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Literature Review

Comparison of Dose-Volume Histograms in Intracavitary Brachytherapy of Cervical Cancer using Manual Plan and Inverse Optimization Technique

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Abstract

Introduction: Brachytherapy treatment planning with manual technique is a common method for high-dose-rate (HDR) cervical cancer. New methods performing inverse optimization technique of the dose distribution have been developed over the recent years. The purpose of this study is to test the feasibility of an inverse optimization technique and compare it to the manual technique in terms of speed and dose-volume histogram (DVH) parameters. The aim is to finding an optimum set of constraints that will produce an inverse optimization result. This will be comparable to a manual plan in terms of coverage for high-risk clinical target volume (HR-CTV) with a prescribed dose; simultaneously decreasing the dose to organs at risk (OARs) and planning process duration.

Materials and Methods: Thirty cervical cancer patients treated with an HDR brachytherapy were included in this study. Each patient had three treatment plans with manual technique, of which each was developed using an inverse optimization technique by an expert treatment planner. The plans were created using the inverse technique, that has constant constraints on the maximum doses of the target volume and different constraints on OARs.

Results: The resulting dose-volume histogram (DVH) were compared for the manual and inverse technique. Following parameters were used: dose covering 90% (D90) of high-risk clinical target volume (HR CTV), HR CTV V100%, dose to point A, and doses to 2cm3 (D2cc) were recorded for rectum, bladder, sigmoid, and bowel. In addition, the total treatment time, and the sum of the total reference air kerma (TRAK) was recorded for each patient. The result shows that the mean of the D90 and V100% of the HR CTV for the inverse plan was similar to the manual plan. This wasn't statistically significant. However, the mean dose of point A in the inverse plan was greater than the mean dose in the manual plan and this difference was statistically significant. Furthermore, inverse plan has a statistically significant reduction of the dose in the all OARs. The TRAK and the total treatment time resulting statistically significant reduction in inverse planning.

Conclusion: Inverse optimization is not inferior to manual treatment planning in terms of high-risk clinical target volume (HR CTV) dose coverage, and offers excellent sparing of organs at risk structures (OARs). The planning time for Inverse optimization is faster than manual plan.

Keywords: Brachytherapy; Cervical Cancer; Inverse Optimization; Treatment Planning

Introduction

Cervical cancer is one of the most common cancers globally, with 569,847 patients diagnosed in 2018 [1]. Chemotherapy, combined with curative radiotherapy, is the standard treatment approach. Brachytherapy is the most commonly used method for gynaecological cervical cancer, and CT is the foundation of computerised three-dimensional (3D) treatment planning. Individual treatment plans can be designed according to optimization approaches, constraints and objectives [2,6].

The aim of this project is to compare dose–volume histograms (DVH) in ICBT for cervical cancer, using a manual plan and an inverse optimization technique. Previous studies have shown that the combination of interstitial and intracavitary inverse optimization techniques is superior in terms of tumor coverage and limiting high-dose regions in surrounding normal tissue [13,18]. However, there have been few studies to compare a manual technique to an invertebrate method. This research aims to fill the gap and find an optimum standard of constraints for final optimization that is accessible to UHG for the Inverse optimization algorithm.

Background to Brachytherapy

Temporary brachy therapy utilises radioactive sources that are positioned and removed a specific time after finishing the treatment. Brachytherapy is classified according to the dose rate such as low dose rate (LDR), Medium dose rate (MDR), pulse dose rate (PDR), and High dose rate (HDR). HDR refers to doses of 12Gy/h or above, while PDR consists of brief, high intensity radiation pulses that are usually transmitted once an hour to simulate LDR therapy [10,22,24]. BT is also classified by the technique whereby the sources are located in the patient. After-loading is more commonly used than hot loading due to its advantages such as eliminated direct contact with the source and reduced radiation exposure for staff, increased treatment capacity and reproducible treatment delivery [7,18,21].

Remote after-loading is the most recent and is mainly used in brachytherapy. The radioactive source is the basis of brachytherapy and is determined by its properties, such as energy and type of radiation emitted. It should be low enough to achieve a sharp dose fall-off, high enough to be treated in depth with acceptable dose heterogeneity, and have a half-life of 73.8 days. Radium-229 was initially used in BT, but Caesium-137 was implemented as a temporary option. Nowadays, most treatment centers use Iridium-192, with lower gamma-ray energy and a shorter half-life [8,18].

Target CTV and OARs

The target of this project is cervical carcinoma, and the target volume is depending on the size of the irradiation tumor. Brachytherapy has been developed to be compatible with CT imaging systems, and the advantage is the ability to determine the tumor volume for a specific patient. Recommendations for delineation and dose reporting for three-dimensional image-based cervical carcinoma brachytherapy were released by a working group of the Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy and Oncology (ESTRO) report 89. Include two classifications: high-risk clinical target volume (CTV-HR), which involves the whole cervix, residual tumor and any adjoining residual pathological tissue, and intermediate-risk CTV-IR, which includes initial tumor volumes and any significant extension of microscopic disease [3,24].

