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A Comparative Analysis of X-Ray-Based and Computed Tomography-Based Treatment Planning for Intracavitary Brachytherapy in Cervical Carcinoma

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Abstract: ***Cervical cancer represents a significant global health burden, particularly affecting women in developing regions where screening programs are less prevalent. Human Papilloma Virus (HPV) infection, particularly types 16 and 18, is the primary etiological factor. Understanding the epidemiology and risk factors associated with cervical cancer is crucial for effective prevention and management strategies. Screening programs, such as the Pap smear, have led to substantial reductions in cervical cancer mortality. However, the implementation of such programs in developing countries faces challenges due to resource constraints. Alternative methods like visual inspection-based screening tests show promise in low-resource settings. Treatment planning for cervical cancer, especially with intracavitary brachytherapy, requires a thorough understanding of the anatomy of the uterine cervix and surrounding structures. Advances in imaging modalities, including X-ray and computed tomography, have improved treatment planning accuracy. This article presents a comparative analysis of X-ray and computed tomography-based treatment planning for intracavitary brachytherapy in cervical cancer. It explores the epidemiology, risk factors, screening methods, and anatomical considerations essential for effective management strategies.***

Keywords: Cervical cancer, Human Papilloma Virus (HPV), Screening programs, Pap smear, Visual inspection-based screening, Intracavitary brachytherapy, X – ray, Computed tomography, Epidemiology, Risk factors, Treatment planning

1. Introduction

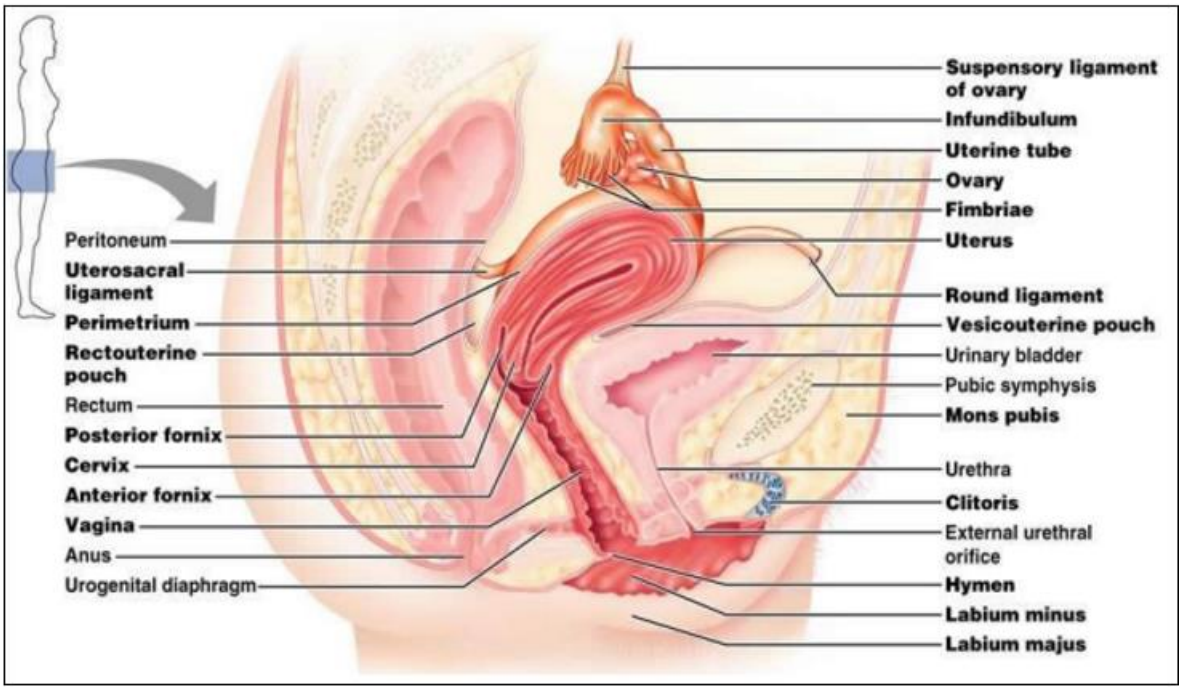
Cervical cancer remains one of the most prevalent cancers among women globally, posing a significant public health challenge. The World Health Organization (WHO) reports that approximately 2.34 billion women aged 15 years and older are at risk of developing cervical cancer, with an estimated 529, 828 new cases and 275, 128 deaths annually (WHO, 2021). Ranking as the third most common cancer in women worldwide, cervical cancer is particularly prevalent among women aged 15 to 44 years, where it is the second most frequent cancer (WHO, 2021). The primary cause of cervical cancer is persistent infection with high-risk Human Papillomavirus (HPV) types, notably HPV 16 and 18, which are responsible for approximately 70.9% of invasive cervical cancers globally (de Martel et al., 2020). The incidence and mortality rates of cervical cancer vary significantly across regions, reflecting differences in cultural attitudes towards sexual behavior, the prevalence of HPV, and the implementation of screening programs. In regions with low screening coverage and high HPV prevalence, such as Latin America, Sub-Saharan Africa, India, and Polynesia, cervical cancer remains a leading cause of cancer-related deaths among women (Sankaranarayanan et al., 2018). In contrast, countries with advanced screening programs, like the United States and Western Europe, or where strict religious norms govern sexual behavior, such as in many Muslim-majority countries, tend to have lower rates of invasive cervical cancer (Arbyn et al., 2020). India, with a population of 366.58 million women at risk, has one of the highest burdens of cervical cancer, accounting for 134, 420 new cases and 72, 825 deaths annually (Bruni et al., 2019). Despite the absence of organized nationwide screening programs, certain regions have witnessed a decline in cervical cancer incidence, likely due to improved healthcare access and awareness (Sankaranarayanan et al., 2019). However, significant disparities persist, particularly between urban and rural populations, underscoring the need for enhanced and more accessible screening strategies. HPV infection is the most significant risk factor for cervical cancer, and it is often associated with early sexual activity, multiple sexual partners, and a history of sexually transmitted infections. The link between HPV and cervical carcinogenesis has been well established, with molecular studies identifying HPV as the primary etiologic agent in most cervical cancers (Bosch et al., 2019). These findings have led to the development of preventive measures, including HPV vaccination and more effective screening methods, which have the potential to significantly reduce the global burden of cervical cancer.

