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Combined photon-electron beams in the treatment of the supraventricular lymph nodes in breast cancer: A novel technique that achieves adequate coverage while reducing lung dose

Ahmed Salem, M.D.,* Issa Mohamad, M.D.,* Abdulmajeed Dayyat, M.D.,* Haitham Kana‘n, M.Sc.,† Nasim Sarhan, M.D.,* Ibrahim Roujob, B.Sc.,† Abdel-Fattah Salem, M.D., F.R.C.O.G.,‡ Shatha Alifi, M.Sc., † Imad Jaradat, M.D., Ph.D.,* Rasmi Mubiden, M.D.,* and Abdelatef Almousa, M.D., Ph.D.*

A R T I C L E  I N F O

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A B S T R A C T

Radiation pneumonitis is a well-documented side effect of radiation therapy for breast cancer. The purpose of this study was to compare combined photon-electron, photon-only, and electron-only plans in the radiation treatment of the supraventricular lymph nodes. In total, 13 patients requiring chest wall and supraventricular nodal irradiation were planned retrospectively using combined photon-electron, photon-only, and electron-only supraventricular beams. A dose of 50 Gy over 25 fractions was prescribed. Chest wall irradiation parameters were fixed for all plans. The goal of this planning effort was to cover 95% of the supraventricular clinical target volume (CTV) with 95% of the prescribed dose and to minimize the volume receiving ≥105% of the dose. Comparative end points were supraventricular CTV coverage (volume covered by the 95% isodose line), hotspot volume, maximum radiation dose, contralateral breast dose, total lung dose, total lung percentage receiving at least 20 Gy (V20 Gy), heart volume percentage receiving at least 25 Gy (V25 Gy), Electron and photon energies ranged from 8 to 18 MeV and 4 to 6 MV, respectively. The ratio of photon-to-electron fractions in combined beams ranged from 5:20 to 15:10. Supraventricular nodal coverage was highest in photon-only (mean = 96.2 ± 3.5%) followed closely by combined photon-electron (mean = 94.2 ± 2.5%) and lowest in electron-only plans (mean = 81.7 ± 14.8%, p < 0.001). The volume of tissue receiving ≥105% of the prescription dose was higher in the electron-only (mean = 69.7 ± 56.1 cm³) as opposed to combined photon-electron (mean = 50.8 ± 40.9 cm³) and photon-only beams (mean = 32.2 ± 28.1 cm³, p = 0.114). Heart V25 Gy was not statistically different among the plans (p = 0.999). Total lung V20 Gy was lowest in electron-only (mean = 10.9 ± 2.3%) followed by combined photon-electron (mean = 13.8 ± 2.3%) and highest in photon-only plans (mean = 16.2 ± 3%, p < 0.001). As expected, photon-only plans demonstrated the highest target coverage and total lung V20 Gy. The superiority of electron-only beams, in terms of decreasing lung dose, is set back by the dosimetric hotspots associated with such plans. Combined photon-electron treatment is a feasible technique for supraventricular nodal irradiation and results in adequate target coverage, acceptable dosimetric hotspot volume, and slightly reduced lung dose.

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Introduction

Radiation therapy is an integral component in the management of breast cancer. The benefits of using radiation therapy in patients with breast cancer have been confirmed by several randomized trials and include improvements in overall survival and decreased incidence of locoregional recurrence and distant metastases.2-16 Unfortunately, the beneficial additions of radiation
therapy come with undeniable long-term adverse events. Numerous studies have addressed the increased incidence of ischemic heart and second primary malignancy following radiation therapy for breast cancer.\text{17–22}\text{.} Similarly, radiation-induced pneumonitis is a well-described consequence in a proportion of patients following radiation therapy for this disease.

The occurrence of radiation pneumonitis is dependent upon several factors including baseline lung function, concurrent use of chemotherapeutic medications, total radiation dose, dose per fraction, and the proportion of lungs inside the radiation field.\text{24}\text{.}\text{ As such,} harmless efforts are used to decrease the mean lung dose in an attempt to limit this undesired adversity.