The OARs close to the treatment area and radioactive sources are the bladder, rectum, sigmoid and bowel, and the 3D dose distribution is based on two methods: a relative DVH and an absolute DVH. ICRU report 89, has recommended monitoring the dose to bladder and rectal points, and for 2cm3 of the rectum, bladder, sigmoid and, bowel [17,20].

Parameters of point and volume of the dose

The Manchester system is a widely accepted and popular technique of cervical brachytherapy due to its concept of a dose statement at a fixed point in the pelvic. GEC ESTRO recommends reporting D100% and D90%, which describe the minimum doses received to 100% and 90% of the target volume, respectively. ICRU report 89 recommends monitoring the dose to the bladder and rectum, with the bladder reference point associated with a caudal Foley balloon in the bladder trigone [5,13].

The aim of the total dose EBRT and BT for HR-CTV according to the ICRU report 89, is to deliver D90% 90-95Gy, while the equivalent dose is limited to 2Gy per fraction (EQD2Gy). The minimum dose for 2 cc of OARs such as the rectum, sigmoid, and bowel is ≤65Gy (EQD2), and for 2 cc of the bladder is ≤80Gy (EQD2). Based on the schedules of fractionation and the specific dose rate, these dose levels for the reported reference volumes must be weighted biologically using EQD2 dose values and the linear-quadratic model with α/β = 10Gy for the tumor and α/β = 3Gy for OARs [14].

Intracavitary brachytherapy

Intracavitary BT is the most common method used for cervical cancer treatment, with different applicators depending on the patient's geometrical anatomy. Applicators include ring and tandem, ovoid and tandem, or hybrid intracavitary-Interstitial [15,24].

Treatment planning

The aim of treatment planning is to combine dose distribution of both BT and EBRT, depending on the information obtained from diagnosis, target volume, and the fractions schedule [12]. EBRT can treat the whole pelvis with doses varying from 45Gy to 50Gy at 1.7Gy/fraction - 2.0Gy/fraction, add to the brachytherapy dose to reach total EQD2 values between 75Gy and 95Gy for D90% of HR-CTV [6,16,23]. Manual source activation and dwell time adjustment have been adapted to standard loading patterns [18,25].

Forward planning

Forward planning involves adjusting the dwell position and dwell times to increase coverage and reduce the received dose and is evaluated after each iteration until either the planning aims are achieved or an appropriate compromise is reached [11,18,24].

Inverse planning

Inverse planning in BT is a similar idea to IMRT, allowing for better target coverage and sparing of OARs. It is responsible for determining dwell positions and dwell time configuration to meet limitations and constraints, as well as considering clinical dosimetry requirements [2,4,9].

Materials and Methods

Patients and treatment

This study included 30 patients with cervical cancer who underwent radiation therapy between the years 2017-2018 at University Hospital Galway (UHG). Of the 30 patients, 22 had been diagnosed with stage IIB, six with IB2, and two with IIIB. All the patient initially received conventional external beam radiation therapy based on a four-field box technique, with doses varying between 45-50.4Gy, equivalent to 1.8Gy per fraction for 25-28 fractions. Each patient then received a boost of three fractions of HDR intracavitary brachytherapy, with a prescribed fraction dose that varied between 7-9.5Gy. The overall treatment time was optimized to provide the full course of combined EBRT and BT treatment over seven to eight weeks, to prevent tumor repopulation and to enable normal tissue repair between fractions. For each of those 30 patients had three HDR-BT fractions; thus, 90 ICBT plans have been used. The manual technique was used for actual treatment, and then, the same plans were used to test the inverse optimization technique.

The BT treatment was delivered using a ring and tandem applicator, Titanium, connected to the HDR GammaMedplus with Ir-192 GammaMedplus 0.9mm.

Implant procedure

The applicator was inserted by the radiation oncologist and required dilation of the endocervical canal in order to insert the tandem, which can be accomplished either under general anesthesia or conscious sedation. A bladder catheter was inserted while the patient was in a dorsal lithotomy position and was filled with 8 ml of sterile water in order to push the frontal urinary wall of the bladder away from the target, and 2 ml of the contrast for improving the vision. This procedure was performed before the CT scan, with the applicator already inserted. The tandem was placed at an angle to match the direction of uterine flexion, with the tandem length based on ultrasound measurements and previous MRI scans. Transabdominal ultrasound was used to ensure the tandem was properly centered before the appropriate ring was inserted around the cervix through the vagina. The rectal retractor was then inserted through the vagina to push the rectum away from the cervix and reduce exposure of the rectum to high-dose radiation. Padding was used to keep the treatment applicator in the same position throughout treatment. The CT scan was acquired with the same position and used as the basis for the patient's treatment plan.

