Compensator-based intensity modulated brachytherapy for cervical cancer

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**Abstract**

We introduce compensator-based intensity modulated brachytherapy (CBT), a non-invasive alternative to interstitial BT that improves the dose conformity to bulky cervical cancer tumors. Conventional brachytherapy sources emit radiation symmetrically about the applicator, thus non-symmetric tumors are treated with symmetric radiation dose distributions, resulting in tumor underdosage. CBT dose distributions are generated by an electronic brachytherapy (eBT) source, wrapped in a novel compensator that is covered in varying thicknesses of high atomic number material. This innovative compensator enables the radiation dose distribution to be tailored to the patient, preventing the underdosage problem that may cause patient cancer recurrence.

CBT has the potential to significantly improve cervical cancer dose distributions without the need for supplementary interstitial BT. The physician will have the freedom to optimize the tradeoff between increased delivery time and tumor dose conformity with CBT. We expect that patient-specific compensators can be constructed rapidly in clinical situations using various mechanical manufacturing approaches.
**Introduction**

Cervical cancer is malignant tumor on cervix. [1] The cervix is the lower, narrow end of the uterus where a baby grows when a women is pregnant. (Figure 1)[2] Cervical cancer has become the third most common gynecologic cancer in the United States, with an estimated 12,000 women are diagnosed each year. In 2011, American Cancer Society estimates 12,710 new cases and 4,290 deaths. [3-6]

Cervical cancer is typically treated with a combination of surgery, chemotherapy, external beam radiation therapy (EBRT), and a brachytherapy (BT) boost to the tumor. [7,8] Among such treatment, BT plays an essential role. In a typical radiotherapy department about 10%-20% of the patients are treated with BT. [1] BT is given by placing radioactive sources directly into or near the tumor volume to be treated. For example, conventional BT (intracavitary BT) uses radioactive source that travels inside a hollow applicator that is placed near the cervical tumor through vagina. The radiation that emitted from the radioactive source then destroy or damage the tumor by delivering its energy to each tumor cells. Today, the vast majority of BT treatments in North America are done using radiation sources like Ir192 and I125. Most common BT sources emit gamma rays that lie within the X-rays spectrum. [9-11]

Conventional BT works efficiently if applied to relatively small tumor. However, it inherits a tumor underdose problem for non-symmetric bulky tumor (> 40cc). The radioactive source that travels inside the applicator emits radiation in an azimuthally-symmetric manner about the applicator axis, while the target tumor treated is not symmetric about the same manner, which causes tumor underdosage illustrated in Figure 2(a). This underdosage may result in possible cancer recurrence and survival. [12-14]
One way of preventing tumor underdose for cervical cancer is by delivering needle-based supplementary interstitial brachytherapy (BT) to tumor regions that are out of reach of conventional intracavitary BT. In simple words, needle-based supplementary interstitial BT forces needles that carry radioactive sources into tumor through patient waist to deliver more radiation. In a 78-patient study for stage IB-IVA cervical cancer tumors (bulky tumors), Ir192 interstitial BT increased a 3-year overall survival rate from 28% to 58% relative to conventional intracavitary BT. However, applying needles to patients makes the needle-based interstitial BT more invasive than conventional intracavitary BT. And the needle-based interstitial BT adds 40-70 minutes treating time as well. [14,16,17]

Another way of solving the tumor underdosage is by introducing rotating shield intensity modulated brachytherapy (RSBT), [18, 19] which uses a partially-shielded, non-isotropic radioactive source that rotates in an optimized fashion to deliver tumor-conformal dose distributions. RSBT would be clinically feasible if it implemented with a radioactive source/shield combination that can fit inside an intracavitary applicator. RSBT would be less invasive than needle-based interstitial BT. But it requires the corresponding radiation shielding parts rotating during treatment, which is a mechanical challenge. And it may also increase the treatment time as well.

Based on the idea of intensity modulated brachytherapy first introduced in RSBT, we propose compensator-based intensity modulated therapy (CBT) for cervical cancer treatment, which is less invasive than needle-based interstitial BT and is less mechanically challenged than RSBT. In CBT, a similar intracavitary applicator to that of Ir192-BT is used, but the source no longer emits radiation in an azimuthally-symmetric manner about the applicator axis as it does in conventional intracavitary BT. Instead, the radiation dose distribution is manipulated and tailored to the tumor shape by wrapping a
patient-specific compensator around the radioactive source, which is the key innovation of CBT. We will discuss CBT in more detail in the Methodology section.

