

# Clinical progress of brachytherapy for cervical cancer

Tianchi Shao\*

School of Public Health, Wenzhou Medical University, Wenzhou, Zhejiang, 325035, China

**Abstract.** Cervical cancer is a prevalent malignant tumour of the female reproductive system, posing a significant threat to women's health and lives in China. Brachytherapy is a crucial component of radiotherapy for patients with locally intermediate and advanced cervical cancer. This includes intracavitary brachytherapy, interstitial brachytherapy, intracavitary and interstitial combined brachytherapy, and radioactive seed implantation brachytherapy. The aim of this article is to provide an update on the use of intracavitary brachytherapy, interstitial brachytherapy, and radioactive particle implantation.

## 1. Introduction

Cervical cancer is a prevalent gynecological malignancy. Despite the existence of the cervical cancer vaccine, according to Global Cancer Statistics 2020[1], cervical cancer is still the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women (Fig. 1). It is also the second most common cause of cancer deaths in women aged 20 to 39 years. In China, the incidence and mortality rates of cervical cancer have been on the rise for the past 20 years (Fig. 2). Furthermore, over 50% of cervical cancer patients are diagnosed with intermediate or advanced cervical cancer at their first visit [2]. Based on the 2020 NCCN guidelines, concurrent chemoradiation is the preferred treatment for patients with stage IB3 and II A2 cervical

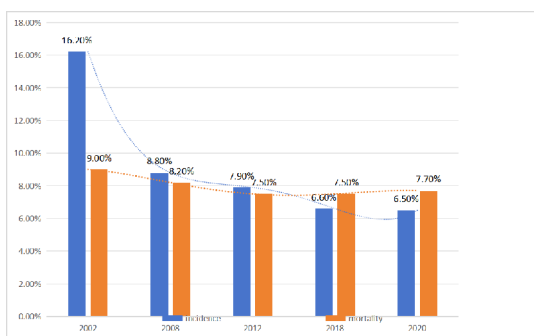


Fig. 1. Global female cervical cancer incidence and mortality rates

## 2. Intracavitary brachytherapy

In the early 1900s, Margaret-Cleaves first used intracavitary brachytherapy (ICBT) as a form of radiotherapy for cervical cancer patients [3].

ICBT involves placing a radioactive source applicator in the uterus and vagina. Initially, the dose to the primary cervical lesion was assessed using two-

cancer and tumours larger than 4 cm in diameter, as well as for patients with stage II B and above and parauterine involvement. For patients with stage IA, IB1-2, and II A1, concurrent chemoradiation can achieve comparable results to surgery, highlighting the significant role of radiotherapy in the comprehensive treatment of cervical cancer. Radical radiotherapy for cervical cancer includes external irradiation and brachytherapy. In recent years, brachytherapy has made significant progress due to the development of image-guided methods such as MRI and CT. The use of 3D perineal templates has greatly increased the target dose and reduced complications. This paper will discuss the clinical progress of brachytherapy in treating cervical cancer.

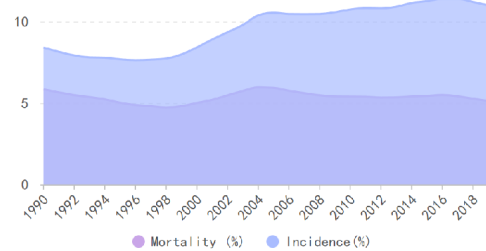


Fig. 2. Analysis of incidence rate and mortality rate trend of cervical cancer of the female in China, 1990 to 2019

dimensional radiographic images, revealing a pear-shaped distribution of the dose curve. ICBT was established based on two-dimensional images, which are significantly impacted by tumour size. When the tumour is large, the prescribed dose line cannot fully encompass the tumour area, resulting in insufficient radiation dose. Conversely, when the tumour is small, the prescribed dose line may include normal tissues and organs, leading to radioactive damage of the cervix and surrounding tissues [4].

\* Corresponding author: shaotch@wmu.edu.cn

The field of imaging technology is constantly evolving, with upgrades to MRI, CT, and other technologies. Three-dimensional imaging technology has been utilized in ICBT [5] for cervical cancer. Compared to traditional two-dimensional X-ray images, three-dimensional imaging technology enables doctors to more accurately assess the size, shape, and position of the target area and surrounding tissues during clinical implementation. This improves the precision of the radioactive source used by the applicator. The combination of ICBT and three-dimensional imaging technology increased the 2-year relapse-free survival rate of patients to 78.5%, while reducing the incidence of radiation toxicity from 22.7% to 2.6% [6].

Therefore, ICBT is suitable for tumour patterns that are commonly found in smaller cervical tumours (less than 4cm x 3cm x 3cm) [7, 8] or those that are symmetrically distributed in the uterine cavity [9, 10].

