The Role Of Image Guided And Intensity Modulated Stereotactic Radiotherapy For Patients With Metastatic And Locally Advanced Cancers

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The Role Of Image Guided And Intensity Modulated Stereotactic Radiotherapy For Patients With Metastatic And Locally Advanced Cancers

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Abstract

Background
Intensity-modulated stereotactic radiotherapy achieves improvements in the ability to produce conformal stereotactic dose distributions by modulation of the intensity of individually delivered beamlets of radiation. Image-guided intensity-modulated stereotactic radiotherapy has emerged as a new treatment option in the multidisciplinary management of metastatic and locally advanced cancers.

Methods
From July 2009 to February 2010, 34 patients with metastatic and locally advanced cancers were treated with an image-guided intensity-modulated stereotactic radiation system, Axesse (Elekta, Crawley, England). The patient position was verified using CBCT of the Elekta Axesse. Patient setup errors were calculated using automatic image registration of the planning CT scan and verification CBCT scan using the Elekta XVI software. Errors were corrected on-line before each treatment.

Results
The group mean errors were ± 1 mm and ± 1°. Radiologic complete response was achieved in 8 patients (23.5%). Radiologic partial response was achieved in 25 patients (73.6%). Development of new intracranial lesion was noted in one patient with brain metastasis from lung cancer (2.9%). Radiologic local control was achieved in 33 patients (97.1%). Clinical symptom improvement, including relief of pain and other symptoms, was achieved in all patients.

Conclusion
Image-guided intensity-modulated stereotactic radiotherapy used in the treatment of patients with metastatic and locally advanced cancer appears to be safe and effective both in terms radiographic tumor control and pain relief. Clinical trials providing standards on treatment parameters, physics quality assurance benchmarks, and tools to measure outcomes are warranted.

Introduction
Recently, significant progress has been made in advancing the state-of-the-art in stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) treatment delivery through the adoption of intensity modulated radiosurgery/therapy (IMRS/IMRT) approaches [1-3]. IMRS/IMRT achieves improvements in the ability to produce conformal stereotactic dose distributions by modulation of the intensity of individually delivered beamlets of radiation [4-6]. The ability to deliver modulated beamlets of radiation is implemented by use of multileaf collimators (MLC) to segment the large linac-produced radiation beam into small beamlets, or pencil beams. Intensity, or dose, is modulated by varying the amount of time that one pencil beam is exposed, relative to the others [7-9].

Linear accelerators capable of kilovoltage cone-beam computed tomography (CBCT) imaging and intensity modulated dose delivery are used in radiotherapy to improve treatment guidance while achieving highly conformal dose distributions [9-13]. Image-guided intensity-modulated stereotactic radiotherapy has emerged as a new treatment option in the multidisciplinary management of metastatic and locally advanced cancers [9, 14-16].

Sahgal et al. published a comprehensive review concerning the emerging technique of stereotactic body radiosurgery for spinal metastases [17]. Using state-of-the-art image-guided intensity-modulated stereotactic approach, radiotherapy can be focused more precisely. It can be used to treat metastatic and locally advanced cancers in which the conventional approach would not allow delivery of adequate radiation doses to the planning target volume (PTV) in combination with sparing of normal tissue [15, 18, 19]. The present study reports the preliminary results of intensity-modulated stereotactic radiotherapy and daily cone-beam computed tomography (CBCT)-based image guidance with on-line correction of setup errors for patients with metastatic and locally advanced cancers.
Methods

