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# COMPARISON OF TWO RADIOTHERAPY TECHNIQUES IN TREATMENT OF PATIENTS WITH INOPERABLE (ADVANCED) CERVICAL CANCER

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**Abstract**

Advanced cervical cancer is treated with radiotherapy, target therapy, chemotherapy or a combination of those. Standardized accepted treatment of inoperable cervical cancer is concurrent chemo-radiotherapy (CCRT) followed by brachytherapy. Radiotherapy techniques used are three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiation therapy (IMRT).

In this study participated 30 female patients, average age of 52 at the time of irradiation.3D-CRT plans were made, patients were treated on linear accelerator (LINAC) with 3D-CRT. IMRT plans were made additionally.

Planning target volume (PTV) dose coverage was 105.36% for 3D-CRT and 105.64% for IMRT. Homogeneity index (HI) was 0.062 for 3D-CRT and 0.048 for IMRT. Conformity index (CI) for 3D-CRT was 1.93 for PTV of 2990.77 ccm. CI for IMRT was 1.305 for PTV of 2019.83 ccm.

Bladder V40 (%) for 3D-CRT averaged 96.61%, while IMRT averaged 73.11%. Rectal V50 (%) for 3D-CRT was 72.55% and for IMRT was 17.80%. Rectal V40 (%) for 3D-CRT and IMRT averaged 92.12% and 73.49% respectively. Quantitative Analysis of normal Tissue Effects in the Clinic (QUANTEC) – V45 for 3D-CRT was 228.80ccm and for IMRT was 104.55ccm. Femoral heads dose for 3D-CRT was 51.50Gy for left and 51.29Gy for right. Absorbed doses for IMRT were 47.28Gy for left and 47.32Gy for right femoral head, respectively.

13 patients had grade 1 cystitis and urethritis, 2 with grade 2. 7 patients developed grade 1 diarrhea, 1 with grade 2.

It can be concluded that dosimetrically IMRT is superior to 3D-CRT in patients treating cervical cancer.

***Keywords:*** cervical cancer, 3D-CRT, IMRT.

## Introduction

One of the undesired characteristics in modern time is the malignant disease existence and among the most frequent malignant diseases in female population is the cervical cancer. Occurrence of cervical cancer many times does not manifest with strong symptoms even in advanced stages. It can begin in the cells of the exocervix, but also inside the endocervical canal.

Most common site of origin is the so-called “transformation zone”[1] which represents the region where the squamous epithelium transforms into glandular epithelium. Cell transformation are in fact a series of changes inside the cells and because of which they become different than regular cells and they form precancerous lesions[2] (cervical intraepithelial neoplasia – CIN, squamous intraepithelial lesion - SIL). Precancerous lesions after a period of time of several months to several years, many will regrade into normal

cells, but some will downgrade into malignant cells and evolve into cervical cancer. Cervical cancer is divided into two major histopathological groups: squamous cancer and adenocarcinoma.

Squamous cancer emerges from the squamous epithelium (around 90% of diagnosed histology types) and adenocarcinoma with all it's subtypes (with estimate of 7-10% of diagnosed histology types[3]). Mixed type along with other types are less common.

Epidemiologically cervical cancer for continental Europe have estimate incidence value of 14.6 on 100.000 population and mortality estimate value of 6.3 on 100.000 population. Our country compares to continental Europe and estimate incidence value of 10.9 on 100.000 population and mortality estimate value of 6.4 on 100.000 population[3].

Cervical cancer treatment is operative in case of localized disease which does not advance towards the parametria and surrounding pelvic organs. However, unfortunately many times it happens that operative treatment is not an option when the disease is advanced and thus declared inoperable.

According to the Federation of gynecology and obstetrics (FIGO), cervical cancer is classified in several stages[5] depending of the loco-regional spread towards nearby tissues and organs and invasion:

- IIB – tumor infiltrates the parametria,
- IIIA – invasion of the lower 1/3 of the vagina,
- IIIB – tumor spreads to the pelvic wall or towards para-aortic region with a risk for possible ureter compression resulting in onset of hydro nephrosis,
- IVA – tumor has spread to surrounding tissue and organs and is infiltrating them (rectum, bladder) or when it spreads beyond the borders of the pelvis,
- IVB – present distant metastases.

In cases of advanced disease patients are to be treated with conservative treatment methods as radiotherapy, target therapy, chemotherapy or a combination of those.

As a standardized accepted in treatment of inoperable cervical cancer is concurrent chemo-radiotherapy (CCRT) followed by brachytherapy. CCRT is a radiation treatment that combines external beam radiotherapy (EBRT) with concurrent application of chemotherapy in the period of an ongoing radiotherapy treatment. Radiotherapy is performed on a treatment machines (Cobalt 60 tele-cobalt-therapy and various linear accelerator machines and variants)[6]. Radiation dose is fractionated accordingly into daily fractions in order to preserve accumulation of high absorbed doses in surrounding tissues and organs and give them much needed respite form radiation.