Methodology

Radioactive source selection

We select the S700 Xoft AxxentTM (Xoft Inc., Sunnyvale, CA) miniature X-ray Source as our electronic brachytherapy source (eBT) instead of the regular Ir192 BT source for several reasons. [20]

- Unlike Ir192, S700 Xoft Axxent can be turned on and off at will and can be operated at variable voltages (20-50kV) to change the dosimetry parameters.
- The S700 Xoft Axxent dose rate in water at 2 cm lateral to the source is greater than 1Gy/min, which is comparable to that of Ir192, preventing a significant treatment time increase for CBT.
- Compensator thickness generated by applying S700 Xoft Axxent is more spatially suitable than that of applying Ir192 based on applicator size limitation. For example, the transmission of low energy (average 26.8keV) photons emitted by eBT can be reduced to 2% with only 100 μm of gold or tungsten shielding (compensator thickness). Over 2cm of gold or tungsten would be required to achieve a same transmission for Ir192 photons, which is too thick for fitting into a 5.4mm catheter. (Figure 3)

Compensator material selection

We select high atomic number (high Z) elements like gold or tungsten as potential compensator materials mainly for two reasons.
High Z elements are better attenuators than low Z elements because they have higher mass attenuation coefficients. According to Beer’s law, under the same photon attenuation requirement \((I / I_0)\), higher mass attenuation coefficient \(\lambda\) results in lower compensator thickness \(\Delta x\):

\[
I / I_0 = e^{-\lambda \Delta x}
\]

For instance, the required thicknesses \(\Delta x\) for 10% photon attenuation \((I / I_0=10\%)\) for gold \((Z=79)\) and tungsten \((Z=74)\) are 58\(\mu\)m and 70\(\mu\)m, respectively. While the required thickness \(\Delta x\) for the same photon attenuation for relatively low Z element copper \((Z=29)\) is 328\(\mu\)m, which is too thick for the compensator since its thickness should be no more than 200\(\mu\)m due to the applicator size limitation. \((1\mu m = 10^{-6} m)\)

**Machinability Rate (MR),** which stands for whether or not a material is easy to machine, is also a factor that determines the compensator material selection. High MR indicates easier to machine. MR for copper is lower than 0.6, while MR for gold or tungsten is higher than 2.4. Some alloys like tungstened-copper and leaded-brass also have high MR.

In summary, gold or tungsten elements would be appropriate compensator materials. Alloys like tungstened-copper would also be good choices.

**Dose Calculation and Optimization**

In this section we discuss how we generate the compensator using the corresponding dose calculation and optimization. Figure 4 shows CBT delivery scheme. A continuous tumor volume is break down to discrete tumor voxel indexed with \(i\). The S700 Xoft Axxent, which is wrapped around by the gold compensator, travels from left to right inside the applicator and stops at multiple dwell positions
indexed by $j$. At each position it delivers radiation (gamma rays) for a certain pre-determined time $t_j$.

The continuous gold compensator is also break down to discrete compensator attenuation elements (attenuators) for computer calculation purposes. Each attenuator indexed by $k$ has a corresponding thickness of $\eta_k$. The dose $d_i$ at an arbitrary tumor voxel $i$ is affected by multiple combinations of S700 Xoft Axxent dwell positions and attenuator thicknesses, as shown in Figure 4 by the lines that start at the S700 Xoft Axxent positions and pass through different attenuators on their way to tumor voxel $i$.

Delivery time $t_j$ and attenuator thickness $\eta_k$ are the two essential parameters we are seeking for. We assume the eBT source can be treated as a point source that isotropically emits gamma rays from a published S700 Xoft Axxent energy spectrum. [20]

The dose $d_i$ at an arbitrary voxel $i$ is then given as:

$$d_i = \sum_j t_j \hat{D}_{ij} T^{n_{ij}/\Delta x \cos \gamma_{ij}}_{\Delta x}$$  \hspace{1cm} (1)

$\hat{D}_{ij}$ is a dose rate determined from the dose rate for an un-compensated radiation source defined by AAPM Task Group 43 (TG-43) formalism.[13] $T_{\Delta x}$ is the source-dependent reference radiation transmission factor for a ray passing through the compensator material of reference thickness $\Delta x$. $\gamma_{ij}$ is the angle of incidence of the radiation transport line $ij$ on the inner compensator surface. So $T^{n_{ij}/\Delta x \cos \gamma_{ij}}_{\Delta x}$ is the factor that represents compensator attenuation. Besides, the x-rays scattering effects due to existence of compensator are neglected in the above assumption.
The dose distribution $d_j$ was optimized to match the prescription $d_i^p$, by finding the set of $t_j$ and $\eta_k$ values that minimized the quadratic objective function:

$$F\left[ \vec{d}(\vec{t}, \vec{\eta}) \right] = \sum_i \left[ d_i(\vec{t}, \vec{\eta}) - d_i^p \right]^2$$  \hspace{1cm} (2)