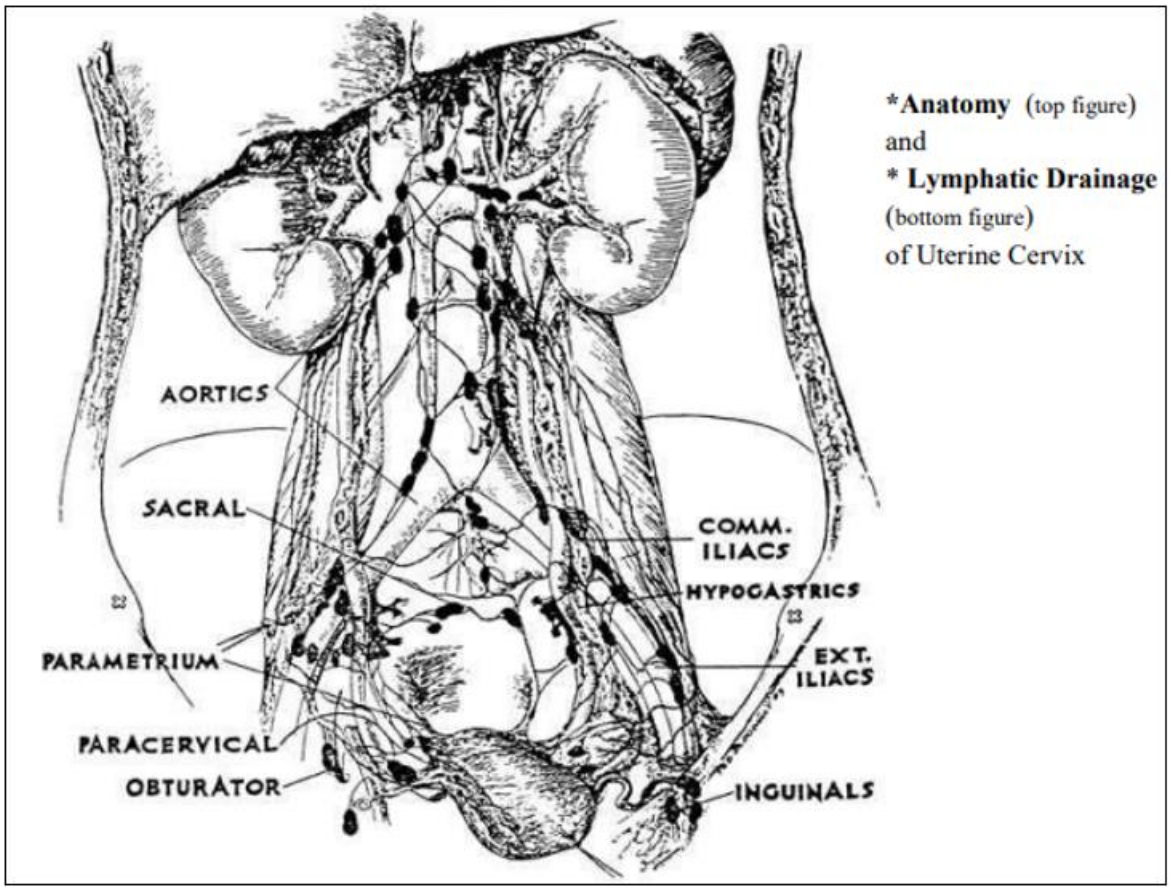
Anatomy of the Uterine Cervix

A thorough understanding of the anatomical structure and relationships of the uterine cervix is crucial for optimizing the therapeutic approaches to managing cervical carcinoma. The cervix is strategically positioned in the pelvis, surrounded by vital structures such as the trigone of the bladder, ureters, anterior rectal wall, and sigmoid colon. Due to this proximity, these organs are often exposed to therapeutic interventions aimed at controlling cervical neoplasms, making precise anatomical knowledge essential for minimizing collateral damage.