### 3. Interstitial brachytherapy

Interstitial brachytherapy (ISBT) involves inserting an implant needle into the tumour for brachytherapy, either manually or through a perineal template. Interstitial brachytherapy techniques include freehand insertion and perineal template implantation.

ISBT can significantly improve tumour target dose, local tumour control rate and quality of life for patients with locally advanced cervical cancer, when compared with intracavitary radiotherapy. In 1914, Stevenson [11] inserted a radium needle through the perineum into a patient with cervical cancer using a freehand technique, without image guidance or anaesthesia. This pioneering approach to treatment is the earliest recorded case of ISBT for cervical cancer.

However, despite its widespread use in clinical practice, the freehand method has several shortcomings. These include difficulty in accurately locating the tumour lesion, performing the operation, and monitoring the position and depth of the implantation needle in real-time. These issues require a great deal of experience and skill on the part of the physician. Until 1978, Feder et al. [12] improved the operation of ISBT by using perineal templates to accurately localize the tumor. This resulted in more accurate dose homogeneity around the target and better sparing of surrounding normal structures. Their work laid the foundation for the modern technique of implantation brachytherapy.

In recent years, 3D printing technology has been evolving for ISBT in the treatment of cervical cancer, improving its feasibility and safety [13]. The time taken to complete the CT scan and adjust the needle track to the ideal trajectory affects the amount of additional radiation the patient receives. To minimize the risk of adverse reactions such as intraoperative bleeding and perforation and to ensure a safer operation, it is important to insert as few needles as possible while meeting treatment needs. Several studies have shown that using 3D printed templates can reduce the frequency of CT scans, shorten the overall treatment duration, and significantly decrease the occurrence of complications,

including bleeding and uterine perforation [13]. Compared to the free-hand method, treatment with a 3D template can more accurately locate the tumour and reduce the risk of off-target effects and damage to normal tissue [14]. Individually customized templates can be used to conform to the shape and size of the tumour, improving coverage and conformity of the target area while minimizing damage to surrounding normal tissues [13, 15, 16].

Chinese scholars [17] have treated patients with recurrent cervical cancer after radical surgery and external beam radiotherapy using free-hand placement of metal needles guided by real-time 3D-CT. Studies have shown that ISBT alone can be used to treat patients with recurrent cervical cancer. Silva et al.'s study [18] also confirmed the efficacy of ISBT in treating cervical pelvic recurrence.

A prospective study [19] has shown that ISBT can reduce the doses delivered to organs at risk (OAR) and/or increase the doses delivered to the tumour. Therefore, the technique of ISBT in three-dimensional brachytherapy for cervical cancer is mainly suitable for bulky tumours, poor tumour regression after external beam radiotherapy, extensive parametrial involvement, and limited vaginal access conditions.

### 4. Intracavitary and interstitial combined brachytherapy

In contrast to ISBT, intracavitary and interstitial combined brachytherapy (IC/ISBT) takes an additional step by placing a uterine tube in the centre of the uterus. This is followed by the insertion of catheters in the surrounding lesions and paracervical tissues based on gynaecological investigations and imaging data.

In 1983, Gaddis et al. [20] reported on IC/ISBT for cervical cancer. However, due to the treatment limitations at that time, a significant number of patients experienced severe radioreactions (21.3%). As a result, no follow-up study was conducted.

A 2017 study [21] found that IC/ISBT, compared to three-tubed brachytherapy, significantly increased COIN (Cervical Oncology Interstitial Dosimetry Nomenclature) without altering the range of the high-dose region in the target volumes and the total treatment time. Additionally, the exposure dose to the bladder and rectum was simultaneously reduced. In another study [22], 124 patients with bulky cervical cancer were treated with ICBT alone or IC/ISBT. Under the same prescribed dose, the high-risk clinical target volume (HR-CTV) of the latter was higher than that of the former in terms of D90 and D100. Additionally, the rectal D2cc, D1cc, and D0.1cc of the latter were lower than those of the former. These results suggest that IC/ISBT can significantly increase the radiation dose to the tumour while reducing the irradiated dose to normal tissues such as the bladder, sigmoid colon, and rectum. According to a study by Yang et al. [23], IC/ISBT was found to be more effective than intracavitary brachytherapy in terms of reducing tumour recurrence or metastasis, improving complete remission rate and objective remission rate, and also

resulted in a lower incidence of radiodermatitis, proctitis and cystitis. This conclusion was also drawn by Zou et al. [24]. These results suggest that for patients with locally advanced cervical cancer and insignificant tumour regression after external beam radiotherapy, the application of IC/ISBT can increase the radiotherapy dose delivered to the tumour volumes, reduce the irradiated dose delivered to OAR, and improve the safety and efficacy of the treatment.

Therefore, the technical indications for IC/ISBT are: large tumour volume or poor regression after external irradiation; eccentrically located tumour with irregular morphology or invasion of para-uterine or para-urethral tissues requiring protection of the surrounding tissues; incomplete coverage by ICBT alone; and poor location of the target area relative to high-risk tissues.

