranded DNA virus that is currently found in more than 200 HPV subtypes. According to the site of infection, it is mainly divided into cutaneous HPV and genital epithelial HPV, among which about 50 subtypes can infect the reproductive system [8]. HPV6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108 and other low-risk subtypes are the main causes of condyloma acuminatum and low-grade cervical intraepithelial lesions. High-risk subtypes such as HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 are the main causes of cervical cancer and high-grade cervical intraepithelial pain in women [9-10]. Among more than 200 HPV subtypes, 15 are directly related to cervical cancer and early cervical injury (HPVI6, 18, 31 and 45 subtypes are most closely related to cervical squamous cell carcinoma, while HPVI8, 31 and 45 subtypes are prone to lead to cervical adenocarcinoma [11].

HPV is often found in cervical cancer, and its infection rate can reach 99.8% [12]. According to epidemiological studies,HPV is related to region. The common subtypes of HPV in cervical cancer in China are different from those in foreign countries. HPV16 and TYPE 18 mainly appear in foreign countries, and the infection rate of HPV6 and type 18 is over 70% [13]. The infection rate of HPV16 is also above 50% [14], while HPV16 and 58 are the main types of HPV infection in China. The infection rates of HPV16 and 58 are 31.9% and 7.6% respectively, while the infection rate of HPV18 is only 1% [15].

International agency for research on cancer (IARC) in 2004, the results suggest that HPV infection is necessary for cervical cancer occur, research shows that about 50% of sexually active women will be affected by HPV infection [16], but more is transient, and persistent high-risk type HPV infection is necessary for

cervical lesions occur, HPV infection with other risk factors, including smoking, long-term oral contraceptives, pregnancy more prolific, cervical chronic inflammation, mycoplasma infection [17] 16 May lead to the occurrence of cervical cancer. For young women, multiple pregnancies also increase the incidence of cervical cancer [19]. When a woman is pregnant, certain hormones will be secreted in her body, so her body is relatively weak and her resistance to the outside world is poor [20]. In addition, the incidence of cervical cancer in China is also closely related to socioeconomic factors such as education level, economic income, nutritional and dietary status, sanitary conditions, working environment and sexual health [21].Since the early manifestation of the disease is non-specific and the course of the disease is relatively long, it is difficult to make early diagnosis.

However, in recent years, clinical practice has found that due to the enhancement of women's awareness of cervical cancer screening, the prevalence of cervical cancer screening and the improvement of cervical cancer level, the incidence of cervical cancer increases year by year, the onset age tends to be younger, and the clinical manifestations and pathological characteristics of patients in different age groups are significantly different [22]. Studies have shown [23] that the incidence of cervical cancer in young women under 35 years old is increasing at the rate of 3%~5% per year, which seriously affects the physical and mental health of young women. Therefore, early detection of HPV infection and regular monitoring are effective methods to prevent cervical cancerTo sum up, the younger trend of cervical cancer incidence has aroused people's great attention. Although rural economically backward areas and middle-aged and elderly women are the focus of cervical cancer prevention and treatment in China, the prevention and treatment situation of urban women and young women is not optimistic. More extensive cervical cancer screening, screening combined with HPV vaccine comprehensive prevention, cervical cancer prevention knowledge popularization is the key direction of cervical cancer prevention in China. Therefore, this study relied on China's large database of cervical cancer clinical diagnosis and treatment to conduct a multi-level analysis of the age distribution of cervical cancer patients. It was divided into three layers. The first layer analyzed the age of patients receiving surgical treatment and radical chemo radiotherapy. In the second layer, the age distribution of patients undergoing surgical treatment was analyzed from the data of the first layer. The third layer selected the patients receiving radical chemo radiotherapy from the first layer to analyze the age distribution.

MATERIAL AND METHOD

Establishment of a large database for the diagnosis and treatment of cervical cancer in China:

The Clinical Diagnosis and Treatment for cervical Cancer in China Database (Four C Database) was established based on a multi-center, retrospective, and cohort study. This project was approved by the Ethics Committee of Southern Hospital of Southern Medical University, ethics No. Nfec-2017-135. Clinical trial registration number CHiCTR1800017778 (International Clinical Trails Registry Platform Search Port,

http://apps.who.int/trialsearch/). A total of 63,926 cervical cancer cases were collected from 47 hospitals in mainland China between 2004 and 2019.