Inverse planned intensity-modulation radiation therapy (IMRT) has been introduced in breast cancer with the aim of decreasing both heart and lung dose, while achieving acceptable target coverage\text{.}\text{ However,} the use of IMRT in breast cancer comes with a number of disadvantages. First, it is technically complex to deliver and as such, is only available in a proportion of radiation oncology centers worldwide. Second, IMRT requires stringent quality assurance protocols that are associated with excessive costs and are heavily labor intensive and time demanding. In addition, although IMRT is generally associated with highly conformal high-/medium-dose coverage and as such steep dose fall-off and subsequently improved lung and heart dose sparing,\text{25}\text{,}\text{26}\text{.} low-dose deposition of radiation inside the lungs is probably higher than that seen with 2- or 3-dimensional conformal radiation therapy. This led some investigators to speculate that the risk of second malignancy might be higher following IMRT\text{.}\text{ Other researchers have proposed partial-breast irradiation as a novel and safe radiation technique, which could significantly limit radiation dose to both the heart and the lungs.}\text{27}\text{,}\text{28}\text{. Nonetheless, partial-breast irradiation is only possible in a small fraction of patients; those presenting with early-stage disease and is not advised for patients with locoregionally advanced breast cancer.}\text{30}\text{.}

As such, alternative methods aimed at decreasing heart and lung dose are immensely required in patients with breast cancer undergoing radiation therapy for locoregionally advanced disease.

In an attempt to decrease lung dose, we performed the following study with the aim of comparing combined photon-electron, photon-only, and electron-only plans in the radiation treatment of the supraventricular lymph nodes in patients with breast cancer.

Methods and Materials

Between January and February 2012, 13 patients with consecutive breast cancer treated in the radiation oncology department at King Hussein Cancer Center (Amman, Jordan) were selected for inclusion in this study. All patients had previously undergone modified radical mastectomy and were found to harbor locoregionally advanced breast cancer.

The corresponding computed tomography simulation images were electronically retrieved and used for this planning study following acquisition of institutional review board approval. In total, 3 radiation plans (combined photon-electron, photon-only, and electron-only supraclavicular nodal beams) were generated for all patients using Pinnacle3 version 9.2 (Philips Healthcare, The Netherlands).

Target volume and risk organ definition

The supraventricular nodal clinical target volume (CTV) was contoured according to the Radiation Therapy Oncology Group (RTOG) atlas.\text{31}\text{.} A 0.5-cm contraction from the external body contour was applied to the supraventricular nodal CTV (Fig. 1). The depth of the supraventricular CTV, determined by measuring the distance from the skin and the deepest CTV point, was recorded in all the cases.

The total (bilateral) lung volume was automatically generated, in the lung-window, using the autocontouring tool of the treatment planning system. Heart volume was defined from the heart apex till the caudal level of the pulmonary trunk and included all visible myocardium and pericardium. The contralateral breast contour encompassed any visible glandular breast tissue from the midline till the anterior edge of the latissimus dorsi muscle and from the second intercostal space to the lowest extension of glandular breast tissue after applying 0.5-cm contraction from the external body contour.

Field arrangement

A monoisocentric technique was used in all patients to eliminate the uncertainty associated with field matching. The isocenter was placed at the caudal aspect of the head of the clavicle at the riblepleural interface.

Chest wall field

Two tangential chest wall fields, using field-in-field technique (forward IMRT), were utilized in all patients. The fields were half-beam blocked in the medial and the cranial aspect to eliminate divergence into the lungs and the supraventricular field, respectively. Attempts were made to minimize the amount of lung and heart (for left-sided tumors) inside the tangential field to approximately 2 cm (Supplementary Figs. S1 and S2, respectively).

Supraventricular field

A single direct anteroposterior supraventricular beam was allowed with the field borders fixed in the 3 radiation techniques (Supplementary Figs. S3 and S4). The use of motorized wedge was allowed, if necessary. The field was half-beam blocked in the caudal aspect to eliminate divergence into the chest wall field.