Contouring

The system used for contouring was the Pinnacle3, developed by Philips, and each patient underwent three sets of CT scans to delineate the target and organ at risk, such as the rectum, bladder, sigmoid, or bowel. For the target, Intermediate-risk CTV was delineated to 1 cm larger than HR CTV, and Point A was delineated via three slices of CT scan, as shown in figure 1.

Figure 1: Cervical cancer RT treatment plan. The coronal view illustrates the contouring of Point A, HR CTV, and IR CTV.

Treatment Planning

The original plan, using the manual technique, was developed for the actual treatment, and the second plan was copied and re-planned using the inverse optimization technique. All plans were carried out using Brach Vision software (version 13.7.29, Varian). The algorithm used to calculate the dose was based on a TG 43, according to recommendations from the American Association of Physicists in Medicine (AAPM) (Rivard., *et al.* 2016).

Manual plan

Workflow for the manual treatment of cervical cancer at UHG was started after a CT scan, based on the Manchester system, with a standard plan prepared by the planner and contouring prepared by the oncologist. The plan used point A as a reference point to normalized the prescribed dose. Then, defined the ICRU rectal point was located 5 mm posterior to the vaginal wall and the ICRU bladder point was located along the posterior wall of the Foley balloon surface (ICRU Report No.38). Contouring of the HR CTV and organs at-risk was applied to the standard plan and calculations were made to optimize the prescribed dose. (ICRU Report No.38).

The results of the dose distribution were evaluated and the DVH was checked, with the aim of covering 90% of HR CTV D90. An additional parameter monitored by UHG is the dose of IR CTV and at Point A.

If the result of this parameter does not meet the plan's objective, adjustments to the dwell positions and manipulations to the individual dwell time may be needed to obtain the best clinically acceptable results.

Inverse plan

The inverse optimization technique uses a different algorithm than the manual technique. The inverse technique optimizes the dose in order to achieve a dose distribution that best suits a sequence of constraints. In this study, all the manual plans were used to re-planned with inverse optimization; however, with this method, the planner used the volume optimization window (as shown in Figure 2), which includes the structure, objectives, DVH, and dwell time objectives. The objectives of the specific structure are to input upper and lower values, dose constraints, and priority.

The upper and lower dose constraints are specified for each of the target volumes, though only the upper dose is specified for OARs. Additionally, for point A, the lower dose is specified. The upper dose constraints mean that selected volume restriction with maximum perspective does. The lower dose constraints mean that selected volume restricted with minimum perspective dose. All dose constraints are associated with a specific contour, so contouring is an essential part of this process as inverse optimization depends on the geometrical structure.

For the target, the aim is to produce adequate coverage of the HR CTV using the prescribed dose. Moreover, the IR CTV needs to be covered by 60% of the prescribed dose, while Point A needs to be covered by 70% of the prescribed dose.

For the HR CTV, the structure settings consist of an upper and lower value.

For the lower value, 90% of the volume received a minimum of 94% of the prescribed dose. For the upper value, 100% of the volume received maximum 118% of the prescribed dose. As shown in table 1, the prescribed dose for this patient was 8.5Gy. Therefore, the optimum dose constraint selected for the lower value is approximately 0.5Gy less than the prescribed dose, and 1.5Gy higher than the prescribed dose for the upper value, regardless of the actual prescribed dose.

Figure 2: Volume optimization window.

Constraints	Volume [%]	Dose [Gy]	Dose [%]	Priority
Lower	90.00	8.00	94.00	200
Upper	100.00	10.00	118.00	150

Table 1: The selected objectives for HR CTV, with a prescribed dose of 8.5Gy.

For the IR CTV, the selected structure had an upper and a lower value. For the lower value, 98% of the volume received 100% of the prescribed dose. For the upper value, the IR CTV received a maximum of 111% of the prescribed dose. These constraints were based on empirical observations; though, in reality, these constraints mean that the IR CTV was covered by 50-70% of the prescribed dose, As shown in table 2.

Constraints	Volume [%]	Dose [Gy]	Dose [%]	Priority
Lower	98.00	8.50	100.00	200
Upper	100.00	9.50	111.00	150

Table 2: The selected objectives for IR CTV, with a prescribed dose of 8.5Gy.

For Point A, 100% of the volume was covered by at least 70% of the prescribed dose. As shown in table 3, the prescribed dose was 8.5Gy, while the dose constraint used was 70% of the prescribed dose, which is 6Gy.