Collection of case data:

All the cases of cervical cancer hospitalized in the hospital from 2004 to 2019 were collected through the medical record management system.

Data entry:

After obtaining the complete clinical data of the patients through the medical record room, the uniformly trained gynecologist would enter the data one by one manually according to the pre-set form. The input indicators covered 315 parameters including basic preoperative information, preoperative examination and treatment, surgical data, postoperative pathology, postoperative adjuvant treatment and prognosis of patients [24, 25].

- Demographic information: name, hospital number /ID number, age, contact number, nationality, native place, education, occupation, marital status, age of menarche, number of pregnancies, age of childbirth, contraceptive method, height, weight, etc.;
- Preoperative clinical data：Gross type of lesion, maximum diameter of lesion, FIGO stage, cervical biopsy pathological results (histological type and grade), complications, etc.
- Preoperative laboratory examination：Cervical cytology (TCT), human papillomavirus infection (HPV), serum squamous cell carcinoma antigen (SCCAg), serum carbohydrate antigen 125 (CA125), serum carbohydrate antigen 199 (CA199), serum carcinoembryonic antigen (CEA), serum human epididymal protein 4 (HE4), hemoglobin concentration (Hb), etc.
- Preoperative Imaging tests: computerized tomography (CT), Magnetic Resonance Imaging (MRI), positron emission tomography (PET), and computerized tomography (PET) tests are performed every time it is tested.
- Preoperative adjuvant treatment data: whether there were preoperative adjuvant chemotherapy, preoperative adjuvant radiotherapy, specific plan, course, time, dose of preoperative adjuvant treatment, and the maximum diameter, middle diameter and minimum diameter of lesions in gynecological examination and imaging examination after each auxiliary treatment;
- Initial treatment: operation or radical chemo radiotherapy;
- Operative information: operative date, operative time, operator, anesthetic method, operative approach, type of hysterectomy, type of lymph node resection, intraoperative blood loss, intraoperative blood transfusion, intraoperative complications, etc.
- Postoperative pathological results: the lesion type, lesion maximum diameter, middle diameter, the path, histological type and differentiation, cervical length, thickness, cervical stromal infiltration depth, from invasion, lymph vascular space infiltration (LVSI), near the palace infiltration, vaginal cut edge infiltration,

vaginal vault involvement, fallopian tube, ovarian metastasis, lymph node excision number and transfer number, etc.;

- Postoperative recovery: postoperative exhaust time, postoperative defecation time, indwelling catheter time, postoperative residual urine volume, and postoperative complications;
- Postoperative adjuvant therapy data: postoperative adjuvant therapy method, plan, course of treatment, time, dose, and final treatment time.

Among them, clinical staging was registered according to THE FIGO 2009 standard [26]. Patients who visited the hospital before 2009 would be re-staged by two experienced gynecological oncologists according to the FIGO 2009 standard. If the clinical stages in the medical records are vacant or incomplete, correction shall be made according to the specialist examination records, imaging examination reports, colposcopy examination records and postoperative pathological records of the patients. The remaining information was obtained from medical documents such as hospital medical records, pathological reports, surgical records, discharge records, etc. Postoperative adjuvant therapy was conducted according to the high-risk factors in postoperative pathology and the habits of each participating unit, including no treatment, chemotherapy alone, radiotherapy alone, concurrent chemo radiotherapy and sequential radiotherapy, etc., and the regimen and course of chemotherapy and the regimen and dose of radiotherapy were recorded.

Follow-up:

After the data collection is completed, all data will be systematically followed up by specially trained gynecologists from the participating units, and the follow-up process will be supervised and managed by specially-assigned persons. In the follow-up procedure of this retrospective study, all patients were followed up 1-2 times after inclusion in the analysis. Main way of follow-up for telephone follow-up, use of medical record management center is derived by follow-up personnel in the hospital medical records recorded in the contact phone number, to ask the patient or family, including living condition, whether relapse and recurrence after treatment, complications and death cases the cause of death and so on, and reminded at his patients in postoperative follow-up of process regularly review or physical examination. For patients with wrong or unreachable telephone Numbers, the outpatient consultation system, PACS system and test report system of the hospital will be further inquired, and the survival time will be taken as the last visit or report time, and relevant information about tumor recurrence and treatment after recurrence will be extracted from the outpatient medical records.

Double input:

After the information entry and follow-up of the case, two specially trained gynecologists conducted double input with Epi Data software to the same case record, and the consistency test of the two data was conducted by the software, and the suspected parameters were checked by two people.