Radiation therapy plan

A dose of 50 Gy in 2 Gy fractions (25 fractions) was prescribed to the chest wall and supraventricular nodal CTV.

Chest wall irradiation parameters were fixed for all treatment plans. The goal of this planning study was to cover 95% of the supraventricular CTV with 95% of the prescribed dose and to minimize the volume receiving $\geq 105\%$ of the dose. Achieving adequate target coverage was balanced with avoiding unnecessary dosimetric hotspots.

A single experienced dosimetrist planned all 13 cases in the following order: photon-only, electron-only followed by combined photon-electron beams with the aim of subjectively achieving a trade-off between target coverage and organ-at-risk/hotspot dose. The choice of the most appropriate electron/photon energy as well as the ratio of photon-to-electron fractions (the number of days a patient would receive either photon-only or electron-only beams) in combined beams was left to the judgment of the dosimetrist.

Plan evaluation

All plans were evaluated by inspecting the dose-volume histograms and documenting the following variables, which were used as comparative end points in this study.

- **Supraventricular CTV coverage**: volume covered by the 95$\%$ isodose line
- **Hotspot volume**: volume receiving $\geq 105\%$ of the prescription dose
- **Maximum radiation dose**: mean radiation dose received by the bilateral lung volume
- **Total lung V$\geq 20\text{ Gy}$**: lung volume percentage receiving at least 20 Gy
- **Contralateral breast dose**: (mean dose received by the contralateral breast) and heart volume percentage receiving at least 25 Gy (V$\geq 25\text{ Gy}$), which are unlikely to be affected by our studied beams, were reported for the sake of completion.

Statistical analysis

Descriptive statistics were used to summarize continuous data. To compare dosimetric results among the 3 radiation plans, one-way analysis of variance was applied. A $p < 0.05$ was considered statistically significant. Bonferroni correction technique for pairwise comparisons was used to perform multiple comparisons between the generated dosimetric results in the 3 radiation plans. An adjusted $p < 0.05$ was considered statistically significant. All statistical tests were performed using Minitab 16 statistical software (Minitab Inc., State College, PA).

Results

Radiation parameters of supraventricular beam portals

<table>
<thead>
<tr>
<th>Field</th>
<th>Supraventricular CTV coverage</th>
<th>Hotspot volume</th>
<th>Maximum radiation dose</th>
<th>Total lung V$\geq 20$ Gy</th>
<th>Contralateral breast dose</th>
<th>Heart volume percentage receiving at least 25 Gy (V$\geq 25$ Gy)</th>
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<td>1</td>
<td>Volume covered by the 95% isodose line</td>
<td>Volume receiving $\geq 105%$ of the prescription dose</td>
<td>Mean radiation dose received by the bilateral lung volume</td>
<td>Total lung V$\geq 20$ Gy</td>
<td>Contralateral breast</td>
<td>Heart volume percentage receiving at least 25 Gy (V$\geq 25$ Gy)</td>
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applied in the photon fractions and the wedge angle ranged from 10° to 40° (mean = 32.2°).

Target coverage

Supraclavicular CTV coverage by the 95% isodose line was highest in photon-only (range: 89% to 100%, mean = 96.2 ± 3.5%), followed closely by combined photon-electron (range: 90% to 99%, mean = 94.2 ± 2.5%) and lowest in electron-only plans (range: 48% to 97%, mean = 81.7 ± 14.8%; p < 0.001) (Supplementary Fig. S5). Using Bonferroni correction, there was a statistically significant difference in the mean supraclavicular nodal CTV covered by the 95% isodose line in favor of photon-only and combined photon-electron plans over electron-only plans (Table 2).

Correlation between target coverage and supraclavicular nodal CTV depth

Overall, 95% of the supraclavicular nodal CTV was covered by the 95% isodose line in 11 patients (84.6%) in photon-only, 5 patients (38.5%) in combined photon-electron, and in 4 patients (30.8%) in electron-only plans. At least 90% of the supraclavicular nodal CTV was covered by the 95% isodose line in all but 1 patient in photon-only, all patients in combined photon-electron, and in 6 patients in electron-only plans. Table 3 shows the correlation between target coverage and supraclavicular nodal CTV depth.