Constraints	Volume [%]	Dose [Gy]	Dose [%]	Priority
Lower	100.00	6.00	70.50	200

Table 3: The selected objectives for Point A, with a prescribed dose of 8.5Gy.

The OARs, which include the bladder, rectum, sigmoid, and bowel, were delineated for each fraction. Contouring varied not only between patients but also between different fractions for the same patient. For this reason, the constraints were more than a single value and were based on the distance between the OARs and the target, as well as the volume involved in the treatment area. Table 4 presents the dose constraints that produced the best distribution while sparing the OARs.

Volume	Upper Dose Constraints [Gy]
Bladder (2cm^3)	3.5
Rectum (2cm^3)	3
Sigmoid (2cm^3)	3.5
Bowel (2cm^3)	3.5
Bowel (5cm^3)	3.5

Table 4: OARs constraints, 2cm^3 and 5cm^3 of the volume, with dose indicated in Gy.

The dose to the OARs specified under their upper values, which means that 2cm3 of the selected volume receive maximum the selected constraint, as presented in table 4. Also, a 5cm3 for the bowel used. If the dose distribution is unsatisfactory, the optimized dose constraints are adjusted and calculations are repeated until the goal achieved.

Bowel Constraints	Volume [cm^3]	Dose [Gy]	Priority
Upper	2.00	3.50	100
Upper	5.00	3.50	100

Table 5: The selected objectives for the Bowel 2cm3 and 5cm3 with the prescribed dose as presented in table 1.

Bladder Constraints	Volume [cm^3]	Dose [Gy]	Priority
Upper	2.00	3.50	100

Table 6: The selected objectives for the Rectum 2cm3 with the prescribed dose as presented in table 1.

Rectum Constraints	Volume [cm^3]	Dose [Gy]	Priority
Upper	2.00	3.00	100

Table 7: The selected objectives for the Sigmoid 2cm3 with the prescribed dose as presented in table 1.

Sigmoid Constraints	Volume [cm^3]	Dose [Gy]	Priority
Upper	2.00	3.50	100

Table 8: The selected objectives for the Bladder 2cm3 with the prescribed dose as presented in table 1.

Figure 3 shows the dwell time objectives, which also include a setting for 'smooth' and 'priority'. The dwell time ranged for all plans, with a maximum time of 30 seconds and a minimum time of 0.5 seconds. Priority is increased for the HR CTV, IR CTV, and Point A.

Figure 3: The input for dwell time objective.

Plan evaluation

The outcomes for each manual treatment plan were compared with the inverse optimization plan from a dosimetric point of view. Dose-volume histograms (DVHs) was used to analyze the target and the OARs. The dosimetric parameters were used to evaluate the D90 of the HR CTV, which is the dose that covered 90% of the target volume. The V100% which is the volume of the HR CTV receiving 100% of the prescribed dose. The D2cc of the bladder, rectum, sigmoid, and bowel, which is the dose limits delivered to 2cm3 of the volume, and the D5cc of the bowel. For each patient' fractions, the sum of the total reference air kerma (TRAK) calculated and compared for the manual plan to the inverse plan. Also, the total treatment time and the number of dwell position activated in the ring and tandem.

Result

Dose parameters

At the time of brachytherapy, HR CTV volume ranged from 12.5cm3 to 36cm3, with a mean of 20.76cm3. A summary of results is provided in table 9, for all patient fractions for both manual and inverse optimization techniques. Table 9, shows the mean, median, and standard division values for the HR CTV (D90), HR CTV (V100%) as well as the dose for Point A. The mean of HR CTV D90 for the inverse plan was similar to the manual plan; the difference was not statistically significant. The mean of the V100% was 96.87% for the inverse plan and 97.04% for the manual plan, the difference was not significant.

Besides HR-CTV, Point A served as an additional parameter in this study. The mean dose of the inverse plan was higher than the mean dose for the manual plan, the difference was statistically significant. The dose value of Point A resulted in heavy HRCTV dose-dependence. The HR-CTV D90 graph corresponded with the dose of Point A (see Figure 4), highlighting a moderately positive relationship between HR-CTV D90 and point for both techniques, increasing the dose to Point A with increased the dose to HR-CTV D90.

Figure 5 shows the relationship between the V100% covered by the prescribed dose and the total volume of HR-CTV for both the inverse and manual plans. Both the inverse and the manual plan showed a negative slope, though there was negligible difference in the degree of slope, which was 0.24 for the manual plan and 0.20 for the inverse plan. This negative slope indicates that neither the manual plan nor the inverse plan adequately covers tumors that have a volume >35cm^3; however, this could be partially compensated by the inverse optimized plan, as the slope increased slightly in comparison with the manual plan at HR CTV volume >35cm^3, but the difference was not significant.

