Gold Fiducial Marker Tracking to Optimize Radiation Therapy for Organ-Preserving Treatment of Muscle-Invasive Bladder Cancer


Purpose/Objective(s): Definitive chemoradiation is an effective treatment option for muscle-invasive bladder cancer. Due to bladder wall motion, large planning target volume expansions are necessary but lead to increased treatment-associated morbidity. The use of gold fiducial markers (GFMs) for improved targeting of the tumor bed during radiation therapy was investigated.

Materials/Methods: Nine consecutive patients with muscle-invasive bladder cancer undergoing bladder preservation therapy from August 2012 through October 2013 were retrospectively identified. All patients underwent maximal transurethral resection of bladder tumor and cystoscopic placement of GFMs 5-10 mm from the surgical margin (average 4 GFMs per tumor, range 2-5) followed by chemoradiation. Continuous orthogonal X-ray imaging for robotic radiosurgery (n = 2), daily megavoltage imaging (n = 5), or both (n = 2) were used to track GFMs. Data were calculated relative to the imaging center for intrafraction measurements, and based on skeletal alignment for interfraction comparisons. Displacement of individual GFMs and the overall GFM coordinate system marking the resection bed (centroid) were calculated relative to the mean position of each within or between fractions. Bladder volumes were calculated from 3-dimensional contours on daily megavoltage images. Data are displayed as mean ± standard deviation.

Results: The median time from GFM placement to initiation of radiation therapy was 25 days. At simulation, 86% (36 of 42) of implanted GFMs were identifiable; however, 2 additional GFMs were lost prior to completion of treatment. Average inter-GFM distance was 27.5 ± 2 mm. Median robotic intensity modulated radiation therapy treatment time was 22 minutes (range 18-28 minutes), and orthogonal images were obtained every 64 seconds on average. Intrafraction displacement of individual GFMs and the overall GFM centroid were 1.6 ± 0.9 mm and 1.5 ± 0.9 mm, respectively, with a rigid body error of 0.42 ± 0.39 mm. Patients receiving linear accelerator- and helical tomotherapy-based radiation underwent an average of 35 daily megavoltage imaging sessions for alignment (range 26-50). Interfraction displacement of individual GFMs and the overall GFM centroid were 4.2 ± 2.1 mm and 3.5 ± 1.9 mm, respectively, with a rigid body error of 1.6 ± 1.3 mm. Mean bladder volume changed by 18 ± 13% per day during radiation therapy, corresponding to an average total volume of 104 ± 23 mL.

Conclusions: GFM tracking within and between radiation fractions to facilitate organ-preservation treatment of muscle-invasive bladder cancer is feasible and reliable. This data may be used to minimize planning target volume expansions for potential dose escalation while sparing more normal bladder than conventional approaches.


In Vivo Assessment of Radiation Damage to Murine Urothelium Using Chondroitin Sulfate Labeled With Texas Red

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Purpose/Objective(s): To develop non-invasive methods to monitor the evolution of radiation cystitis in individual mice exposed to pelvic radiotherapy. Chondroitin sulfate is a major component of the glycosaminoglycan layer of the urothelium. Texas Red, a standard fluorophore, has been used to label chondroitin sulfate, and has demonstrated preferential adherence to damaged urothelium. We hypothesized that chondroitin sulfate adhesion to the urothelium will increase as the sequelae of radiation damage increases over time, and that in vivo fluorescence imaging could quantify urothelial injury, thus enabling repeated assessment across time.

Materials/Methods: Twelve Balb/c female mice were irradiated at 26 Gy using Cs137. Six mice were given weekly transurethral intravesical instillations of chondroitin sulfate labeled with texa red (ChS-TR) and 6 were given a single instillation after 30 days. The ChS-TR instillation was allowed to rest in the bladder for 10 minutes, and then was removed with 3 consecutive flushes. Imaging was performed every minute for 10 minutes to describe fluctuations in fluorescence intensity during physiologic bladder accommodation. ChS-TR fluorescence was estimated across 30 days using a multispectral imaging system. The fluorescence was quantified using measurement regions of interest (ROIs). ROIs were auto selected by the system supplied software at a threshold of 25%. The threshold % specifies the minimum per cent of peak pixel intensity that a pixel must have to be included in the ROI.

Results: Baseline and control values for ChS-TR were found to have a mean radiance of 1.1e10 photons/sec/cm2/sr. ChS-TR images at 1 minute intervals displayed an increase in radiance as the area of the bladder increased. In 10 minutes, the average ROI increased 17% in area and radiance increased 17-22%. This was an unexpected association. ChS-TR urothelial fluorescence increased over 30 days after radiation exposure consistent with the expected onset of cystitis.

Conclusions: This is the first use of an in vivo imaging method to describe changes in urothelial GAG binding with the progression of radiation damage. The unexpected association between the change in fluorescence values and bladder volume reflected in the 2D projection area demonstrate a need to account for this phenomenon. The bladder area or bladder volume must be controlled or described in studies of this type. Since the effects of radiation are not static, in vivo methods to assess urothelial damage are needed to evaluate the potential effectiveness of intravesical treatments and to associate urothelial injury with functional assessment of radiation cystitis.

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CSS and OS in multivariate Cox analyses (p <0.01). For controlling for these factors, there was no difference in CSS between surgery and RT (HR 0.99, 95% CI = 0.91-1.08), but RT was associated with marginally lower OS (HR 1.08, 95% CI = 1.00-1.16). Propensity score analyses gave essentially identical results.

Conclusions: The use of RT for bladder cancer varies widely in Ontario and its use has been declining over the last two decades. Lack of good information about stage precludes a valid comparison of the effectiveness of RT and surgery, but their outcomes in routine practice are not dissimilar. This suggests that RT deserves wider recognition as a reasonable treatment option that some patients may prefer to surgery.