From July 2009 to February 2010, 34 patients with metastatic and locally advanced cancers were treated with an image-guided intensity-modulated stereotactic radiation system, Axesse (Elekta, Crawley, England). Patient characteristics are shown in Table 1. Median age of the patients was 63 years (range, 38 to 89 years). Twenty-three patients were male and 11 patients were female. Karnofsky performance status (KPS) score was 90-100 in 21 patients, 70-80 in 13 patients. Sixteen patients had locally advanced cancers in which tumor volumes were very large and adjacent to critical structures, 7 patients had limited brain metastases, 3 patients had complicated and extensive vertebral metastases in which the critical structure, spinal cord, was involved, and 8 patients had metastatic diseases other than brain and vertebral metastases. Site of radiotherapy was brain (n = 7), head and neck (n = 3), thorax (n = 6), abdomen (n = 6), pelvis (n = 6) and skeletal system (n = 6), respectively. Site of primary tumor was head and neck (n = 4), lung (n =11), liver (n = 5), rectum (n = 3), uterine cervix (n = 3), prostate (n = 2), urinary bladder (n = 2) and others (n = 4), respectively (Table1).

Immobilization of the patients

The patients were immobilized with a vacuum pillow for treatment of tumors of the brain, head and neck region. This system was attached to a stereotactic localization device HeadFIX (Medical Intelligence, The Elekta Group).

For treatment of thoracic, abdominal and pelvic tumors, a customized total body vacuum cushion (BodyFIX, Medical Intelligence, The Elekta Group) was used [20]. The double vacuum was applied for all treatment fractions to minimize intrafraction patient motion [21].

Treatment planning

The Pinnacle treatment planning system (Philips, ADAC, Milpitas, CA) was used for treatment planning. Step-and-shoot IMRT plans were generated for an Elekta Axesse equipped with the beam modulator with a 4-mm leaf width.

For head and neck tumors, the target volume was defined after registration of the planning magnetic resonance imaging scan to the planning CT scan. The gross target volume (GTV) was defined as the gross extent of tumor shown by imaging studies. The clinical target volume (CTV) surrounded the gross target volume (GTV) with additional margin of at least 5 mm depending on the anatomical relationship of adjacent structures and of potential microscopic spread. The planning target volume (PTV) surrounded the clinical target volume (CTV) with additional margin of 3 mm. A total dose of 70-72 Gy was prescribed to the isodose line that encompassed at least 95% of the PTV, and 50-65 Gy to the regional lymph nodes at risk of potential microscopic spread. Dose was delivered at 1.8-2.0 Gy/fraction/day, 5 days a week [22].

For patients with brain metastases, the whole brain radiation therapy (WBRT) was delivered followed by stereotactic radiosurgery to metastatic lesions (24, 25). The WBRT dosage schedule was 30 Gy in 10 fractions over 2 weeks. For metastatic lesions, the target volume was defined after registration of the magnetic resonance imaging scan to the planning CT scan. The planning target volume (PTV) for metastatic lesions surrounded the gross target volume (GTV) with additional margin of 2 mm [23]. The dosage schedule of stereotactic radiosurgery to metastatic lesions was described as follows. For metastases up to 2.0 cm in diameter, metastases larger than 2 cm but equal to or less than 3 cm, and metastases larger than 3 cm and less than 4 cm, a dose of 24 Gy, 18 Gy, and 15 Gy was prescribed to the isodose line that encompassed at least 95% of the PTV respectively [24, 25].

For patients with complicated vertebral metastases, the target volume was defined after registration of the magnetic resonance imaging scan to the planning CT scan. The affected parts of the vertebrae were delineated as the gross target volume (GTV). For coverage of areas with potential microscopic disease, additional margin of at least 5 mm around the GTV defined the clinical target volume (CTV). The whole vertebra was defined as the CTV if significant parts of vertebral body and vertebral arch were affected simultaneously. PTV was generated with additional margin around the CTV. The PTV was not allowed to overlap the spinal canal but touched it in all cases. The spinal canal was contoured as the critical structures, rather than the spinal cord, to allow for the safety margin [26, 27]. A total dose of 30 Gy was prescribed to the isodose line that encompassed at least 95% of the PTV. The dosage schedule was 30 Gy in 5 fractions over 1 week.

For patients with metastatic diseases other than brain and vertebral metastases, a total dose of 30 Gy was prescribed to the isodose line that encompassed at least 95% of the PTV. The dosage schedule was 30 Gy in 5 fractions over 1 week.