The manual plan generated a high level of HR-CTV coverage, with a mean V100% value of 97.76% for comparatively small tumors (<23 cm3), whereas the inverse plan resulted in a decrease in coverage due gives priority to sparing of the OARs (97.54%, p = 0.005). However, in the case of a large tumor (>23 cm3), the inverse plan produced a slightly higher rate of coverage (94.84% vs 94.80%), although the difference was not significant.

Organ at risk dose

A summary of the results is provided in table 10, for each patient fraction, including the mean, median, and s standard deviation values for the DVH of the OARs, which includes the dose to the most exposed area which is 2cm3 of the OARs volume (D2cc), such as the rectum, bladder, sigmoid, and bowel. Also, the dose to the 5cm3 of the bowel.

Parameter	Manual (N = 90)	Inverse (N = 90)	P-value
HR-CTV D90 [Gy] Mean (SD) Median [Min, Max]	9.00 (0.67) 9.00 [7.80, 11.80]	9.01 (0.69) 9.00 [7.80, 12.00]	0.689
Point A [Gy] Mean (SD) Median [Min, Max]	6.34 (0.70) 6.15 [4.50, 8.50]	6.43 (0.74) 6.40 [4.70, 8.60]	<0.020
V100% HR-CTV Mean (SD) Median [Min, Max]	97.04 (4.43) 99.9 [89.8, 100]	96.87 (4.51) 99.9 [88.0, 100]	0.129

Table 9: Comparison of two techniques across HR-CTV D90, Point A, and HR-CTV V100%.

Figure 4: Scatterplot of Point A (Gy) in relation to HR-CTV D90 (Gy).

Figure 5: Scatterplot of HR-CTV V100% in relation to HR-CTV volume (cm3).

The mean dose to the bladder was lower for the inverse planning technique than for the manual plan; this difference was statistically significant. The minimum bladder dose received in inverse planning is 1.0Gy and the maximum dose is 7.90Gy, with a median dose of 5.05Gy, while the minimum dose for the manual plan is 1.30Gy and the highest dose is 7.50Gy, with a median dose of 5.25Gy, which implies that, even with the reduced mean dose for inverse planning, some patients may receive a higher dose from the inverse plan versus the manual plan, due to the difference in maximum dose values. For the bowel, the mean dose for the volume of 2cm3 and 5cm3 in the inverse plan was 3.62Gy and 2.92Gy, respectively; which is lower than the mean dose for the manual plan, 3.88Gy and 3.17Gy, respectively; this difference is statistically significant.

The rectum dose appears a significant reduction in inverse planning, where the mean dose was 1.85Gy versus the 2.13Gy mean dose for the manual plan. The minimum dose used in the inverse plan was 0.60, and the maximum dose was 4.0Gy, while the minimum dose used in the manual plan was 0.8Gy, and the maximum dose was 4.70Gy, which indicates a significant reduction in dose to the rectum for all patients through inverse planning. The sigmoid dose showed that with an inverse plan the mean dose (4.13Gy) lower than the manual plan's mean dose (4.37Gy); this difference is statistically significant. The sigmoid received a minimum dose of 2.30Gy from both plans, but the maximum dose for the inverse plan was 6.40Gy, less than the 6.50Gy dose for the manual plan, which means that all patients receive a reduced dose from the inverse plan versus the manual plan.

The relationship between OARs and the HR-CTV volume, and between OARs and the D90 of the HR-CTV for the manual plan and the inverse optimization plan are shown in figures 6-10. For both techniques, as shown in figure 6, the (A) panel there appears to be no relationship between the dose to the bladder and the HR-CTV D90 dose. However, the (B) panel shows a positive relationship for both techniques, where the dose to the bladder increased as the HR-CTV volume increased. The dose to the bowel shows a positive and direct correlation to the dose of HR-CTV (D90), the dose to the bowel increasing as the HR-CTV dose increased for both 2cm3 and 5cm3 volumes for either technique. On the other hand, the bowel dose decreased as the volume of HR-CTV increased; this is true for both techniques, as shown in figures 7 and 8.

There appears to be a moderate to strong positive relationship between the dose (D90) and the volume of HR-CTV to the rectum dose for both the manual and inverse plans, where the dose to the rectum increased with the increased dose and volume of HRCTV, as seen in figure 9, The dose to the sigmoid is also affected by the dose and volume of HR-CTV, as seen in figure 10, For both manual and inverse planning techniques, this relationship is directly positive and shows an increased dose to the sigmoid as the HR-CTV volume increased and, subsequently, the HR-CTV D90 dose.

