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Research Article

Dosimetric Comparison of Endorectal Brachytherapy with Three Image Guided Radiation Therapy Modalities for the Delivery of a Rectal Tumor Boost

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Abstract

Introduction: Pre-operative short course pelvic radiation or chemotherapy with concurrent pelvic radiation is the standard of care for patients diagnosed with Locally Advanced Rectal Cancer (LARC). There is a growing bulk of literature supporting the use of a conservative approach for patients who achieve a clinical complete response (cCR) after neoadjuvant therapy. Radiation dose escalation is a strategy worth exploring to increase cCR. The present analysis compares the radiation dose distribution resulting from Endorectal Brachytherapy (eRBT) with three different image guided Stereotactic Body Radiation Therapy (SBRT) techniques that might be used to deliver a radiation boost to the primary rectal tumor.

Material and Methods: The planning Computed Tomography (CT) scans of 10 patients who underwent eRBT were retrieved. Treatment plans were generated adopting similar dose coverage for Helical Tomotherapy (HT), Linac-Based (LB), and Cyber Knife (CK) Image Guided Radiation Therapy (IGRT) plans. In all plans, the prescription dose was covering 95% of the Planning Target Volume (PTV) and the PTV received a minimum of 90% of the prescribed dose. The Con-formality Index (CI) and the Homogeneity Index (HI) were used to compare dose coverage among the four modalities. One-way ANOVA testing was done to compare maximal and mean values observed for selected Organs at Risk (OARs).

Results: All SBRT techniques provided better target CI and HI compared to eRBT. The CI for HT, LB and CK was 1.5, 1.5 and 1.2 respectively; while the CI for eRBT was 4.1 ($p=0.01$). The HI was 0.03, 0.13 and 0.22 respectively; whereas the HI for eRBT was 2.79 ($p<0.01$). The eRBT plans were associated with significantly higher maximal doses to the uninvolved rectum and anal canal. The difference in the maximal dose delivered by the four techniques to the other OARs did not reach a statistically significant level.

Conclusion: Our analysis shows that all SBRT techniques studied here offer better sparing of surrounding normal rectal mucosa and CI than eRBT. Based on these findings, image guided SBRT might be the technique of choice over eRBT for a boost to the primary tumor when a conservative approach is considered for patients with LARC.

Keywords: Endo Rectal Brachytherapy; Image Guided Radiation Therapy; Rectal Boost; Rectal Cancer

Introduction

The standard of care for patients diagnosed with Locally Advanced Rectal Adenocarcinoma (LARC) is either a long course of pelvic radiation (45-50.4 Gy delivered in 25-28 fractions) combined with chemotherapy or a short course of pelvic radiation (25 Gy delivered in 5 fractions), both followed by surgery. The recommended surgery is a Total Mesorectal Excision (TME) performed with a Low Anterior Resection (LAR) or an Abdominoperineal Resection (APR) for the most distal tumors

where sphincter preservation is not possible.

There is a growing bulk of literature advocating for the use of a conservative approach in which selected patients with LARC are treated with a combination of chemotherapy and pelvic radiation and the surgical procedure is reserved for patients who do not achieve a Clinical Complete Response (cCR) [1-8] with negative biopsy. This approach might benefit especially elderly patients, those with significant comorbidities and patients with low rectal tumors who would otherwise require an APR [1,3]. This conservative approach has also been studied for patients with early stage rectal cancer. Patients with early stage disease (primary tumor contained within the rectal wall, no nodal involvement seen on imaging) are usually treated with surgery alone. Preliminary data suggest that a course of chemo radiation therapy might be a treatment alternative to avoid surgery in this patient population as well [9,10].

When standard neo-adjuvant therapy is being used, the rate of pathological Complete Response (pCR) observed at the time of surgery is in the range of 15-25%. To improve the rate of cCR after a course of chemo radiation, two strategies might be considered: intensifying the neo-adjuvant chemotherapy regimen and/or delivering a higher radiation dose to the primary tumor [1,10-14]. Part of the evidence for a radiation dose-response effect [1, 7,10-12,14] in rectal cancer was described by Appelt et al. [14]. Appelt studied the surgical specimens of 222 patients after the combination of External Beam Radiation Therapy (EBRT) with Endorectal Brachytherapy (eRBT) boost and concomitant chemotherapy. He performed an analysis integrating the combined radiation equivalent dose in two gray fractions (EQD2) with five different histological regression grades and concluded that a CR could be achieved with a median dose of 92Gy EQD2.

Figure 1

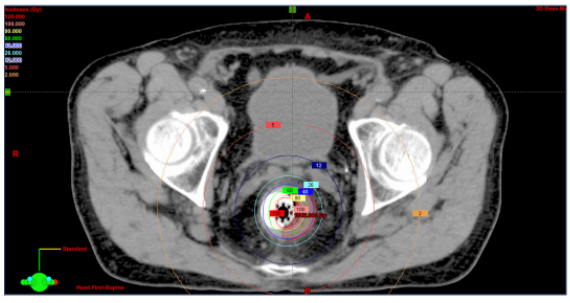

Figure 1: Dosimetric Distribution Endorectal Brachytherapy. GTV shown in red treated with 26 Gy in four fractions.