Storage:

A unified database will be established through the collection and management of all the data entered by specially-assigned persons to form a large database for the clinical diagnosis and treatment of cervical cancer in China.

Construction of a database of severe surgical complications of cervical cancer:

While collecting data to build a large database of clinical diagnosis and treatment of cervical cancer in China, we also established a database of severe surgical complications of cervical cancer to identify cases with severe postoperative complications. The definition of severe surgical complications was reported in references [27], and level-2 (main symptoms requiring prolonged hospitalization for further diagnosis and treatment) and Level-3 (severe symptoms threatening the health or life of the patient and requiring invasive operation or surgical treatment) associated with gynecological tumor treatment were collectively referred to as severe surgical complications. A total of 63,926 cases of cervical cancer were collected from China's large database of clinical diagnosis and treatment of cervical cancer, including 48,727 cases of surgery, 11,433 cases of radical chemo radiotherapy and 3766 cases of other treatments. From 48,727 surgical cases, we selected one by one the cases with severe postoperative complications for additional data entry to construct the database of severe complications of cervical cancer.

Collection of case data:

The gynecologists with unified training and the participating units were assigned the uniform medical record code of "cervical malignant tumor". Through the medical record management system, the hospitalized cases of cervical cancer receiving surgical treatment in the hospital from 2004 to 2019 were collected, and the medical records were reviewed one by one to identify the cases with serious postoperative complications.

Data entry:

The input indicators covered 217 parameters including the basic preoperative information of patients, preoperative examination and treatment, operator information, surgical data, postoperative pathology, and intraoperative and postoperative complications [28].

Double entry:

After the information entry of the case was completed, two specially trained gynecologists conducted double input with Epi Data software to the same case record, and the consistency test of the two data was conducted by the software, and the suspected parameters were checked by two people.

Storage:

All the entered data will be collected and managed by specially-assigned persons, and a unified database will be established to form a database of serious surgical complications of cervical cancer.

Inclusion and exclusion criteria:

Analysis of age distribution of cervical cancer patients in China:

Level 1 Inclusion criteria:

- Having a diagnostic age;
- Patients receiving surgical treatment or radical chemo radiotherapy;
- Exclude other special types of cervical cancer.

Level II Inclusion criteria:

- Receive surgical treatment;
- The surgical approaches are laparotomy and laparoscopy;
- Receive QM-B or C hysterectomy;
- There is a survival outcome.

Level III Inclusion criteria:

- The initial treatment was radical chemo radiotherapy;
- There is a survival outcome.

RESULTS

1. The first layer into the standard, the age of surgery and radical radiation and chemotherapy patients were analyzed, and the results show that the distribution of age and year of histology, diagnosis trend, FIGO staging, hospital type, region, city level, occupation, marital status, family status, venereal disease, preoperative neoadjuvant or not relevant, but age is the independent risk factors influencing the prognosis of cervical cancer oncology.
2. The second layer into the standard, analyze the surgical treatment of the patient's age, the results show that the distribution of age and year of histology, diagnosis trend, FIGO staging, hospital type, region, city level, occupation, marital status, family status, venereal disease, preoperative neoadjuvant or not relevant, but age is the independent risk factors influencing the prognosis of cervical cancer oncology.
3. The third layer into the standard, the age of the in patients undergoing radical radiation and chemotherapy were analyzed, and the results show that the distribution of age and year of histology, diagnosis trend, FIGO staging, hospital type, region, city level, occupation, marital status, family status, venereal disease, preoperative neoadjuvant or not relevant, but age is the independent risk factors influencing the prognosis of cervical cancer oncology.

DISCUSSION

Based on the Database of Clinical diagnosis and treatment of cervical cancer in China, the average age of 59,759 surgical cases and patients with radical chemo radiotherapy in 47 hospitals in Mainland China was (49.05±10.31) years old, and the median age was 48 years old. The proportion of cases in different age groups

was successively from large to small: 40-49 years old, 50-59 years old, 30-39 years old, 60-69 years old, 70-70 years old, 20-29 years old, ≥80 years old and < 20 years old. The diagnostic age of patients showed an increasing trend with year.