## 5. Radioactive seed implantation brachytherapy

Radioactive seed implantation brachytherapy utilises continuous low-energy rays from radioactive particles to damage and destroy tumour tissue. This is achieved by implanting radioactive particles inside the tumour or in tissues infiltrated by the tumour.

Radioactive seed implantation brachytherapy was first used to treat cervical cancer in the late 19th and early 20th centuries. Sharma [25] and Monk [26] treated 21 and 20 gynaecological tumour patients, respectively, with 11 and 18 of them having cervical cancer.

At that time, particle implantation could only be performed intraoperatively due to the lack of imaging data. However, identifying lesions during surgery can be challenging due to the complex pelvic structure and extensive fibrosis caused by radiotherapy.

Fortunately, advances in technology have made image-guided implantation of radioactive particles a popular option. According to Zhang et al. [27], CT-guided radioactive  $^{125}\text{I}$  seed implantation can prolong patient survival and is a safer alternative. According to a study [28], ultrasound-guided radioactive  $^{125}\text{I}$  seed implantation can effectively control local tumours, reduce complications, alleviate clinical symptoms, and improve patients' quality of life. Chen et al. [29] treated recurrent cervical cancer patients with CT-guided radioactive  $^{125}\text{I}$  seed implantation, resulting in overall survival rates of 81.8% and 51.3% at 1 and 2 years respectively, without any serious adverse reactions or complications. Image-guided radioactive seed implantation brachytherapy can improve the precision of needle positioning by providing a clear display of the tumour boundary. This contributes to adequate dosing for target volumes and safe dosing for essential normal structures.

In addition to providing advantages for local tumour control and reducing complications, radioactive seed implantation brachytherapy can also alleviate patient suffering and enhance their quality of life. QU A et al. [30] demonstrated that 36 patients with pelvic recurrent cervical cancer experienced a significant survival benefit while also having a reduction in local pain. In a study by

[31], it was found that physical strength, body mass, and pain were significantly improved compared to the control group. Additionally, the QLQ-C30 scores were also significantly higher in the study group than in the control group. A retrospective study [32] evaluated changes in preoperative and postoperative pain in patients using the Numerical Rating Scale (NRS). The study found that the effective rate of pain relief was 90.2% one week after surgery, and pain scores decreased from  $3.8\pm 2.7$  preoperatively to  $1.2\pm 1.0$  at one month ( $P<0.05$ ).

According to the guideline [33], radioactive seed implantation brachytherapy is indicated for patients with recurrent cervical cancer after surgery or radiotherapy.

## 6. Conclusion

This paper provides a retrospective summary of four common brachytherapy techniques for cervical cancer, namely ICBT, ISBT, IC/ISBT, and radioactive seed implantation brachytherapy.

ICBT has shown positive outcomes for patients with early-stage cervical cancer. The integration of imaging technologies, such as MRI and CT, has significantly improved the precision and efficacy of this treatment. However, the application of ISBT in the treatment of locally advanced cervical cancer has limitations in achieving ideal dose distributions [34].

ISBT offers unique advantages for locally advanced cervical cancer by allowing a rational arrangement of implant needles according to the tumor shape and extent, thereby increasing the radiation dose to the tumor center. However, it may result in insufficient dosing in the central area of the cervix [35].

The IC/ISBT (IC/IS-BT) technique combines the advantages of the two aforementioned techniques, delivering high doses to the cervical center while providing more conformal coverage of the target volume. This approach is suitable for larger or irregularly shaped tumors.

Radioactive seed implantation brachytherapy is mainly used for recurrent cervical cancer patients. It effectively reduces patient suffering and improves quality of life with fewer complications, offering a viable alternative treatment option [28].

Radiotherapy for cervical cancer has a history of 100 years of development. The technology has evolved from simple radium spindle radiation sources to modern high-precision accelerators. Advanced technologies such as 3D conformal radiotherapy and intensity-modulated radiotherapy are now available for external irradiation, while radioactive seed implantation brachytherapy and intracavitary and interstitial combined brachytherapy are available for internal irradiation. These technologies can be well adapted to irregular tumours, reducing damage to surrounding normal tissues. The development of 3D printing technology meets the individualized needs of patients, achieving accurate dose coverage of tumours and solving the problem of processing and shaping traditional source devices into parts to reduce medical injuries [5, 6, 13, 14, 15, 16]. The research on artificial

intelligence in the field of targeting and automatically outlining high-risk organs has injected new vitality into this field [36, 37]. It is not sufficient to improve the technical means of brachytherapy alone; attention must also be paid to other factors, such as important biological markers in cervical squamous carcinoma [38], in order to determine the patient's physical condition. A major breakthrough has also been made in radiobiology, ionising radiation, and immune cell interactions.

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