The uterus itself is a hollow, muscular organ that is functionally divided into two parts: the body (corpus uteri) and the cervix, separated by the isthmus. The body of the uterus is covered by a layer of peritoneum, which anteriorly reflects over the bladder and posteriorly extends over the cervix, the posterior fornix of the vagina, and the anterior portion of the rectum and sigmoid colon. This anatomical arrangement facilitates the communication between the uterus and surrounding structures, particularly through the broad ligament—a double layer of peritoneum that houses the blood

supply, lymphatics, and nerves of the uterus. The broad ligament connects the lateral aspects of the uterus to the pelvic side walls and contains three important ligaments: the round ligament, the ovarian ligament, and the suspensory ligament of the ovary. Support for the uterus within the pelvis is provided by two primary ligaments: the cardinal ligament and the uterosacral ligament. The cardinal ligament, composed of the fascial tissues surrounding the cervix and upper vagina, extends laterally to anchor these structures to the pelvic side walls. Posteriorly, the uterosacral ligament, which is an extension of the same fascial tissues, anchors the cervix and lower uterine segment to the sacral vertebrae, ensuring that the uterus maintains its anteflexed position within the pelvic cavity. The lymphatic drainage of the cervix is extensive, with three interconnecting plexuses that drain the mucosal, muscularis, and serosal layers. These lymphatics also communicate with those of the lower uterine segment, which may explain the frequent uterine extension observed in endocervical tumors. The primary lymphatic drainage of the cervix occurs through three lateral collecting trunks: the upper branches, which follow the uterine artery and terminate in the hypogastric nodes; the middle branches, which drain into the deeper hypogastric (obturator) nodes; and the lower branches, which drain posteriorly to the gluteal, common iliac, presacral, and subaortic nodes. Additionally, lymphatic channels from the posterior cervix may drain into the superior rectal nodes or continue upwards to the subaortic nodes over the sacral promontory. The vaginal lymphatic drainage varies by region, with the upper vagina draining into both the internal and external iliac nodes, the middle third draining primarily into the internal iliac nodes, and the lower third draining towards the superficial inguinal nodes. Given the potential for cervical tumors to spread along these lymphatic pathways, understanding the specific lymphatic drainage patterns is critical for effective treatment planning, particularly in relation to the involvement of the iliac, para-aortic, sacral, and inguinal nodes.





Pathology and Natural History of Cervical Cancer

Cervical cancer primarily arises from the transformation of epithelial cells in the uterine cervix, the lower part of the uterus that connects to the vagina. The cervix is anatomically divided into two regions: the ectocervix, which protrudes into the vagina and is lined by stratified squamous epithelium, and the endocervical canal, lined by columnar epithelium. The junction between these two types of epithelium, known as the squamocolumnar junction, is the most common site for the development of cervical cancer. This area undergoes continuous squamous metaplasia, a process where columnar cells are replaced by squamous cells, which makes it particularly susceptible to viral-induced neoplastic transformation, especially by high-risk Human Papillomavirus (HPV) types. Cervical cancer is predominantly classified into two major histological types: squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma accounts for 80% to 90% of all cervical cancers and typically originates from the ectocervix. These tumors are further categorized into subtypes, including large cell keratinizing, large cell non-keratinizing, and small cell carcinomas. Small cell carcinomas are rare and should not be confused with the highly aggressive small cell neuroendocrine carcinomas, which resemble similar tumors found in the lung. Adenocarcinoma of the cervix, representing 10% to 20% of cases, often arises from the endocervical canal and includes subtypes such as mucinous, endometrioid, clear cell, and serous carcinomas. The increasing incidence of adenocarcinoma, particularly in younger women, has been noted in recent years. The progression of cervical cancer typically follows a well-defined pathway. Tumors usually originate at the squamocolumnar junction, where they can invade the underlying cervical stroma either directly or through vascular channels. As the disease advances, tumors may extend locally, involving adjacent structures such as the lower uterine segment, vagina, and paracervical tissues, including the broad and uterosacral ligaments. In advanced stages, the tumor may become fixed to the pelvic wall or invade adjacent organs, leading to a range of symptoms, including pelvic pain, dyspareunia (painful intercourse), abnormal vaginal discharge, and bleeding. In some cases, the tumor may compress local structures, causing referred pain in the lower back or gluteal region, or obstruct the ureters, leading to hydronephrosis and uremia. In severely advanced and untreated cases, fistulas may form, leading to urinary or fecal incontinence. The spread of cervical cancer occurs predominantly through lymphatic channels, following an orderly pattern. Initially, the internal and external iliac lymph nodes are affected, with subsequent involvement of the common iliac and para-aortic nodes as the disease progresses. The likelihood of lymph node involvement correlates strongly with the stage and extent of the primary tumor. In early-stage disease (Stage I), the risk of pelvic lymph node involvement ranges from 11% to 18%, increasing to 32% to 45% in Stage II, and up to 66% in Stage III. Para-aortic lymph node involvement becomes more common in advanced stages, reaching as high as 57% in Stage IVA disease. While lymphatic spread is the most common route of dissemination, hematogenous (through the bloodstream) metastasis is also possible, though it is typically less common at the initial diagnosis. The most frequent sites of distant metastasis include the lungs, liver, bones, and distant lymph nodes. The predictable patterns of both local and distant spread of cervical cancer underscore the importance of comprehensive staging and management strategies aimed at controlling both the primary tumor and potential metastases.