IGRT protocol

Before every treatment fraction, 3D volume imaging was performed. The patient position was verified using CBCT of the Elekta Axesse. Patient setup errors were calculated using automatic image registration (correlation coefficient algorithm) of the planning CT scan and verification CBCT scan using the Elekta XVI.
software. Errors were corrected on-line before each treatment. Combined translational and rotational errors were corrected using a robotic treatment table with 6 degrees freedom of movement (HexaPOD evo RT System, Medical Intelligence, The Elekta Group). Translational and rotational setup errors were evaluated. The group mean error was defined as the average of all systematic errors; Σ was defined as the standard deviation of the systematic errors. The root-mean-square of the random errors was calculated as σ. Errors were calculated separately for all three axes: lateral (left–right), longitudinal (superoinferior), and vertical (anteroposterior) [27-29).

Results

Setup errors
Patient setup errors were calculated using 760 CBCT studies acquired before treatment. The results were summarized in Table 2. The group mean errors of Axesse in combination with a HexaPOD robotic treatment table were ? 1 mm (translational) and ? 1°(rotational). The systematic positioning errors (translational) of Axesse in combination with a HexaPOD robotic treatment table were 2.87 mm anteroposteriorly, 2.26 mm laterally, and 2.77 mm superoinferiorly; while the systematic positioning errors (rotational) were 0.79° anteroposteriorly, 0.85° laterally, and 0.79° superoinferiorly. These translational errors and rotational errors were corrected online before each treatment fraction. There were no rotational errors that exceeded the motion range of the robotic HexaPOD (3° around all three axes).

Clinical response
The follow-up period ranged from 1.3 to 7.8 months (median 3.7 months). During radiotherapy, patients were evaluated once a week. After completion of radiotherapy, patients were evaluated every 1-2 months for the first year. Physical examination was performed at each follow-up visit. A post-treatment CT or MRI scan was obtained 1-3 months after completion of radiotherapy and then every 6 months or when clinically indicated. Complete response was defined as total radiologic disappearance of all lesions. Partial response was defined as greater than a 50% decrease in size of all lesions. Stable disease was defined as a 0-50% decrease in size of all lesions. Local control was defined as a complete response, partial response, or stable disease. Progressive disease was defined as an increase in the size of any lesion or the development of new lesions. The radiologic reappearance of tumor constituted recurrent disease [24].

Radiologic complete response was achieved in 8 patients (23.5%). Radiologic partial response was achieved in 25 patients (73.6%). Development of new intracranial lesion was noted in one patient with brain metastasis from lung cancer (2.9%). Therefore, radiologic local control was achieved in 33 patients (97.1%).

Clinical symptom improvement
Clinical symptom improvement, including relief of pain and other symptoms, was achieved in all patients.

Acute and late toxicities
Acute and late toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria [30]. Acute toxicities were mild in most of the patients. Grade 1 toxicity was observed in 23 patients (67.7%). Grade 2 toxicity was observed in 10 patients (29.4%). One patient (2.9%) with locally advanced head and neck cancer treated with a total dose of 72 Gy in 36 fractions developed grade 3 moist desquamation of the skin. An absence of grade 4 toxicity was noted. Normal tissue effects occurring more than 90 days after irradiation, or acute toxicities persisting beyond 90 days were scored as late toxicities. During the limited follow-up period, no grade 3 of greater late toxicity was observed. The patient with grade 3 moist desquamation of the skin developed grade 2 induration of the skin and subcutaneous tissue.

Discussion

Radiotherapy is essential for the appropriate management of patients with metastatic and locally advanced cancer and constitutes nearly 50% of the modern radiation therapy workload [31]. Brain metastases occur in 20–40% of patients with systemic cancer; 30–40% present with a single metastasis. Prognosis for these patients is poor with a median survival time of 1–2 months with corticosteroids, which can be extended to 6 months with whole brain radiation therapy (WBRT), and some investigators report that survival can be further extended when WBRT is preceded by surgical resection. Radiosurgery is a technique that involves single treatment radiation precisely focused at intracranial targets. Radiosurgery is frequently used to treat brain metastases and is sometimes preferred as a less invasive alternative to surgery [24]. Approximately 40% of cancer patients may develop metastatic disease involving the vertebral spine [32].
and metastatic spinal cord compression occurs in 5-10% of all cancer patients [33]. Radiotherapy is accepted as a key treatment of painful bony metastases and metastatic spinal cord compression. Standard treatment regimens vary from a single dose of 8 Gy to protracted fractionation for a dose ? 40 Gy [27].