Dosimetric hotspots

The volume of tissue receiving ≥ 105% of the prescription dose ranged between 13 and 206 cm³ (mean = 69.7 ± 56.1 cm³) in electron-only, between 6 and 156 cm³ (mean = 50.8 ± 40.9 cm³) in combined photon-electron, and between 0.2 and 84 cm³ (mean = 32.2 ± 28.1 cm³) in photon-only plans (p = 0.114; Table 2).

Owing to the unacceptably large dosimetric hotspots documented in electron-only beams, we reviewed these plans to...
Dose to organs at risk

Contralateral breast dose was similar in the 3 radiation plans (0.3 Gy; Table 2).

As no significant heart dose is expected in patients with left breast cancer, heart dose was documented only for patients with left breast cancer (n = 9). Heart \( V_{25 \text{ Gy}} \) ranged from 1% to 15% (mean = 7.1 ± 6.1%) in electron-only, from 1% to 15% (mean = 7 ± 6.2%) in combined photon-electron, and from 1% to 15% (mean = 7.1 ± 6.1%) in photon-only plans (\( p = 0.999 \); Table 2).

Mean total lung dose ranged from 4 to 8 Gy (mean = 6 ± 1.2 Gy) in electron-only, from 5 to 8 Gy (mean = 6.8 ± 1.1 Gy) in combined photon-electron, and from 5 to 10 Gy (mean = 7.5 ± 1.3 Gy) in photon-only plans (\( p = 0.014 \)). This statistically significant difference in the total mean lung dose was confirmed by the Bonferroni correction technique only when comparing electron-only and photon-only plans (\( p = 0.0108 \); Table 2 and Supplementary Fig. 59). Total lung \( V_{20 \text{ Gy}} \) ranged from 7% to 14% (mean = 10.9 ± 2.3% in electron-only, from 10% to 17% (mean = 13.8 ± 2.3%) in combined photon-electron, and from 11% to 22% (mean = 16.2 ± 3%) in photon-only plans (\( p < 0.001 \)). This statistically significant difference in total lung \( V_{20 \text{ Gy}} \) dose was confirmed by the Bonferroni correction technique when comparing electron-only vs photon-only (\( p < 0.0001 \)) and electron-only vs combined photon-electron plans (\( p = 0.0208 \); Table 2 and Fig. 2).

Discussion

The standard radiation therapy technique used at our department for the treatment of locoregionally advanced breast cancer dictates the use of appropriate energy photon tangent beams for the whole breast/chest wall, and a single direct anterior photon beam for the supraventricular nodal basin. Over the years, we have noticed that a number of patients treated using this technique were burdened by high lung doses exceeding constraints that predict 5% incidence of radiation pneumonitis in 5 years. Based on clinical judgment, we speculated that this is mostly due to the inadvertent inclusion of the lung apex in the supraventricular nodal photon beam portal. In an attempt to investigate the effects of using electron-only and combined photon-electron beams on lung dose, we performed this study.

Supraventricular nodal CTV coverage

Supraventricular nodal CTV coverage by the 95% isodose line was highest in photon-only followed closely by combined photon-electron and lowest in electron-only plans. Following statistical analysis, we found a significant difference in the mean supraventricular nodal CTV coverage by the 95% isodose line in favor of both photon-only and combined photon-electron as opposed to electron-only plans. However, there was no statistically significant difference in the mean volume of supraventricular nodal CTV covered by the 95% isodose line when comparing photon-only and combined photon-electron plans. The inadequate coverage offered in electron-only plans is likely due to sharper dose drop-off beyond the maximum radiation dose in electron vs photon beams.