Staging of Cervical Cancer

The staging of cervical cancer is a critical component in determining the appropriate treatment strategy and assessing prognosis. The current staging system used globally is provided by the International Federation of Gynecology and Obstetrics (FIGO), with the most recent update made in 2009. This update introduced several key changes, including the elimination of Stage 0 (preinvasive disease) and the subdivision of Stage IIA into Stage IIA1 (tumors ≤4 cm in size) and Stage IIA2 (tumors >4 cm in size), mirroring the subdivisions within Stage IB. These changes reflect a growing understanding of the prognostic significance of tumor size.

FIGO Staging System for Cervical Cancer:

Stage I: The carcinoma is confined strictly to the cervix, disregarding any extension into the uterine corpus.

Stage IA: Invasive cancer identified only microscopically, with invasion limited to measured stromal invasion up to 5 mm in depth and no wider than 7 mm.

Stage IA1: Measured stromal invasion no greater than 3 mm in depth and no wider than 7 mm.

Stage IA2: Measured stromal invasion greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm.

Stage IB: Clinical lesions confined to the cervix or preclinical lesions greater than Stage IA.

Stage IB1: Clinical lesions no greater than 4 cm in size.

Stage IB2: Clinical lesions greater than 4 cm in size.

Stage II: The carcinoma extends beyond the cervix but does not reach the pelvic wall or involve the lower third of the vagina.

Stage IIA: No obvious parametrial involvement.

Stage IIA1: Clinical lesions no greater than 4 cm in size.

Stage IIA2: Clinical lesions greater than 4 cm in size.

Stage IIB: Obvious parametrial involvement.

Stage III: The carcinoma has extended to the pelvic wall, with no cancer-free space between the tumor and the pelvic wall upon rectal examination, or it involves the lower third of the vagina. This stage also includes cases with hydronephrosis or a non-functioning kidney, unless these conditions are due to another cause.

Stage IIIA: Extension to the lower third of the vagina without extension to the pelvic wall. Stage IIIB: Extension to the pelvic wall and/or presence of hydronephrosis or a non-functioning kidney.

Stage IV: The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum.

Stage IVA: Spread to adjacent organs.

Stage IVB: Spread to distant organs.

Diagnostic Procedures and Considerations

According to FIGO, clinical staging is primarily based on physical examination and a series of specific diagnostic tests. These include palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and plain radiographs of the lungs and skeleton. Although advanced imaging techniques such as CT, MRI, and PET scans, as well as surgical findings from lymphadenectomy, provide valuable information for treatment planning, they cannot alter the official stage classification according to FIGO guidelines. Nonetheless, these imaging and surgical methods are recognized for their prognostic value and influence on treatment decisions, particularly in regions where they are accessible. Joint evaluation by a multidisciplinary team, including radiation and gynecologic oncologists, is essential for optimal staging and management. Routine diagnostic procedures include cytological smears (if not contraindicated by bleeding), colposcopy, and biopsy of gross tumors. For patients with advanced disease (Stage IIB and beyond), cystoscopy and proctosigmoidoscopy are recommended to assess for potential invasion of the bladder and rectum. Standard radiographic studies include chest radiography and intravenous pyelography, with additional studies such as CT or MRI scans used as complementary tools in evaluating the extent of disease. The FIGO staging system remains the cornerstone of cervical cancer management, ensuring consistency in reporting and facilitating comparison of outcomes across studies and clinical practices worldwide.

2. Materials and Methods

Study Area

The study was conducted in the Department of Radiology at MPMMCC.

Study Population

The study population comprised female patients attending the Radiotherapy Outpatient Department (OPD) at MPMMCC and HBCH Varanasi. All patients were diagnosed with Carcinoma Cervix Stage IB–IVA, appropriately staged according to FIGO guidelines, and consented to participate in the clinical trial.

Patient Selection

Inclusion Criteria:

1) Histopathologically proven squamous cell carcinoma of the uterine cervix.
2) Local or locally advanced disease (FIGO Stage IB–IVA) with a definite indication for brachytherapy.
3) Adequate bone marrow function: hemoglobin > 11 g/dL; WBC > 4, 000/mm^3; platelets > 100, 000/mm^3.
4) Adequate renal function: serum creatinine < 1.5 mg/dL.
5) Normal blood biochemical parameters, including serum bilirubin, liver enzymes, serum calcium, and serum electrolytes.
6) Karnofsky Performance Status > 70.
7) Signed informed consent specific to the study.

Exclusion Criteria:

1) Prior treatment with pelvic radiotherapy, chemotherapy, or hysterectomy.
2) Poor geometry for intracavitary brachytherapy (e. g., very narrow vagina, poor visibility of cervical os).
3) Presence of serious co-morbid conditions (e. g., hypertension, diabetes mellitus, chronic renal failure) or abnormal hematological/biochemical parameters.
4) Enrollment in another clinical trial.
5) Histological diagnoses other than squamous cell carcinoma, such as adenocarcinoma, adenosquamous carcinoma, small cell carcinoma, clear cell carcinoma, glassy cell carcinoma, adenoid cystic carcinoma, or carcinoid.