Parameter	Manual (N = 90)	Inverse (N = 90)	P-value
Bladder D2cm3 Mean (SD) Median [Min, Max]	 4.92 (1.71) 5.25 [1.30, 7.50]	 4.60 (1.67) 5.05 [1.00, 7.90]	<0.001
Rectum D2cm3 Mean (SD) Median [Min, Max]	 2.13 (0.76) 2.00 [0.80, 4.70]	 1.85 (067) 1.70 [0.60, 4.00]	<0.001
Sigmoid D2cm3 Mean (SD) Median [Min, Max]	 4.37 (0.91) 4.40 [2.30, 6.50]	 4.13 (0.89) 4.10 [2.30, 6.40]	<0.001
Bowel D2cm3 Mean (SD) Median [Min, Max]	 3.88 (1.68) 4.00 [0.00, 7.60]	 3.62 (1.73) 3.75 [0.00, 8.30]	<0.001
Bowel D5cm3 Mean (SD) Median [Min, Max]	 3.17 (1.48) 3.20 [0.00, 6.00]	 2.92 (1.53) 2.80 [0.00, 6.40]	<0.001

Table 10: Comparison of two techniques across 2 cc and 5 cc OARs.

Figure 6: Scatterplot of the bladder D2cm3 (Gy) versus (A) D90 (Gy) and (B) volume (cm3) of the HR-CTV.

Figure 7: Scatterplot of the bowel D5cm3 (Gy) versus (A) D90 (Gy) and (B) volume (cm3) of the HRCTV.

Figure 8: Scatterplot of the bowel D2cm3 (Gy) versus (A) D90 (Gy) and (B) volume (cm3) of the HRCTV.

Figure 9: Scatterplot of the rectum D2cm3 (Gy) versus (A) D90 (Gy) and (B) volume (cm3) of the HR-CTV.

Figure 10: Scatterplot of the sigmoid D2cm3 (Gy) versus (A) D90 (Gy) and (B) volume (cm3) of the HR-CTV.

Source loading patterns

The total reference air kerma for the sum of each patient's three fractions was found to be 11,836 cGy.cm2 for the manual plan higher than 10,450 cGy.cm2 for the inverse optimization plan. This decrease in the TRAK could be due to the dose sculpting used in the inverse plan around the HR-CTV and to the attempts to reduce the dose to the OARs. Table 11, presents a comparison between the inverse and manual plans with respect to TRAK.

TRAK cGy. cm2	Manual (N = 30)	Inverse (N = 30)	P-value
Mean (SD) Median [Min, Max]	11836 (1510) 11633 [9285,15786]	10450 (2296) 10368 [1095, 16236]	<0.001

Table 11: Comparison of two techniques with respect to the TRAK, where TRAK is the sum of each patient's three fractions.

Figure 11, illustrates the positive relationship between the HR-CTV (D90) and the TRAK parameter, implying that TRAK is dependent upon the HR-CTV dose in both manual and inverse techniques. The relationship between TRAK and the volume of the HR-CTV is illustrated in the (B) panel of figure 11, which shows that TRAK's dependency on the HR-CTV volume is positive for both the manual and the inverse optimization plans.

The total treatment times for the manual and inverse optimization plans for all patients' fractions are listed in table 12.

The average total treatment time was 349 seconds for the manual plan and 317 seconds for the inverse plan. There is sufficient evidence to indicate that there is a significant difference in the total treatment time, in favour of the inverse technique (P =< 0.001).

Figure 12, illustrates the relationship between total treatment time to the HRCTV D90 and HR-CTV volume, with both techniques showing a positive relationship. A closer look at the data shows that there is a significant difference between the two methods. In other words, although a higher HR-CTV dose and volume result in longer treatment time, the time required for the manual technique is considerably longer than the time required for the inverse technique.

Figure 11: Scatterplot of the D90 (Gy) (A) and volume (cm3) (B) of the HR-CTV versus TRAK (cGycm2).

Total Treatment Time (sec.)	Manual (N = 90)	Inverse (N = 90)	P-value
Mean (SD) Median [Min, Max]	349 (49.18) 346 [246, 483]	317 (48.92) 317 [223, 483]	<0.001

Table 12: Comparison of total treatment time (sec.) for the two techniques.

Figure 12: Scatterplot of the D90 (Gy) (A) and volume (cm3) (B) of the HR-CTV versus total treatment time (Sec.).

Number of Dwell Positions	Manual (N = 90)	Inverse (N = 90)	P-value
Tandem Mean (SD) Median [Min, Max]	10.0 (1.69) 10.00 [7.0, 12.00]	11.15 (1.64) 12.00 [8.0, 12.0]	< 0.001
Ring Mean (SD) Median [Min, Max]	6.94 (1.81) 6.00 [6.00, 13.00]	18.00 (0.00) 18.00 [18.00, 18.00]	< 0.001

Table 13: Comparison of the dwell position in the ring and tandem for the two techniques.