When using less strict dose-volume histogram parameters for plan acceptance (at least 90% of the supraventricular nodal CTV to be covered by the 95% isodose line), one notices the near equivalence of photon-only (all but one plan would pass) and combined photon-electron beams (all plans would pass) in achieving adequate target coverage that is far greater than that achieved in electron-only plans (only 5 plans would pass).

Following correlation of the supraventricular nodal CTV depth with the target coverage achieved in the 3 plans, we found that the mean depth of the supraventricular nodal CTV was slightly larger in the plans failing to achieve as opposed to the plans that successfully achieved the desired target coverage (Table 3). However, this difference appears to be a very small and is not of any clinical significance.

Acceptability of plans in terms of dosimetric hotspots

The International Commission on Radiation Units and Measurements report 62 (ICRU-62) recommends dose limits of +7% and...
Effect of the use of wedge compensators on contralateral breast dose

Refer to Supplementary Material S11.

Heart dose

Heart V_{25 Gy} was found to be nearly identical in all 3 plans. Heart dose, in similarity to contralateral breast dose, is a consequence of either the direct inclusion of a proportion of the heart in the chest wall field or the result of scattered dose originating from the chest wall fields. This has been narrated in a previous study by Kong et al., where the effect of certain radiographic parameters on the delivered radiation dose to the heart. In this study, the authors demonstrated that the heart dose in a 2-dimensional radiation technique using tangential breast beams is mainly dependent on the maximum heart distance and length inside the beam.

According to Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommendations, heart V_{25 Gy} < 10% is associated with less than 1% probability of cardiac mortality after 15 years. In our study, all but 4 patients (patients number 4, 6, 8, and 12) abide by these recommendations (Supplementary Table S12).

Lung dose

Mean total lung dose was found to be highest in photon-only followed by combined photon-electron and lowest in electron-only plans. The difference between the plans, in terms of mean total lung dose, was statistically significant only when comparing electron-only vs photon-only plans. Although there appeared to be an obvious difference in the mean total lung dose between combined photon-electron as compared with electron-only and photon-only plans, these differences did not reach the level of statistical significance. On the contrary, we found a statistically significant difference in the total lung V_{20 Gy} when comparing electron-only vs combined photon-electron and photon-only plans. As the lung apex is directly beneath the supraclavicular nodal CTV, the difference in lung dose between electron and photon beams is due to the rapid drop-off in dose with depth associated with the former modality.

Clinical effect of the difference in lung dose among the 3 plans

To assess the expected clinical effect of the difference in lung dose among the 3 plans, we reviewed the QUANTEC lung data, which addressed dose-outcome response, defined as the incidence of symptomatic pneumonitis. According to this collaborative effort, the incidence of symptomatic pneumonitis is expected to be 5%, 10%, 20%, 30%, and 40% if the mean total lung dose is 7, 13, 20, 24, and 27 Gy, respectively. These data were plotted on a scattergraph and a best-fit line drawn (Supplementary Fig. S13). We then inserted our mean total lung dose results according to the 3 plans assessed in this study. Unfortunately, QUANTEC data do not specify dose-outcome response lesser than a mean total lung dose of 7 Gy. As both combined photon-electron and electron-only plans demonstrated lower mean total lung dose, we had to extrapolate the curve down to 6 Gy without applying any change in the shape or inclination of the slope. We acknowledge that such methodology is rather empirical as it is impossible to predict the dose-outcome response lesser than 7 Gy; the curve might level off or become steeper in inclination. Nevertheless, according to this crude method, we estimate that the expected incidence of symptomatic pneumonitis is 4.1% in electron-only, 4.8% in combined photon-electron, and 5.4% in photon-only plans (Supplementary Fig. S14). Therefore, our results confirm the previously reported low incidence of symptomatic pneumonitis in patients with breast cancer following radiation therapy.