Figure 2

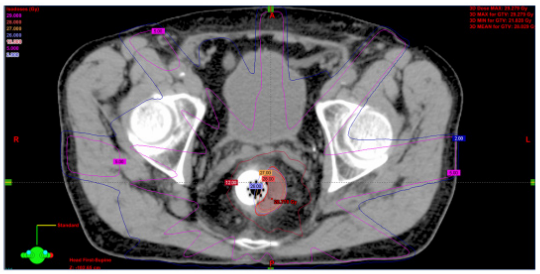

Figure 2: Dosimetric Distribution SBRT. GTV shown in red treated with 26 Gy in four fractions.

To deliver a dose approaching 92 Gy EQD2 to the tumor, one would have to deliver a boost in the range of 30 EQD2 to the primary rectal tumor after completing a course of pelvic radiation therapy (45-50.4 Gy in 25-28 fractions). This boost might be delivered by using Image Guided Radiation Therapy (IGRT) or eRBT. To guide the selection of a boost technique, we have performed a dosimetric analysis comparing eRBT to three different modalities of IGRT Stereotactic Body Radiation Therapy (SBRT) namely Helical Tomotherapy (HT), Linac Based (LB) and Cyber Knife (CK) SBRT. The results of this dosimetric analysis are presented here.

Material and Methods

A protocol to compare the dosimetry of eRBT with three different external beam IGRT delivery systems was written and submitted to the McGill University Institutional Review Board (IRB). After IRB approval, the planning Computed Tomography (CT) scans of 10 patients who underwent eRBT were retrieved. The planning studies were de-identified and used as the planning material for this exercise.

These planning CT scans were acquired with an endorectal brachytherapy applicator in place, which distends the rectal wall and facilitates rectal immobilization and tumor localization. Dose distributions were generated for HT, LB and CK on each planning CT scan using the same dose fractionation that was used for eRBT, 26Gy in 4 fractions prescribed to the Gross Tumor Volume (GTV). For this exercise, the GTV was identical to the Planning Target Volume (PTV). All plans met a PTV isodose coverage of 95% of the prescribed dose and 99% of the target received a minimum of 90% of the prescribed dose.

To analyze the PTV coverage characteristics, the Conformality Index (CI) defined as prescription volume in Cubic Centimeters (cc) divided by the target volume in cc (prescription volume cc/target volume cc) was applied to each modality plan.

To measure the consistency of the dose distribution, the Homogeneity Index (HI), classically defined as the relation between the maximal dose and minimal dose within the target volume, was employed. The HI was calculated by (D2% - D98%) / D50%, where D2% is the minimal dose to the 2% of the target volume indicating the maximal dose; D98 is the minimum dose to the 98% of the target volume indicating the minimal dose [16]; and D50% is the median absorbed dose in the target volume.

The plans were also compared in terms of Organs at Risk (OARs) sparing. The OARs selected were the uninvolved rectum (rectum minus GTV), the anal canal, the bowel, the bladder, and the right and left femoral heads. One-way ANOVA testing was used to compare the observed maximum and mean doses in these OARS among the different treatment modalities.

Results

The PTV was covered by 95% of the prescription dose for all modalities studied. The target maximal dose (D2%) was 27Gy, 29.1Gy, and 31.96 Gy for HT, LB and CK respectively whereas for eRBT it was 175.9Gy (p=0.005). The CI was 1.5, 1.5, and 1.2 respectively for the same modalities whereas for eRBT it was 4.1 (p=0.01). The HI ([D2% - D98%] / D50%) was 0.03 for HT, 0.13 for LB and 0.22 for CK while for eRBT it was 2.79 (p=<0.01).

The maximal/mean doses to the OARs for HT, LB and CK were: rectum minus GTV 26.5/9.4 Gy, 27.4/5.8 Gy and 27.9/8.0 Gy respectively; whereas for the eRBT it was 181.5/22.7 Gy (p<0.005). The anal canal maximal/mean dose for HT, LB and CK were 4.9/1.5 Gy, 3.2/0.6 Gy, and 5.9/1.9 Gy respectively and 14.3/4.3 Gy for eRBT (p<0.005). The maximal and mean doses in the bowel, bladder, and right and left femoral heads where not statistically significantly different when the three IGRT modalities where compared to eRBT (Table 1).