Pre-Treatment Evaluation

1) Comprehensive history and physical examination, including assessment of height, weight, body surface area, and Karnofsky Performance Status.
2) Confirmation of carcinoma cervix through histopathology; slide reviews or repeat biopsies were conducted when necessary.
3) Complete hematological and biochemical profiling, including complete hemogram, serum urea, creatinine, liver function tests, and serum electrolytes.
4) Radiographic evaluations, including chest X-ray (PA view), ultrasonography of the whole abdomen, intravenous pyelography, barium enema study, and contrast-enhanced CT scan of the abdomen and pelvis, primarily for diagnostic purposes and external beam radiotherapy (EBRT) planning.
5) Cystoscopy and proctosigmoidoscopy with endoscopy-guided biopsy were performed when indicated, with histopathologically proven bladder or bowel involvement rendering the patient ineligible for the study.

Study Protocol

Patients meeting the inclusion criteria and without any exclusion criteria were registered for the study after providing informed consent. A total of thirty patients were enrolled.

External Beam Radiotherapy (EBRT):

All patients received EBRT to the whole pelvis up to a total dose of 50 Gy in 25 fractions (2 Gy per fraction) over 5 weeks (5 days per week). EBRT was delivered using a Nucletron B. V (An Elekta company) Flexitron Co: 60, Radioisotope: Co-60 with a source strength of 200 RMM and a Source-to-Surface-Distance (SSD) of 80 cm. Treatment portals included Antero-Posterior and Postero-Anterior (AP-PA) pelvic fields, treated daily. Patients with Stage IIB to IVA disease received concomitant chemotherapy with Inj. Cisplatin 40 mg/m² weekly along with EBRT.

High-Dose Rate Intracavitary Brachytherapy (HDR-ICBT):

HDR-ICBT was administered starting one week after completion of EBRT. The standard dose per fraction was 7 Gy, with a total of 21 Gy delivered to point A in three fractions, on a once-weekly basis. The modified Fletcher Suit type applicator was used, consisting of one curved central tandem and a pair of shielded ovoids. Treatment was delivered using the micro-Selectron HDR Brachytherapy System (Nucletron B. V., Veenendaal, Netherlands) with 192 Iridium sources. Treatment planning was conducted using the PLATO planning system (Nucletron B. V., Veenendaal, Netherlands). The application was performed under sedation in the Brachytherapy Operation Theatre (OT) using proper aseptic techniques and conventional X-ray and CT-based 3D planning.

Dose Calculation and Treatment Planning:

For conventional X-ray-based planning, two orthogonal films were taken to determine prescribing points, and the dose was optimized to Point A without modifications. For CT-based 3D planning, a CT scan with 2.5-mm slice thickness was performed with the applicator in place. The target volumes (HR-CTV and IR-CTV) and organs at risk (OARs) were contoured, and Dose Volume Histograms (DVHs) were generated for analysis. Statistical analysis included calculating mean values, standard deviations, standard error of the mean, confidence intervals, and applying paired t-tests to compare conventional and CT-based planning data, with a significance level of $P < 0.05$ considered statistically significant. Historical Development of Brachytherapy

1) Origins and Early Discoveries

Discovery of Radioactivity: Henri Becquerel discovered radioactivity in 1896. Marie Curie and Pierre Curie isolated radium from pitchblende ore in 1898. The Nobel Prize in Physics was awarded to them and Becquerel in 1903 for this discovery.

Early Treatments: The first therapeutic use of radium occurred in the early 20th century. Notable early treatments included Danlos and Bloc's work on lupus in 1901 and Abbe's radium implants in 1905.

2) Development of Institutions and Methods

Founding of Key Institutions: Significant brachytherapy centers included the Radium Hemmet in Stockholm, the Memorial Hospital in New York, and the Radium Institute in Paris, founded by Regaud and Lacassagne.

Intracavitary Radiation Methods: Descriptions of these methods emerged from Stockholm and Paris in 1914 and 1919, respectively.

Manchester System: The rules for interstitial radium therapy, published in the 1930s by Patterson, Parker, and Meredith, became foundational.

3) Advancements in Radioactive Sources

Discovery of Artificial Radioactivity: In 1934, Irene Curie and Frederick Joliot's discovery of artificial radioactivity opened new possibilities for brachytherapy.

Evolution of Sources: After World War II, cobalt needles were briefly used, succeeded by tantalum and gold, and later by iridium, which became the predominant material by 1958.

4) Technological Innovations

After loading Techniques: The 1950s and 1960s saw the development of after loading technology, allowing for safer and more controlled application of radiation.

Paris System of Dosimetry: New rules for implantation and dose calculation, developed by Pierquin, Chassagne, and Dutreix, improved treatment outcomes.

5) Modern Advances

Remote After loading: Modern remote after loading machines enhance safety by providing complete radiation protection.

Imaging and Dosimetry: Advances in imaging and computerized dosimetry have improved accuracy in treatment planning and delivery.