The dwell position was used as an additional parameter to understand the conduct of inverse planning. In inverse planning, the entire dwell position in the ring was activated and a mean 11 of dwell positions in the tandem, with a minimum time of 0.5 seconds and a maximum time of 30 seconds, which means that not all dwell positions were activated in the tandem for the inverse plan. While the dwell position in the manual plan was activated with mean 6 of the dwell positions in the ring and mean 10 of the dwell positions in the tandem, as shown in 2017.

Discussion

The purpose of this research was to evaluate and compare inverse brachytherapy treatment planning using the Brachy Vision system with the manual treatment planning that is currently performed at the University Hospital of Galway. The inverse planning was found to be a useful alternative to manual plan, which is consistent with other studies of the inverse optimization technique for interstitial or intracavitary HDR-BT for prostate and cervical cancer [5,12].

Dosimetric analysis of the target

The aim of our study was to produce an inverse treatment plan that used a similar dose to the manual plan for the purpose of comparing both plans. HR-CTV, in particular, received a similar prescribed dose in both plans, thus, the evaluation of improved dose distribution and the lower dose received by OARs will be appear in the better plan based on the comparison. As mentioned in Section 4.1, the mean dose used for both the manual and the inverse plan had no statistical significance. This was expected and supported by the previous study [12], which found that a similar manual plan resulted in the inverse plan, except that the dose to the rectum was reduced in the inverse plan.

Evaluation of the prescribed dose to the HR-CTV did not produce sufficient evidence to show that the inverse planning method produces a comparable result to the HR-CTV coverage by the manual plan. Thus, the volume covered by 100% of the prescribed dose was evaluated (V100%) and compared for both plans. From the results provided in Section 4.1 and figure 5, it is clear that the relationship between the volume and V100% of the HR-CTV is similar to the results reported by Jamema [12]. which is the V100% decreased as the HR-CTV volume increased for both the manual and inverse plans.

From this study, involving smaller-volume HR-CTV, the manual plan generated better HR-CTV coverage. However, inverse optimization produced an accepted coverage of the smaller-volume of the HR-CTV, due to the difference between HR-CTV volume and V100% for the manual and inverse plans was not statistically significant. The manual plan reduced coverage for the HR-CTV volume > 25 cm3, while coverage by the inverse plan increased with a volume exceeding 25 cm3. In some cases, inverse planning reduced the coverage in order to achieve a limited dose to the OARs; this was particularly true for the smaller-volume HR-CTV.

Manual treatment principles are based on planner experience and knowledge, the plan is based on the planner's selection of individual dwell time and dwell position. Inverse optimization eliminates this and the plan is based on the constraints and objective of the structure, not on the planner experience.

Inverse optimization treatment planning assigns different the dwell times and dwell positions to conform the dose to the target However, large variations in dwell times might lead to an accumulation of hot spots or cold spots within the dose distribution. The clinical consequences of target coverage and effects to the OARs must be carefully considered.

In our experience, when the inverse planning technique was applied, visual inspection showed that isodoses were appropriate for the particular target location, which is HR-CTV. These results were confirmed upon conducting a quantitative analysis of the DVH. Constraints were defined in order to control activation of the dwell positions and individual dwell times. Through this approach, the inverse planning technique retained its ability to adequately cover the target while sparing OARs within a reasonable dwell time.

The difficulty was when attempting to extend the dose distribution to include the IR-CTV. It was challenging to expand the dose distribution in BT without creating hot spots or increasing the dose to the HR-CTV.

As stated in reference [15], faced the same issue, and one of their suggestions was to add additional volume, such as a sub-volume, and to use the constraints of this volume in order to improve the dose distribution, as the inverse optimization technique works on the basis of a volumetric structure. The additional volume used in this study was Point A. The contouring for Point A was created, and constraints were used to improve the dose distribution and cover Point A with the prescribed dose.

Organ at risks dose

In order to decide whether the inverse plan produced better results, the higher D90 and/or V100% were considered insufficient, while simultaneous improvement to OAR constraints was considered crucial. Generally, OARs were more consistently spared for most patients in the inverse optimization plan compared to the manual plan. The constraints most suitable for our patients (see Table 4). However, for all patients, the initial constraints used for the OARs varied between 2.5Gy and 3.5Gy. After evaluating the DVH, changes can be made to improve the outcome by increasing or reducing the constraints.

The OARs were spared for all patients in the inverse optimization plan, except for some patient in the bladder dose (2cc) and bowel dose (2cc, 5cc), as they have a larger volume of HR-CTV. The primary reason behind the increased dose to the bladder and bowel with larger HR-CTV is because inverse planning attempts to force increased coverage to the large target (HR-CTV), as clarified in Section 4.2. detailed analysis of Figure 6, The dose to the bladder was lower in inverse planning than manual planning. The plan which received a highest dose to the bladder, also had volume of HR-CTV > 35cc. That supports our statement about the increased dose to the bladder caused by attempts to cover a large HR-CTV with inverse planning.