Conventional palliative treatment usually consists of a single direct or parallel-opposed beam arrangement for each treatment site. This type of treatment provides no avenue for dose conformation in three dimensions. Studies have demonstrated that CT-based imaging and planning of palliative radiotherapy is superior to that with conventional approaches that use clinical mark-ups or fluoroscopy [34, 35]. Numerous locally advanced or recurrent tumors that are very large and that have complex geometric configurations are difficult to treat with conventional approaches, especially when adjacent to critical structures [15].

In order to adequately treat these situations of metastatic or locally advanced cancer using state-of-the-art image-guided intensity-modulated stereotactic radiotherapy, recent work has investigated streamlining the radiotherapy process, including online planning of radiation therapy using kilovoltage cone-beam CT and external treatment planning and verify and record systems [36]. The Ottawa Hospital Cancer Center investigated the framework which integrates the processes of treatment planning, image guidance, verify and record, and delivery of intensity-modulated radiation therapy [15, 37].

The system error analyses of various image-guided intensity-modulated stereotactic radiotherapy apparatus are discussed. Using the patient-based measurements of Cyberknife (Accuray Inc., Sunnyvale, California), the average Xsight tracking error component was 0.49 ± 0.22 mm [38] and the alignment of the treatment dose with target volume was within ± 1 mm [39].

Using the patient-based measurements, precision of the Novalis (Brain Lab Inc., Munich, Germany) defined as the degree of variation between the isocenter location by fusing images taken at the time portal imaging to that at the time of CT simulation was 1.36 ± 0.11 mm [40].

Using the patient-based measurements, the standard deviation of interfraction isocenter displacement of TomoTherapy HiArt helical tomotherapy (TomoTherapy Inc., Madison, Wisconsin) was ±4.0 mm anteroposteriorly, ±4.1 mm laterally, and ±4.3 mm superoinferiorly [41].

Using the patient-based measurements, the systematic positioning errors (translational) of Synergy S (Elekta, Crawley, England) in combination with a HexaPOD robotic treatment table were 2.0 mm anteroposteriorly, 2.7 mm laterally, and 2.9 mm superoinferiorly; while the systematic positioning errors (rotational) were 0.79° anteroposteriorly, 0.85° laterally, and 0.79° superoinferiorly. The group mean errors of Synergy S in combination with a HexaPOD robotic treatment table were 2.87 mm anteroposteriorly, 2.26 mm laterally, and 2.77 mm superoinferiorly; while the systematic positioning errors (rotational) were 0.79° anteroposteriorly, 0.85° laterally, and 0.79° superoinferiorly. The group mean errors of Axesse in combination with a HexaPOD robotic treatment table were ± 1 mm (translational) and ± 1° (rotational). The results were similar to that of Guckenberger et al. During conventional palliative treatment, 1.5 -2.5 cm margins around the areas of tumors were used in delivery of radiotherapy. With an image-guided intensity-modulated stereotactic approach, small margins (0.5-1.0 cm) around the areas of tumors were used in treatment planning [15]. The dose distributions achieved a much more homogeneous dose to PTV and minimize dose to the adjacent normal tissues. The setup errors were small during treatment with application of the following techniques: daily CBCT-based image guidance, robotic correction of setup errors in 6 degrees freedom of movement, and effective intrafraction immobilization of the patients [42, 43].