Organ At Risk	eRBT	Tomotherapy	Linac SBRT	Cyberknife	p Value
	(Max/mean Gy)	(Max/mean Gy)	(Max/mean Gy)	(Max/mean Gy)	(eRBT vs IGRT)
Uninvolved rectum	181.5/22.7	26.5/9.4	27.4/5.8	27.9/8.0	<0.05
Anal canal	14.3/4.3	4.9/1.5	3.2/0.6	5.9/1.9	<0.05
Bowel	17.4/3.2	9.3/2.0	9.4/1.4	14.7/4.9	NSS
Bladder	23.4/5.2	15.2/4.2	14.5/3.6	16.0/5.6	NSS
Left Femoral Head	4.6/2.0	5.8/3.0	8.4/2.4	5.0/2.8	NSS
Right Femoral Head	4.5/1.9	5.4/2.8	6.6/2.3	3.5/3.3	NSS

Table 1: Maximal and mean doses to Organs at Risk (OARs).

Discussion

A combination of high dose radiation with chemotherapy can achieve a 30-50% rate of cCR in patients with LARC [1-8,10,17] and spare a large amount of patients from a debilitating surgery. There are numerous factors influencing the rate of pCR, such as initial primary tumor size, cancer stage, radiation therapy dose, the use of concomitant chemotherapy and the interval to surgery [4,10-13].

There is evidence suggesting that higher radiation dose [1,7,10-12,14] will increase the rate of pCR. As shown by Appelt et al., a dose-response effect was found after combined treatment with concurrent chemotherapy and pelvic radiation with an eRBT boost [14] with higher chance of pCR with a dose equivalent to 92Gy EQD2 [10,11,14]. In the conservative approach protocol published by this group, patients with cT2-3 cN0-1 low rectal cancer were treated with concurrent chemotherapy and pelvic radiation with a 5 Gy eRBT boost [1]. Most of the patients were able to forego surgery [1,2,6-8,17]. However these results were achieved at the expense of significant toxicity, namely 6% grade 3 rectal bleeding at two years and a rate of fecal incontinence of 31%. The high dose gradient characteristics of eRBT might have contributed to the toxicity observed.

Our dosimetric analysis could guide the choice of the technique to deliver a boost to a primary rectal tumor when designing a protocol for conservative management of rectal cancer. Brachytherapy is generally perceived as a technique with better conformality than external beam radiation. In many clinical situations, the steep dose falloff characteristic of brachytherapy offers an advantage over external beam radiation for OARs sparing. Thirty years ago, Papillon et al. [18] published their results on the use of interstitial brachytherapy in the conservative treatment of anal and distal rectal cancer. The dose distribution achieved with interstitial brachytherapy (using catheters inserted

in the rectal wall, in the center of the tumor) is optimal. However, for more proximal lesions not accessible for insertion of interstitial brachytherapy needles, the use of a multichannel endocavitary brachytherapy applicator is an alternative which has been used at the cost of high dose to the surrounding normal rectal mucosa. While endocavitary brachytherapy might be compatible with the radio tolerance of surrounding normal tissue in certain parts of the body (upper vaginal for example), it is not the case for the mucosa of the gastrointestinal tract. When eRBT is used in a neo adjuvant setting for patients who are planned to have surgery, risk of long term complications (rectal bleeding, incontinence) is not a concern since the segment of rectum irradiated to a very high dose will end up being resected; however, when the goal is to select the best treatment technique for a conservative approach, potential long term toxicity of the radiation technique becomes a major concern.

Our dosimetric analysis shows that eRBT plans had a mean D2% of 175.9Gy and a poor HI compared to all three IGRT modalities. The HI is a useful tool to evaluate the uniformity of dose distribution in a target volume. The HI for all external beam IGRT was superior by more than a 10-fold factor when compared to eRBT. The CI of the IGRT techniques was also superior to the one achieved in the eRBT. The high CI observed with eRBT plans also leads to higher dose to key surrounding normal OARs, namely the anal canal and uninvolved rectum. Delivery of a high dose of radiation to these OARs is potentially associated with a higher risk of long term radiation toxicity.

One of the risks of using EBRT IGRT for the delivery of a boost to the primary tumor is inherent to the risk of suboptimal target coverage caused by inter- and intra-fraction motion observed during the course of radiation treatment for rectal cancer. One way of dealing with organ motion would be to add a PTV margin to the GTV. A margin was not added to the GTV in the IGRT treatment plans for this analysis. This decision was taken to keep all parameters identical. The use of high quality daily imaging (on board MRI) and an inflatable rectal probe during the delivery of the rectal boost are measures which could minimize the risk of suboptimal target coverage, thus allowing for a PTV of only 3mm.

Conclusion

As the use of a conservative approach for the treatment of patients diagnosed with LARC is gaining interest, new strategies to increase the rate of cCR need to be tested. The dosimetric analysis performed here suggests that the IGRT EBRT leads to better normal tissue sparing and CI compared to eRBT. The use of an IGRT EBRT rectal boost to a dose approaching a 90 Gy EQD2 on the primary tumor should be tested in a prospective clinical trial to improve the rate of complete response and spare from surgery a higher number of patients diagnosed with LARC.

Conflicts of Interest: None.

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