The dose distribution of inverse planning is determined not only by the size of the target (HR-CTV), but also by the position of the OAR with respect to target. Such as the distance between the OAR and IR-CTV and inclusion of the OAR volume into the IR-CTV. Results similar to those found in the bladder were found when we evaluated the dose to the bowel. The 2 cm3 and 5 cm3 dose to the bowel was lower in inverse planning than in manual planning. The relationship between the bowel and HR-CTV D90 was positive, but the relationship between the bowel and the volume of HR-CTV was negative for both techniques, according to Figures 7 and 8. A closer examination of both bowel volumes, according to the HR-CTV volume, indicated that the dose to the bowel occasionally increased as the HR-CTV volume increased in the inverse plan.

The inverse optimization plan resulted in a significant dose reduction to 2 cm3of the rectum and sigmoid for all patients. By reviewing Figures 9 and 10, which show 2 cm3of the rectum and sigmoid with respect to the HR-CTV D90 volume, it appears that the positive regression line suggests that the dose increases as the target volume increases, which therefore increases the dose to the target in both the manual and the inverse plan.

Source loading patterns

The total reference air kerma (TRAK) is directly proportional to the HR-CTV volume in both the manual and inverse optimization plans, according to Figure 10. The difference in loading pattern was anticipated as the manual loading plan uses a standard loading pattern for the ring and tandem, requiring the planner to adjust the standard loading pattern according to the HR-CTV coverage. The inverse plan is based on algorithm in order to attain tumor coverage and avoid OARs.

In inverse planning, all dwell positions in the ring are activated; however, the individual dwell times vary based on tumor coverage and OAR sparing, with a minimum time of 0.5 seconds and a maximum time of 30 seconds at a high-dose region. In the tandem, loading is activated in most of the dwell positions, but some patients have reduced dwell positions. Depending on the total length of the HR-CTV the optimiser can reduce the number of active dwell positions in the tandem. In this study, the loading pattern of the manual plan appeared greater (TRAK = 11,836 cGy.cm2) than the loading pattern of the inverse plan (TRAK = 10,450 cGy.cm2).

Treatment planning time

The time required to produce a clinically acceptable treatment plan is an important, and one of the goals of inverse planning is to reduce treatment planning times. The time needed to create an inverse optimization treatment plan ranged form 5 to 12 minutes, while the time needed to create a manual plan ranged from 15 to 25 minutes. At most, inverse planning takes 12 minutes if the dose distribution does not meet the requirement and the OAR constraints must be adjusted. This total time involves contouring Point A, evaluating the DVH, and evaluating dose distribution.

For both manual and inverse planning, the overall time treatment reduced in an inverse plan. As shown in the results section, the average total treatment time for inverse planning (317 sec.) was statically significantly reduced compared to the treatment time for a manual plan (349 sec.).

Conclusion

This project provides a comparison of the inverse optimization plan and manual treatment plan for intracavitary brachytherapy for cervical cancer. The objective was to produce an inverse optimization result that is comparable to the manual plan in terms of HR-CTV coverage while simultaneously reducing the dose to OARs. From the results of this study, it can be concluded that inverse optimization is non-inferior to manual treatment planning in terms of HR-CTV coverage. Inverse optimization decreases the dose to OARs to an average of 4.60Gy for the bladder, 1.85Gy for the rectum, 4.13Gy for the sigmoid, 3.62Gy for a 2cm3 bowel, and 2.92Gy for a 5cm3 bowel. The difference was significant for all OARs compared to manual planning with a P-value < 0.01.

The manual plan depends upon the planner's experience and knowledge, which is eliminated through inverse optimization, where the plan depends upon the constraints and objectives. Moreover, the time required to treatment planning is an important aspect of brachytherapy, and the planning time for inverse optimization is five to 12 minutes, versus the 15 to 20 minutes required for manual planning. The total treatment time for inverse optimization is also 317 seconds, on average, which is significantly less than the 349 seconds required, on average, for manual planning.

The inverse optimization technique used all dwell positions, particularly in the ring. However, the results indicate that the average TRAK was statically reduced for inverse planning (10,450 cGy.cm2) compared with manual planning (11,836 cGy.cm2). The results also indicated no statistically significant difference in the coverage of HR-CTV, which may be due to the fact that inverse planning reduces the dose to the OARs. However, a combination of intracavitary and interstitial technique for our patient group with HR-CTV volume > 25 cm3 could be the optimal treatment technique; therefore, further study is required.

The result of the dosimetric evaluation comparing the inverse optimization technique to manual treatment planning indicates that inverse planning may be promising for brachytherapy treatment of cervical cancer and may be successfully implemented into clinical use at UHG.

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