In the review article of Sahgal et al., local control for unirradiated patients with spinal metastases was achieved in 67/77 (87%) tumors treated, and in 23/24 (96%) reirradiated patients' tumors [17]. Andrews et al. reported that the local control of brain metastatic lesions was 41/50 (82%) in the whole brain radiotherapy plus radiosurgery group [24]. In our study, local control rate was defined according to progression or recurrence by imaging. Radiologic local control was achieved in 33/34 patients (97.1%). The results were similar to the above series. In the referenced literature, both acute and late toxicity were mild or moderate [22, 24, 27, 44-47]. In our study, similar results of toxicities were noted. With these favorable results, image-guided intensity-modulated stereotactic radiotherapy is feasible for the treatment of patients with metastatic and locally advanced cancer.

Some limitations of this study need to be considered in the interpretation of our data. The shortcomings of this study included the limited number of patients, the...
heterogeneity of the patient cohort, short follow-up and the retrospective nature of the analysis.

Conclusion(s)

Image-guided intensity-modulated stereotactic radiotherapy used in the treatment of patients with metastatic and advanced cancer appears to be safe and effective both in terms radiographic tumor control and pain relief [15, 17, 27]. It is anticipated that obstacles to the routine practice of image-guided intensity-modulated stereotactic radiotherapy will gradually be overcome. Clinical trials providing standards on treatment parameters, physics quality assurance benchmarks, and tools to measure outcomes are warranted.

Reference(s)

## Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (total= 34)</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>67.6</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>32.4</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ 50</td>
<td>7</td>
<td>20.6</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>27</td>
<td>79.4</td>
</tr>
<tr>
<td><strong>KPS</strong></td>
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<td></td>
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<tr>
<td>90-100</td>
<td>21</td>
<td>61.8</td>
</tr>
<tr>
<td>70-80</td>
<td>13</td>
<td>38.2</td>
</tr>
<tr>
<td><strong>Type of diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced cancers</td>
<td>16</td>
<td>47.1</td>
</tr>
<tr>
<td>Limited brain metastases</td>
<td>7</td>
<td>20.6</td>
</tr>
<tr>
<td>Complicated vertebral metastases</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Metastatic diseases other than brain and vertebral metastases</td>
<td>8</td>
<td>23.5</td>
</tr>
<tr>
<td><strong>Site of radiotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>7</td>
<td>20.6</td>
</tr>
<tr>
<td>Head and neck</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Thorax</td>
<td>6</td>
<td>17.6</td>
</tr>
<tr>
<td>Abdomen</td>
<td>6</td>
<td>17.6</td>
</tr>
<tr>
<td>Pelvis</td>
<td>6</td>
<td>17.6</td>
</tr>
<tr>
<td>Skeletal system</td>
<td>6</td>
<td>17.6</td>
</tr>
<tr>
<td><strong>Primary tumor site</strong></td>
<td></td>
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<tr>
<td>Head &amp; neck</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Lung</td>
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</tr>
<tr>
<td>Liver</td>
<td>5</td>
<td>14.7</td>
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Table 2 Setup errors during treatments

<table>
<thead>
<tr>
<th>Errors</th>
<th>M</th>
<th>Σ</th>
<th>σ</th>
</tr>
</thead>
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<tr>
<td><strong>Translational (mm)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SI</td>
<td>-0.18</td>
<td>2.77</td>
<td>3.14</td>
</tr>
<tr>
<td>AP</td>
<td>-0.74</td>
<td>2.87</td>
<td>3.17</td>
</tr>
<tr>
<td>LR</td>
<td>-0.02</td>
<td>2.26</td>
<td>3.04</td>
</tr>
<tr>
<td><strong>Rotational (°)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SI</td>
<td>-0.06</td>
<td>0.79</td>
<td>0.87</td>
</tr>
<tr>
<td>AP</td>
<td>0.09</td>
<td>0.79</td>
<td>0.86</td>
</tr>
<tr>
<td>LR</td>
<td>0.07</td>
<td>0.85</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Abbreviations: M = group mean error; Σ= systematic positioning errors; σ= random positioning errors; SI = superoinferior; AP = anteroposterior; LR = left-right
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