HPV infection is the most important factor [29]. The International Centre for Research on Cancer (IARC) concluded in 2004 that: HPV infection is necessary for cervical cancer occur, research shows that 50% of sexually active women will be affected by HPV infection [30], but more is transient, but persistent high-risk type HPV infection is the necessary condition of the cervical lesions occurred from the HPV infection to the development and incidence of cervical cancer is a slow and gradual process, is a process from quantitative change to qualitative change, gradual change to mutation, CIN1 takes about 10 to 15 years to develop into invasive cancer, namely from high-risk type HPV infection to the development of cervical cancer interval of about 15 years, carcinoma in situ to invasive cancer takes about 3-4 years (31, 32), Therefore, early detection of HPV infection and regular monitoring are effective methods to prevent cervical cancer. Currently, the "three-step" procedure of cervical screening is used clinically to intervene cervical cancer and control the incidence of cervical cancer in the pre-cancerous condition, including HPV virus examination, TCT (thin-layer liquid based cell technology) and colposcopy + biopsy when necessary to identify the lesions. The results of this study suggest that compared with other age groups, the patients with higher HPV infection rate are concentrated in unmarried women aged 20-29 and childbearing women aged 40-49, which is closely related to the risk factors of HPV infection. This is because HPV virus mainly through sexual transmission, high-risk HPV infection and female sexual behavior is closely related, such as the first sexual intercourse age, sexual activity, multiple sexual partners, while syphilis and other sexually transmitted diseases in women 40-49 years old more concentrated. Like to have sex in the early, early delivery and vaginal delivery, perinatal and childbirth is bad or induced abortion for many times, can make sex organs are more susceptible to the intrusion of harmful factors, pathogenic microorganism invasion and infection, cause a transition zone of cervical squamous epithelium and abnormal proliferation [33] for cervical has similar to destroy the effect, the destroy years accumulated can lead to cervical cancer. In 2004, Wang Jintao et al. [34] found that the younger the age of marriage, the younger the age of first gestation and the higher the probability of cervical cancer during pregnancy. In 2012, Through statistical analysis, Peng Can et al. [35] found that the incidence of cervical cancer in women with ≥3 vaginal deliveries was higher than that in women with <3 deliveries, and the difference was statistically significant, indicating that ≥3 deliveries were a risk factor for cervical cancer.

Therefore, it should be one of the work contents to strengthen the publicity and education of disease knowledge and popularize the knowledge of cancer prevention. Improving the cultural quality of the group, developing healthy living habits and strengthening the awareness of disease prevention are also inseparable with health education. It is of great clinical and practical significance to carry out planned early intervention on cervical cancer, reduce cervical cancer patients and improve people's life quality.

The age distribution was significantly different and statistically different in different hospital types. Patients with cervical cancer ≤49 years old tend to choose general hospitals, while > patients aged 50 years old

have the largest proportion of visits to specialized oncology hospitals, which may be due to the subjective preference of patients in different age groups to different types of hospitals. For example, elderly cervical cancer patients are more likely to visit specialized oncology hospitals.

China has a vast territory, and the differences in economy, culture and medical level make the incidence of cervical cancer vary greatly. In this study, the case sources were widely distributed in seven administrative regions of China, including North China, South China, Central China, East China, southwest China, Northwest China, and Northeast China. The proportion of patients in north China in different age groups was the largest, and the proportion increased with age. Meanwhile, this study found that the proportion of rural patients in different regions was higher and the ratio of rural patients in North China was the largest. Agricultural and forestry production personnel also had a higher proportion in different age groups, the difference was statistically significant. Meanwhile, other studies have also shown that the incidence rate in rural areas of China is higher than that in cities [36]. The reason is that due to the backward awareness of individual cancer prevention and the lack of universal cervical cancer screening, the diagnosis and treatment of cervical cancer are not timely performed in the early stage, and are only detected after the onset of symptoms. At this time, the patients are often older and the best treatment time is missed. Therefore, it is necessary to increase the knowledge of cervical cancer prevention and screening in economically backward areas to reduce the incidence of cervical cancer. In city level we also found that the patients in the age section in the second-tier cities is much higher than the proportion of the first - and third-tier cities, but as a result of first-tier cities economic and medical level is higher, the popularization of the knowledge of cervical cancer screening is also compared with the economically backward regions advanced and complete medical resources, cervical cancer early diagnosis, so for young patients is higher, and this study different parts of the age distribution of the conclusion cervical cancer patients. The pathological types of cervical cancer include squamous cell carcinoma, adenocarcinoma, adenosquamous cell carcinoma, clear cell carcinoma and neuroendocrine small cell carcinoma. The results of this study suggest that the proportion of squamous cell carcinoma histologically increases with age, while the proportion of adenocarcinoma is reversed. The study by Rutledge[37] showed that non-squamous cell carcinoma of cervical cancer in women < 35 years old was more common, with high rate of lymph node metastasis and high incidence of parathymic infiltration, and rapid progression and poor prognosis. Dong Hong et al. [38] reported that most patients with adenocarcinoma were young cervical cancer patients, which was consistent with the results of this study.