3. Results and Analysis

The mean age of the patients enrolled in the study was 50.03 years (Range: 29-75 years). Majority of the patients were between 40 and 60 years of age. (Table 1)

Table 1: Age- wise distribution of patients

Age group of patients	No. of patients
< 30	1
30- 39	3
40- 49	15
50- 59	6
60- 69	3
70+ years	2

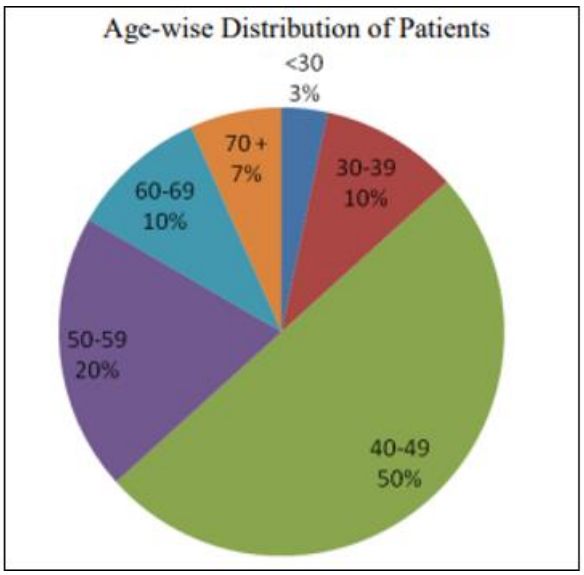


Figure 1: Age- wise distribution of patients

Tumor stage was evaluated according to the International Federation of Gynecology and Obstetrics (FIGO) classification. Commonest presentation of patients was in Stage III B, followed by Stages II B, II A, III A, and IV A, in decreasing order of frequency. (Table 2)