For a long period of years, as a standardized radiotherapy technique was used the three-dimensional conformal radiotherapy (3D-CRT) with it's most used delivery method the so-called "box-technique" which utilized 4 radiation pelvic fields, arranged on 90 degrees from each other used to improve dose homogeneity[7]. Conformal radiotherapy focuses the radiation dose inside the tumor volume (target) while reducing the absorbed dose in organs at risk (OAR) – rectum, bladder, intestines, etc. This is possible due to installed multi-leaf collimator system (MLC) on treatment machines which protects the tissues and OAR which are not positioned near the target. The MLC is in a fixed position during the treatment delivery process.

Prior the irradiation a computer tomography (CT) or magnetic resonance imaging (MRI) is used for purpose of radiotherapy planning.

As a newer technique in cervical cancer radiotherapy treatment, emerged the intensity modulated radiation therapy (IMRT). Absorbed doses are modulated because on different depths a different portion of the dose is given. As a result the absorbed doses in OAR and tissues surrounding the target are lower than doses in 3D-CRT.

IMRT uses greater number of treatment fields (usually 5-9 fields) and according to the way it is done and machines used, it is divided on several separate techniques:

1. "Step and shoot" IMRT – uses larger number of treatment fields with fixed MLC (non-dynamic collimator) which focus in the target[9].
2. "Sliding window" IMRT – it uses dynamic collimator, i.e. collimator is moving during the irradiation,

3. Intensity modulated arc therapy (IMAT) – the LINAC's head moves on an arc trajectories around the target [9],
4. Robotic IMRT Stereotactic body radiation therapy (SBRT) – separate type of IMRT defined with high precision on "Cyberknife" – machines[9],
5. Volumetric modulated arc therapy (VMAT) – the LINAC's head moves 360 degrees around the patient [10],
6. Stereotactic body radiation therapy (SBRT) – high precision IMRT on LINAC with hypofractionated regimens [10].

After completing the radiation therapy, treatment continues with placing brachytherapy applicators inside or in direct target vicinity. According to the applicators used it is mainly divided as:

1. Intracavitary brachytherapy (ICB) with applicators placed inside the body cavities (such as vagina or uterine cavity) [11],
2. Interstitial brachytherapy (ISBT) utilizes a tubes (carriers) that are placed inside the target [11],
3. Combination of the prior two types [11].

In cases when there is unsatisfactory response to treatment, i.e. primary large tumor volume, locally advanced disease or presence of positive lymphatic nodes, an additional treatment (consolidating chemotherapy, target therapy) may be prescribed [12].

**Materials and methods**

In this retrospective study participated 30 female patients, with average age of 52 (25 – 70) at the time of irradiation.

They all had CT-scans on a CT-simulator with bladder-filling protocol (500ml of liquids 30-45min. prior the simulation) with a target of getting sustainable bladder volume in average of 250-350ml.

After the contouring the target volume and the OAR, regular 3D-CRT plans were made and after the approval they had been treated on a linear accelerator (LINAC) at our institution with 3D-CRT. IMRT plans were made additionally for dosimetric comparison purposes.

Prior giving the chemotherapy all patients planned for CCRT were sent to a cardiac ultrasound checkup and laboratory analyses (blood count, degradation products – urea and creatinine). After confirming the eligibility for Cisplatin concomitant chemotherapy, they started the treatment. Chemotherapy was concomitantly applied once a week (Cisplatin a 30mg/m$^2$) for a total of 5 weeks.

All patients at least once a week had a checkup in ambulatory setting and regular daily checkups in stationary conditions. Peripheral blood count was made once a week for the duration of the treatment.

28 patients received radiotherapy in 28-daily fractions, with 1.8Gy daily dose and a total dose of 50.4Gy in the target volume. 2 patients received radiotherapy in 25-daily fractions, with 2Gy daily dose and a total dose of 50Gy in the target volume.

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

No written informed consent was obtained as this was a retrospective observational study.

**Results**

Results apply for all 30 patients concerning their 3D-CRT and IMRT plans.

Results regarding the target – Planning target volume (PTV) PTV measured in average 1552.43 ccm (1110 – 2855 ccm).