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Treatment of Adrenal Metastases Using Hypofractionated Stereotactic Body Radiosurgery
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Purpose/Objective(s): Hypofractionated Stereotactic Body Radiosurgery (HFSR) is a non-invasive focused beam technique that delivers high dose radiation to extracranial cancers. The use of HFSR was evaluated for the treatment of adrenal metastases.

Materials/Methods: Forty-five patients with 49 adrenal metastases underwent HFSR during a 74 month period. Sixty-one percent of the metastases were from a lung cancer origin. All the patients were evaluated prospectively before and after treatment. Age ranged from 42 to 78 years (mean 60.6) with 19 females and 26 males. 75% of patients had prior chemotherapy. Tumor volumes ranged from 2.3 to 892 cc (mean 116.35 cc). Patients were treated with 300-900 cGy (median 800) in 5-8 fractions (median 5) for a total dose of 2500-4500 cGy (median 4000). Cancers were radiographically evaluated with contrast CT and/or MRI studies and reviewed independently by radiologists. Control of the treated cancer is defined as cessation of growth, shrinkage or disappearance of the cancer after treatment.

Results: Follow up ranged from 1 to 54 months (mean 10.4). The overall control rate was 88%. For tumors <116.35cc there was an 87% control rate, and a 91% control rate for tumors ≥116.35cc. For tumors receiving <4000 cGy there was an 80% control rate compared to 93% for adrenal metastases that received ≥4000 cGy. Of the tumors treated with ≥4000 cGy, the control rate for those <116.35cc was 91%, and 100% for metastases ≥116.35. Adrenal metastases from lung cancer had an 83% control rate, while those from non-lung primaries had a 95% control rate.

Conclusions: HFSR for adrenal metastases offers a generally well-tolerated, non-invasive method with a high rate of tumor control. A larger patient group may show a dose-response analysis, as is suggested in this study. Patients will continue to be evaluated for longer follow up, possible benefits of local control and potential survival advantage. HFSR for adrenal metastases remains an option for those whom standard approaches have not produced desired results or in patients seeking an alternative to surgical or chemotherapeutic treatment.


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Predictors of Locoregional and Intravesical Recurrence Among Patients Treated With Nephroureterectomy for Urothelial Tract Carcinoma
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Purpose/Objective(s): Recurrence rates following curative intent nephroureterectomy (NU) for urethelial tract carcinoma (UTC) remain high. As such, high risk site directed adjuvant therapy may improve disease free survival. We reviewed the medical records of 119 patients with UTC treated with curative intent NU followed by conservative management to describe predictors of Locoregional (LR) and intravesical (IV) recurrence according to patient, disease and treatment related factors.

Materials/Methods: From 2006 to 2013, 119 patients with UTC of the renal pelvis (50%), ureter (24%) or both (26%) underwent robotic (38.6%), laparoscopic (41.2%), or open resection (20.2%) at our institution. Advanced T stage (T3/4) was present in 43 (36%) patients, 11 (13.4%) were node positive and 22 (18%) showed evidence of lymphovascular invasion. Resection of bladder cuff (84%) and lymphadenectomy (41%) were performed at the surgeon’s discretion. Thirteen patients (10.9%) received adjuvant chemotherapy and two received adjuvant radiotherapy (1.7%). Time to local, regional, (LR) and distant recurrence as well as death were described using the Kaplan-Meier method and compared using the log rank statistic. We performed a univariate (UVA) and multivariate (MVA) Cox Proportional Hazards analysis to evaluate the adjusted hazard for LR & IV recurrence.

Results: The 3 year freedom from disease progression was 47%. LR and IV recurrence predominated with 46 (38.7%) experiencing relapse at last follow-up. Among recurrences, IV was present in (60%), followed by regional lymph nodes (37%), renal pelvis (8.7%), ureter (4.3%), bladder cuff (2.2%) and surgical field (2.2%). Freedom from distant recurrence was 78% at three years. Two-year LR, IV-only, and distant failure rates were 36%, 35%, and 18%, respectively. Median overall survival was 54 months (95% CI = 41.2-NR). UVA identified number of positive lymph nodes, robotic vs. open approach, concurrent CIS, T3/T4 primary, LVSI, and positive margins as predictors of LR and IV recurrence. There were no significant risk factors associated with IV-only recurrence. On MVA, T3/4, number of positive lymph nodes and concurrent CIS influenced the risk for LR and IV recurrence although only the effect of T3/4 tumor status approached statistical significance (aHR 2.4 95% CI = 0.95-5.95, p = 0.09).

Conclusions: We identify advanced T-stage as the dominant predictor of LR and IV recurrence in this retrospective review of patterns of recurrence for UTC after NU. Our systematic description of UTC recurrence will allow further investigation of adjuvant therapy to minimize the treatment failures defined herein.


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Toxicity of Concurrent Radiation Therapy With Mitotane Compared to Radiation Therapy Alone in the Adjuvant Treatment of Adrenocortical Carcinoma
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Purpose/Objective(s): Adrenocortical carcinoma (ACC) is a rare malignancy with an annual incidence of 1 to 2 per million. Our institution has reported a large series on the role of adjuvant radiotherapy (RT) in preventing local relapse following gross total resection (GTR). At our center, RT is often given concurrently with mitotane, an adrenolytic derivative of the insecticide DDT with demonstrated prolongation of recurrence-free survival as a single agent in the adjuvant setting. This improvement in outcomes, along with in vitro evidence suggesting mitotane and RT function synergistically, provide the rationale for utilizing these modalities concurrently. Nonetheless, there is a paucity of data on the toxicity of a concomitant regimen. Given this, we present the only reported series of acute toxicity of concurrent RT and mitotane as compared to RT alone in the adjuvant setting.