Table 2: Stage- wise distribution of patients

Stage of Disease	No. of patients
IV A	2
III B	14
III A	3
II B	7
II A	4

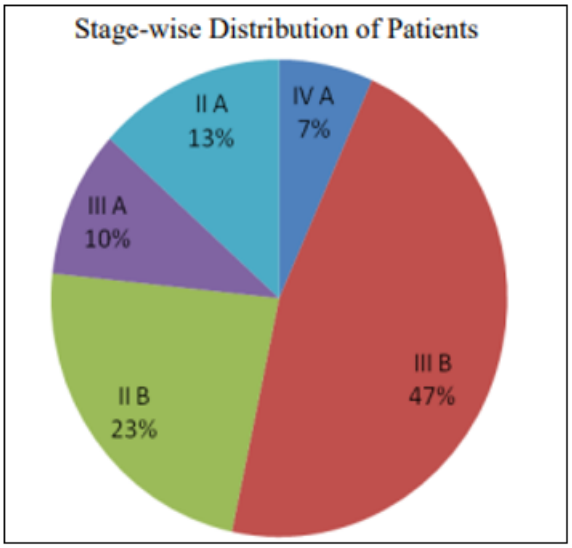
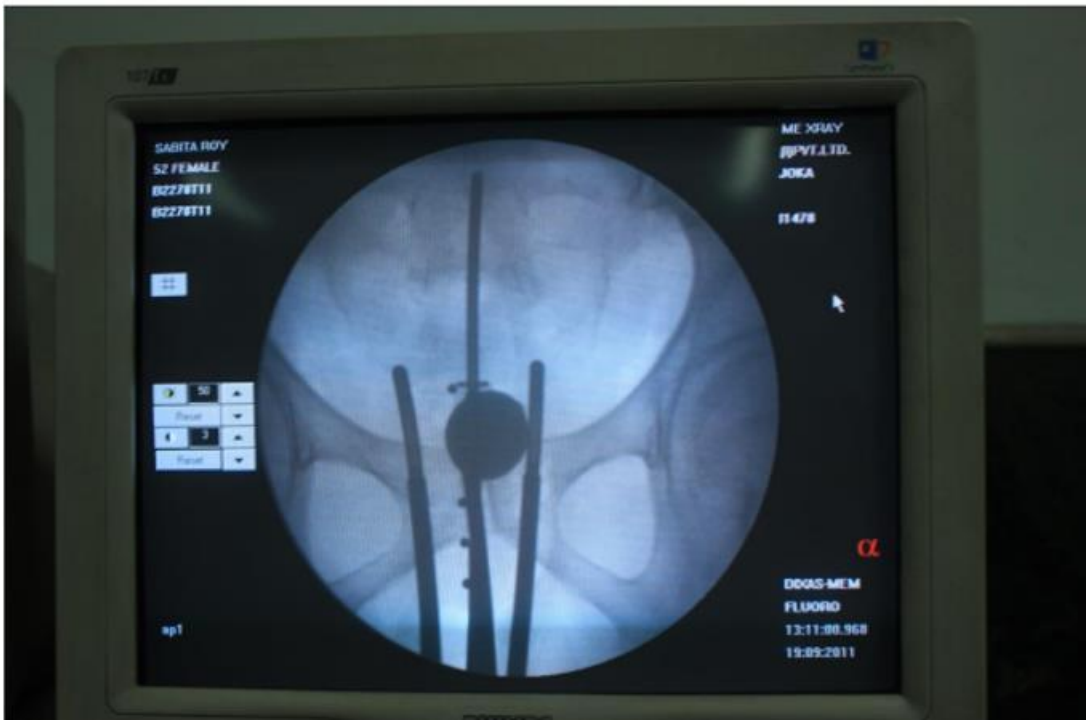
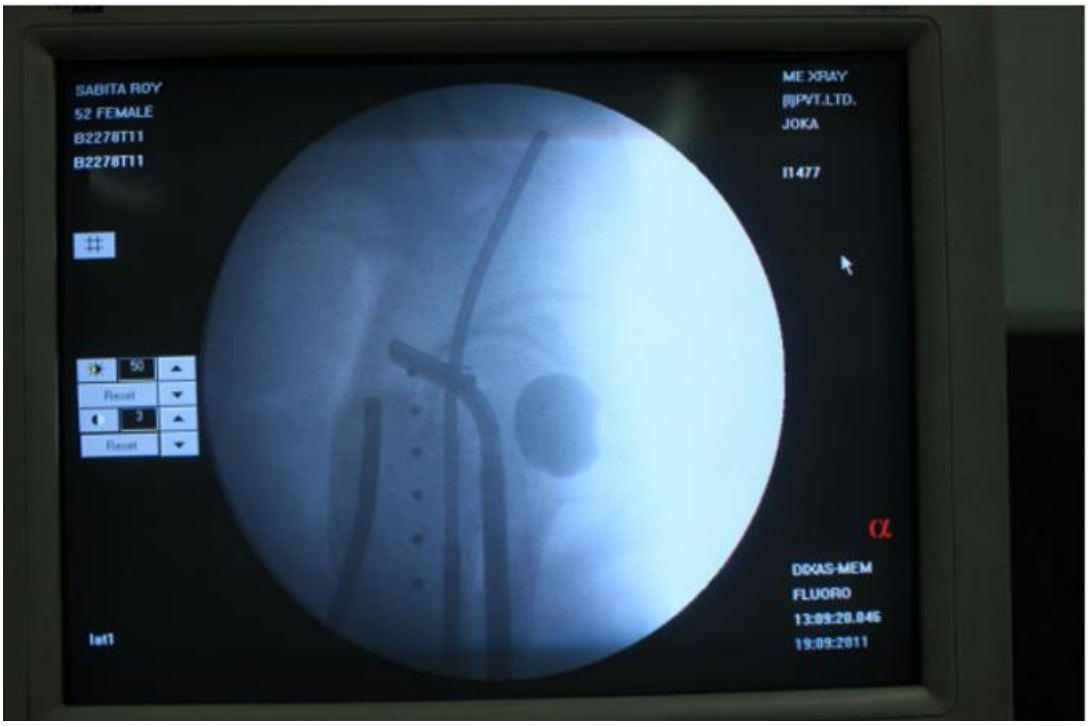
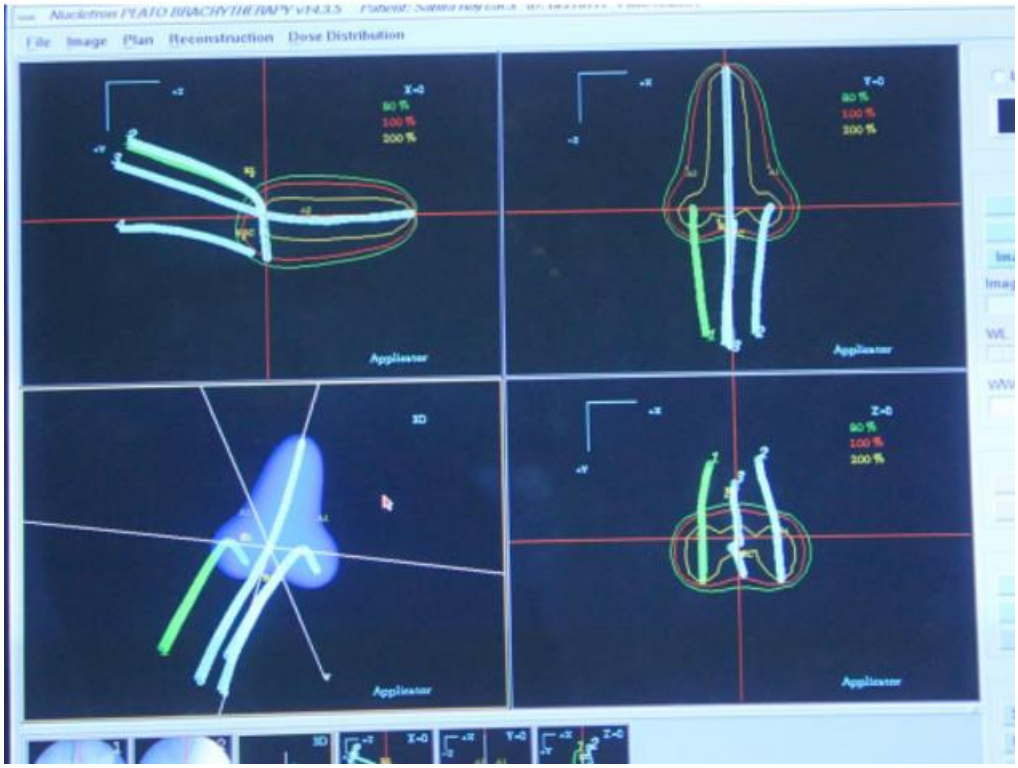