Dose coverage was in average 105.36% for 3D-CRT (104.2 – 105.7%) and 105.64% for IMRT (103.3 – 107.5%). Homogeneity index (HI) was in average 0.062 for 3D-CRT (0.043 – 0.083) and 0.048 for IMRT (0.024 – 0.063). Conformity index (CI) for 3D-CRT (95%max) was 1.93 (1.063 – 2.514) regarding the volume of PTV (3D-CRT V95%max) of 2990.77 ccm in average (1540 – 4625 ccm). Conformity Index (CI) for IMRT (95%max) was 1.305 (1.162 – 1.476) regarding the volume of PTV (IMRT V95%max) of 2019.83 ccm in average (1486 – 3502 ccm) (Table 1).

**Table 1**
Dosimetry results regarding the target – Planning target volume (PTV)

| **Dose coverage (%)** | | | |
|---|---|---|---|
| Technique | Average | Range | |
| 3D-CRT | 105.36 | 104.2 - 105.7 | |
| IMRT | 105.64 | 103.3 - 107.5 | |
| **Homogeneity Index (HI)** | | | |
| Technique | Average | Range | |
| 3D-CRT | 0.062 | 0.043 - 0.083 | |
| IMRT | 0.048 | 0.024 - 0.063 | |
| **Conformity Index (CI) 95% max.** | | | |
| Technique | Average | Range | PTV average (ccm) |
| 3D-CRT | 1.93 | 1.063 – 2.514 | 2990.77 |
| IMRT | 1.305 | 1.162 – 1.476 | 2019.83 |

Results regarding the organs at risk (OAR):

Bladder volume (49.4 – 891.2 ccm) in average: 344.46 ccm.

Bladder Dmax. (Gy) for 3D-CRT was in average 52.20Gy (50.03 – 53.00Gy) and for IMRT the average was 51.99Gy (47.15 – 53.32Gy). Bladder V40 (%) for 3D-CRT averaged 96.61% (69.95 – 100.00%), while for IMRT the average value was 73.11% (46.31 – 99.70%) (Table 2).

**Table 2**
Dosimetry results for organs at risk (OAR) - Bladder

| **Bladder Dmax. (Gy)** | | |
|---|---|---|
| Technique | Average | Range |
| 3D-CRT | 52.20 | 50.03 – 53.00 |
| IMRT | 51.99 | 47.15 – 53.32 |
| **Bladder V40 (%)** | | |
| Technique | Average | Range |
| 3D-CRT | 96.61 | 69.95 - 100.00 |
| IMRT | 73.11 | 46.31 - 99.70 |

Rectal volume averaged 95.37 ccm (36.8 – 214.8 ccm).

Rectal V50 (%) for 3D-CRT was in average 72.55% (42.94 – 91.62%) and for IMRT was 17.80% (7.32 – 41.26%). Rectal V40 (%) for 3D-CRT averaged 92.12% (77.72 - 99.55%) and for IMRT average was 73.49% (47.41 – 93.88%) (Table 3).

| **Table 3**<br>Dosimetry results for organs at risk (OAR) - Rectum | | |
|---|---|---|
| **Rectal V50 (%)** | | |
| Technique | Average | Range |
| 3D-CRT | 72.55 | 42.94 – 91.62 |
| IMRT | 17.80 | 7.32 – 41.26 |
| | | |
| **Rectal V40 (%)** | | |
| Technique | Average | Range |
| 3D-CRT | 92.12 | 77.72 - 99.55 |
| IMRT | 73.49 | 47.41 - 93.88 |
| | | |

Intestinal volume was in average 1301.10 ccm (555.5 – 2106.4 ccm).

Quantitative Analysis of Normal Tissue Effects in the Clinic (*QUANTEC*):

V45 for 3D-CRT was 228.80 ccm in average (80.49 – 412.01 ccm), while V45 for IMRT averaged at 104.55 ccm (2.17 – 214.41 ccm).

Intestinal D (25%V) (Gy) for 3D-CRT was 39.30Gy (29.60 – 49.99Gy), while for IMRT was 32.76Gy (25.34 – 40.60Gy). Intestinal D (50%V) (Gy) for 3D-CRT averaged 24.31Gy (14.16 – 34.15Gy) and for IMRT averaged 22.02Gy (12.90 – 27.59Gy). Intestinal D (67%V) (Gy) for 3D-CRT was 15.39Gy (6.51 – 21.39Gy) and for IMRT was 15.44Gy (5.98 – 20.82Gy) (Table 4).

Femoral heads absorbed dose for 3D-CRT had an average of 51.50Gy (50.23 – 52.31Gy) for left head and 51.29Gy (50.13 – 52.14Gy) for right femoral head. Absorbed doses for IMRT were 47.28Gy (37.94 – 52.29Gy) for left femoral head and 47.32Gy (39.40 – 53.36Gy) for right, respectively. (Table 5).