Preoperative adjuvant chemotherapy for cervical cancer plays an important role in locally advanced cases. The fundamental reason is that neoadjuvant chemotherapy can reduce tumor diameter, reduce clinical stage, improve surgical resection rate, eliminate microlesions and subclinical lesions at the same time, and reduce spread during surgical operation. In areas with less developed economic and medical resources, radiotherapy equipment is not yet accurate, and surgery after early chemotherapy is beneficial to improve the quality of life of patients to a certain extent, providing the possibility for young female patients to retain their fertility function. Although there have been many international and domestic studies on the clinical efficacy

and application value of CERVICAL cancer NACT in the past 10 years, there are still different conclusions. The results of this study showed that patients with cervical cancer ≤50 years old tended not to receive preoperative neoadjuvant therapy, and the tumor diameter of patients ≥60 years old was significantly larger, so we considered the reason that this result was related to the FIGO stage and tumor diameter of older cervical cancer patients. There is no consensus on the value of PREOPERATIVE NACT for cervical cancer. Therefore, the research on preoperative neoadjuvant therapy has been developing in exploration and controversy.

Among them, for clinical staging for I stage A2 to II A2 as the muck of cervical cancer patients with cervical cancer radical clinical commonly used treatment, operation scheme using the radical hysterectomy combined pelvic lymph node cleaning, cutting operation range is relatively wide, and often have large trauma, so the incidence of various complications after will heighten [40]. At present, there are few studies on the complications after radical hysterectomy for cervical cancer in China, and they mainly focus on the influence of different surgeries and drug methods on the occurrence of complications [41]. There are insufficient studies on the influence of age on postoperative complications of cervical cancer.

At the same time, we also found that the average age of patients receiving radical chemo radiotherapy was older than the average age of patients receiving surgical treatment, but age was not an independent factor influencing the treatment mode of cervical cancer patients.

This study on the correlation between age and cervical cancer effect a radical cure postoperative complications of the analysis results indicate that different age groups of patients with cervical cancer was statistically difference between the incidence of postoperative complications, no matter with or without complications after cervical cancer treatment, 40 - accounts for cervical cancer than are the biggest, 49, and we have complications in patients with the age of 41.5%, compared with patients without complications of low, at just 36.3%. Due to the decline in physical function of patients in this age group, they could not better tolerate surgery, which was consistent with the results of Wei Qing's study [42].

In patients with cervical cancer aged > 30 years, the proportion of postoperative risk factors of no high school decreased with the increase of age, but FIGO stage showed an increasing trend. Further analysis of the prognosis of cervical cancer patients in different age groups showed that the OS and DFS of cervical cancer patients in different age groups gradually decreased with the increase of age, and the difference was statistically significant. Meanwhile, age was an independent risk factor affecting the prognosis of cervical cancer patients. Lau et al. [43] showed that tumors of young cervical cancer patients were more aggressive, and age was associated with multiple adverse prognostic factors. He suggested that young patients should receive more aggressive treatment regardless of whether they had lymph node metastasis. Cao et al. [44] believed that lymph node metastasis, LVSI and FIGO stage were prognostic factors for cervical cancer patients. Zhou et al. [45] suggested that pelvic lymph node metastasis, age and FIGO stage were independent prognostic factors for survival and disease-free survival. Monk, etc. [46] research shows that cervical cancer patients under 35 5-year survival rate is lower than that of the more than 35 years old, the analysis reason for cervical cancer patients under 35 tumors larger diameter, higher percentage of squamous carcinoma and postoperative pathological

high risk factors, prone to tumor recurrence and metastasis, worsen, the prognosis of patients in accordance with this research conclusion.

CONCLUSION

To sum up, by analyzing the age of cervical cancer patients receiving surgery and radical chemo radiotherapy from multiple perspectives and at multiple levels, it was found that the age of cervical cancer was correlated with multiple clinicopathological factors and was an independent risk factor affecting the prognosis of oncology.

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