Take the first derivatives with respect to of $t_j$ and $\eta_k$:

$$\frac{\partial F}{\partial t_j} = 2 \sum_i \left( d_i - d_i^p \right) \dot{D}_{ij} \frac{T_{\Delta x}}{\Delta x \cos \gamma_{ij}} \text{ and } \frac{\partial F}{\partial \eta_k} = 2 \sum_{i \in I_k} \left( d_i - d_i^p \right) \sum_j t_j \dot{D}_{ij} \frac{\ln T_{\Delta x}}{\Delta x \cos \theta_j}.$$ \hspace{1cm} (3)

where $I_k$ is the set of voxel indices affected by compensator element $k$ and any dwell position $j$. Set the above first derivatives to zero we then find:

$$\sum_i d_i^p \dot{D}_{ij} = \sum_i d_i \dot{D}_{ij} \Delta x \text{ and } \sum_{i \in I_k} \sum_j d_i \sum t_j \dot{D}_{ij} / \cos \gamma_{ij} = \sum_{i \in I_k} d_i^p \sum t_j \dot{D}_{ij} / \cos \gamma_{ij}. \hspace{1cm} (4)$$

According to the Linear Least Squares method of Shepard et al (2000) [21], we divide the right hand side by the left hand side for both equations in Equation (4) to obtain the following iterative optimization scheme for $t_j$ and $\eta_k$:

$$\begin{align*}
(t_j)_i &= t_j \sum_i d_i^p \dot{D}_{ij} / \sum_i d_i \dot{D}_{ij} \Delta x \text{ and } \eta_k &= \frac{\sum_{i \in I_k} d_i \sum t_j \dot{D}_{ij} / \cos \gamma_{ij}}{\sum_{i \in I_k} d_i^p \sum t_j \dot{D}_{ij} / \cos \gamma_{ij}}, \hspace{1cm} (5)
\end{align*}$$

Results

Here a treatment planning comparison result between conventional intracavitary BT and CBT is displayed. A Patient with 41.3cc stage IB cervical cancer is considered. The cross sectional view of the
patient organs and dose distributions are shown in Figure 2 where the tumor lies within the HR-CTV (red irregular circle). In Figure 2(a), the dose distribution generated not with the compensator is symmetric and does not cover much of the tumor volume. In Figure 2(b), with the help of compensator, dose distribution is effectively manipulated. We can observe this manipulated dose distribution covers much more of the tumor volume than that in Figure 2(a), making treatment more effective if this specified compensator design is adopted.

Figure 5 shows what the compensator looks like if it was unwrapped from S700 Xoft Axxent catheter and laid on a flat surface. We assume the compensator is made of gold for computer modeling that is discussed above in Methodology. Each attenuator element have dimension of 0.5mm× 1mm. This element size is chosen to be realistic from a manufacturing perspective.

Further discussions

We plan to fabricate the compensator prototype using LPKF ProtoMat S103 circuit board printer. LPKF ProtoMat S103 has a depth accuracy of 0.2μm, which is more than sufficient for our application since the attenuator is on the order of 0.5mm ×1mm. And we will construct cylindrical phantoms for the dosimetry measurements: penumbra measurement using Gafchromic EBT2 film and depth dose curve measurement using thermoluminescence dosimetry (TLD). Corrections will be derived experimentally in collaboration with University of Wisconsin Calibration Laboratory.
Appendix---Figures

Figure 1: The cervix connects the vagina (the birth canal) to the upper part of the uterus [3].

Figure 2: Brachytherapy (BT) dose distributions. (a) eBT, (b) eBT+CBT.

Figure 3: Cross section of a CBT applicator of inner radius $r_{ID}$ and outer radius $r_{tot}$. The radiation source has an outer radius of $r_s$. The source travels through a catheter tube of outer radius $r_c$. CBT is feasible if ample space (no more than $200 \mu m$) exists in the applicator between $r_c$ and $r_{ID}$ for a compensator.

Figure 5: Distribution of gold attenuator on the optimized compensator used to generate the dose distribution. The attenuator heights are shown on a grossly exaggerated scale.
Figure 4: CBT delivery scheme. The radiation source travels inside the applicator from left to right and stops at the dwell position indexed by \( j \) to emit radiation for a pre-determined time, \( t_j \).

Each compensator attenuation element indexed by \( k \) has a thickness of \( \eta_k \) and affects the dose delivered at many points on the tumor surface. Similarly, the dose at an arbitrary tumor voxel \( i \), \( d_i \), is affected by all dwell positions and multiple attenuation element combinations.
Appendix---References

1. NCI, “what you need to know about cervix cancer” National Cancer Institution, Sep.2008, NIH Publication No. 08-2047