Figure 2: Stage- wise distribution of patients

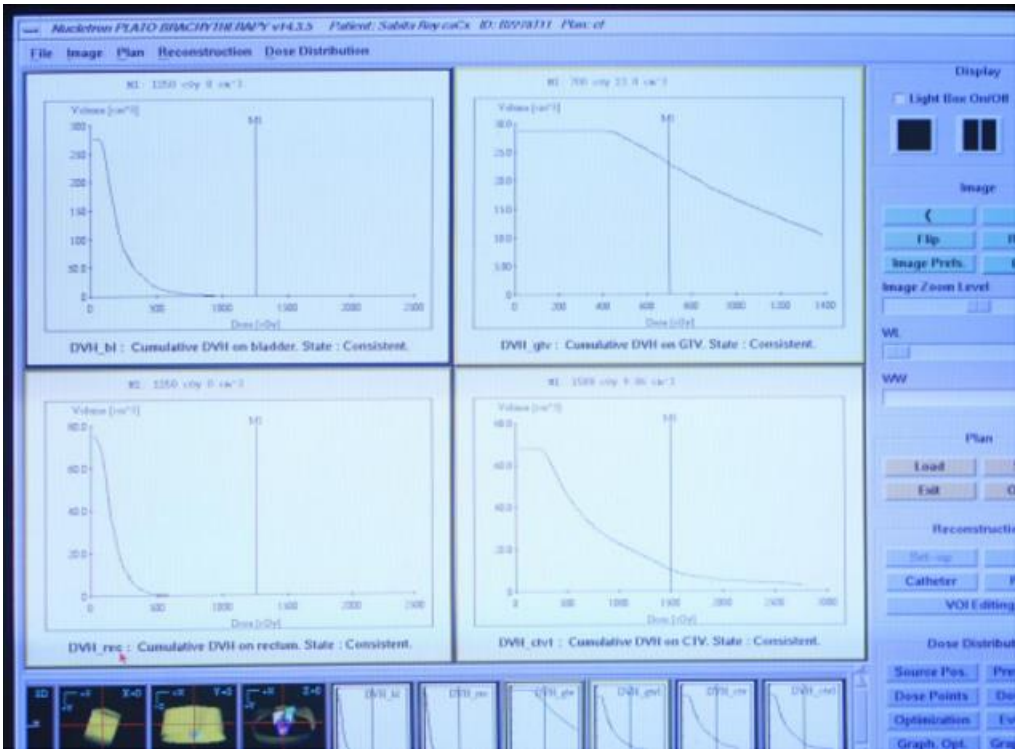


Orthogonal radiographs for conventional planning





Applicator Reconstruction and DVH analysis for CT based planning



4. Discussion

1) Study Overview: The study was conducted between January 2011 and June 2012, involving 30 patients with carcinoma cervix (Stages II B – IV A). Patients were treated with external beam radiotherapy followed by high-dose-rate (HDR) intracavitary brachytherapy using a standard dose of 7 Gy per fraction for 3 fractions.
2) Objective 1: Comparison of dose distribution between X-Ray based and CT-based treatment planning. The study found that conventional X-Ray based plans overestimated the tumor dose compared to CT-based plans, leading to inadequate tumor coverage, particularly in advanced cases.
3) Objective 2: Investigation of the relationship between tumor size and dose coverage. The study demonstrated that larger tumors received less adequate dose coverage, confirming the need for CT-based planning, especially in more advanced stages of the disease.
4) Objective 3: Comparison of dose to the bladder and rectum (organs at risk, OARs) between conventional and CT-based plans. Results indicated that conventional plans underestimated the dose to OARs, potentially leading to overdosage and associated complications.
5) Objective 4: Development of a brachytherapy protocol for cervical cancer in settings without MRI access. The study suggested that while MRI remains the gold standard, CT-based planning can be a viable alternative, provided that standardized contouring guidelines are followed. However, issues with metal artifacts in CT imaging and the high cost of MRI-compatible applicators were noted as challenges.

The discussion section appears to delve into the broader implications of these findings, particularly the feasibility of implementing CT-based brachytherapy in resource-limited settings. The study supports the potential for CT-based planning to achieve reasonable accuracy in dose delivery, although the need for affordable, indigenous solutions for applicators is emphasized.

The conclusion of the study emphasizes the critical need to adapt international guidelines and recommendations for the treatment of cervical cancer to the Indian context. Given that 80% of new cervical cancer cases occur in developing countries like India, where advanced stages are common and resources are limited, optimizing treatment is essential.

5. Conclusion

Prevalence and Challenges
India reports approximately one-fourth of the world's cervical cancer cases, with the majority diagnosed at advanced stages. The lack of advanced equipment, imaging infrastructure, and trained personnel in many centers poses significant challenges to effective management.

Need for Resource Optimization
In addition to aggressive screening programs for early detection, there is a pressing need to make optimal use of available resources to improve disease control and minimize toxicities.

Study Insights
A comparative study of X-Ray and CT-based treatment planning for intracavitary brachytherapy was conducted at mpmmcc varanasi. The study showed that CT-based planning provided better dose coverage to tumors and reduced exposure to the bladder and rectum, particularly in more advanced cases. The results were consistent with international literature, underscoring the effectiveness of CT-based planning.

6. Limitations and Future Directions

Due to the short study period, long-term toxicity profiles for the rectum and bladder could not be assessed. Further studies are necessary to correlate the dosimetric advantages of CT planning with clinical outcomes. The study highlights the absence of comprehensive data on brachytherapy practices across India, calling for a national survey to inform the creation of national guidelines that align with international standards.

In conclusion, the study supports the implementation of CT-based brachytherapy planning in India as a feasible and effective approach, particularly in resource-limited settings. However, it also calls for further research and national-level efforts to standardize and improve the quality of care for cervical cancer patients.

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