Results regarding biological effects:

13 patients developed grade 1, while 2 developed grade 2 cystitis and urethritis. 7 patients developed grade 1 and 1 developed grade 2 diarrhea.

**Table 4**
Dosimetry results for organs at risk (OAR) - Intestines

| **Quantitative Analysis of Normal Tissue Effects in the Clinic (*QUANTEC*), V45 (ccm)** | | |
|---|---|---|
| Technique | Average | Range |
| 3D-CRT | 228.80 | 80.49 - 412.01 |
| IMRT | 104.55 | 2.17 - 214.41 |
| | | |
| **Intestinal D (25%V) (Gy)** | | |
| Technique | Average | Range |
| 3D-CRT | 39.30 | 29.60 - 49.99 |
| IMRT | 32.76 | 25.34 - 40.60 |
| | | |
| **Intestinal D (50%V) (Gy)** | | |
| Technique | Average | Range |
| 3D-CRT | 24.31 | 14.16 – 34.15 |
| IMRT | 22.02 | 12.90 – 27.59 |
| | | |
| **Intestinal D (67%V) (Gy)** | | |
| Technique | Average | Range |
| 3D-CRT | 15.39 | 6.51 – 21.39 |
| IMRT | 15.44 | 5.98 – 20.82 |

**Table 5**
Dosimetry results for organs at risk (OAR) – Femoral heads

| **Femoral heads (Left) Dmax. (Gy)** | | |
|---|---|---|
| Technique | Average | Range |
| 3D-CRT | 51.50 | 50.23 - 52.31 |
| IMRT | 47.28 | 37.94 - 52.29 |
| | | |
| **Femoral heads (Right) Dmax. (Gy)** | | |
| Technique | Average | Range |
| 3D-CRT | 51.29 | 50.13 - 52.14 |
| IMRT | 47.32 | 39.40 - 53.36 |

**Discussion**

3D-CRT has been the mainstay of radiotherapy treatments for decades, providing a high degree of dose conformity. While irradiating the target, offering higher degree of protection for OAR compared to previous two-dimensional radiotherapy (2D-RT).

This study arised from the need to further advance radiotherapy treatment from 3D-CRT to more advanced conformal techniques that will provide lower doses to OAR, while keeping sufficient dose coverage to the target. Concerning the results obtained regarding target volume dose, both techniques are

comparable in dose coverage. IMRT has lower values for homogeneity index compared to 3D-CRT and is superior in PTV coverage with lower values for conformity index compared to 3D-CRT.

Regarding absorbed doses in OAR, IMRT is superior to 3D-CRT:

Bladder volume was sufficient (bladder filling protocol target of bladder volume ranging from 250-350ml). Concerning the Bladder Dmax, both techniques had almost identical values. Bladder volume V40 (%) was more spared from high doses with IMRT.

It has to be noted that the bladder is the organ that is used for protection of the intestines by using the bladder-filling protocol. Although, the bladder is more radiation resistant compared to surrounding soft tissue organs at risk (rectum, sigmoid, intestines), it is sensitive to higher doses and with IMRT it has reduced bladder areas overlaying the PTV [13] .

Rectal volume of V50 (%) had the most benefit in terms of dose reduction with IMRT. Most notable biological effect after pelvis radiotherapy is the chronic radiation proctitis. Considering that data are limited, they suggest that the risk of chronic radiation proctitis varies according to the type of radiation therapy delivered, the dose of radiation delivered and the volume of tissue being radiated [14]. Yet again, accenting the reduced organ volume obtained from IMRT.

Intestines according to QUANTEC V45 (ccm) greatly favors the IMRT. Percentage values for 25% and 50% intestinal volume gives advantage to IMRT, while equalizing the effect of both techniques for 25% volume due to reduction of intestinal volume. Therefore, with IMRT, sparing the small bowel is obtainable while sufficiently covering the targets.

In 3D-CRT with four-field box technique, small bowel within the radiation field is homogeneously irradiated with the targets [16].

Femoral heads had benefit in dose reduction from IMRT in comparison to 3D-CRT, with a note that sometimes absorbed doses in both techniques exceed the total dose – notably more in 3D-CRT.

Results from observed biological effects affect only 3D-CRT because the patients were treated with 3D-CRT only. They are in expected and comparable ranges for 3D-CRT. Compared with the results from other studies, and previously noted, IMRT irradiated patients have fewer biological effects during and/or after the treatment.

## Conclusion

At the end, according to the results from this retrospective study, it can be concluded that dosimetrically IMRT is superior to 3D-CRT in patients treating cervical cancer. It is comparable in target coverage and obtains reduced doses in surrounding tissues of OAR, thus giving fewer biological effects and with it – improving the patient condition during the radiotherapy treatment and further improving patient's quality of life.

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