Fig. 2. Bar chart representation of the total lung V_{20 Gy} (%) among the 3 plans. (Color version of figure is available online.)
Previously published studies that attempted at decreasing heart and lung dose

To review previously published studies that attempted at decreasing heart and lung dose in patients with breast cancer undergoing radiation therapy, we conducted a comprehensive PubMed search on May 15, 2013. Reports describing the use of various radiation techniques that attempt at decreasing dose deposition inside the heart and lungs in patients with locoregionally advanced breast cancer requiring radiation therapy to the primary as well as regional lymph nodes were considered. Full-text articles of eligible abstracts were reviewed. Furthermore, reference lists of included studies were hand-searched to identify relevant missing publications. Data pertaining to date of publication, study design, number of included patients, radiation technique, target coverage, and heart and lung dose were extracted in a predefined table.

Studies that addressed the use of proton beams,\(^39\) partial-breast irradiation,\(^40,41\) intraoperative electron radiation therapy,\(^42\) and breath-holding or respiratory maneuvers\(^43,44\) were not included in this review, as they are beyond the scope of this work. Furthermore, and as our study fixed chest wall irradiation parameters and mainly aimed to investigate heart and lung dose and dosimetric hotspots following 3 irradiation techniques for the supravacular nodal basin, articles that describe radiation to the intact breast/chest wall in the absence of supravacular nodal irradiation were not addressed.\(^45\)\(^-\)\(^54\)

All in all, 2 studies were eligible for full review and inclusion.\(^55,56\) Table 4 summarizes the pertinent findings in both the studies.

Limitations of the study

Limitations of our study include the small number of included patients and the lack of standardization in the implementation of combined photon-electron and electron beams in our plans.

Table 4

A summary of the pertinent aspects in both the studies

<table>
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<tr>
<th>Study</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Technique</th>
<th>Target coverage</th>
<th>Heart dose</th>
<th>Lung dose</th>
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<tr>
<td>Cavey et al.(^55)</td>
<td>Prospective planning study of retrospective patient data</td>
<td>12</td>
<td>Chest wall and IMC: forward IMRT vs partially wide photon-only vs photons-electron plans</td>
<td>Chest wall and IMC: forward IMRT improved dose homogeneity as compared with photon-electron beams (p &lt; 0.001)</td>
<td>Photon-electron plans resulted in lowest heart V(_{30}) (not statistically significant)</td>
<td>Addition of posterior supravacular lymph node field increased lung V(<em>{20}) and V(</em>{50}) (not statistically significant)</td>
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<td>Supravascular/ infraclavicular lymph nodes: a single anterior field (prescribed to a depth of 3 cm), a single anterior field (prescribed to a depth of 5 cm), an anterior and posterior forward IMRT, and an anterior and posterior 3-dimensional conformal technique</td>
<td>Supravacular/ infraclavicular lymph nodes: best homogeneity and coverage offered by forward IMRT</td>
<td>Forward IMRT reduced heart dose as compared with photon-only plans</td>
<td></td>
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<tr>
<td>Sethi et al.(^56)</td>
<td>Prospective planning study of retrospective patient data</td>
<td>12</td>
<td>Four radiation therapy techniques in both positions were compared</td>
<td>Nodal PTV coverage was found to be statistically superior in CT-generated 3-dimensional and IMRT plans; this parameter was also slightly improved in the prone rather than supine position</td>
<td>Heart dose was not found to be statistically significant among the treatment plans</td>
<td>Prostate position significantly reduced ipsilateral lung V(_{20}) as compared with the supine position</td>
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<td>CT data not permitted: 3-field technique; 2 tangential breast fields, and 1 anterior supravacular field Four-field technique; similar to the 3-field technique but with the addition of a posterior axillary field</td>
<td>CT data permitted (plans were generated to account for target coverage by the respective beams): 3-dimensional conformal technique IMRT technique</td>
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CT = computed tomography; IMC = internal mammary chain; PTV = planning target volume.
Person-to-person planning variation was controlled (a single dosimetrist performed all the plans); however, this study failed to address whether dosimetrist training (or lack of) is partly responsible for the less than satisfactory results associated with the use of electron-only beams. In addition, the order in which the plans were generated poses an additional source of bias as it disadvantages the first (photon-only) and somewhat the second (electron-only) over the third plan (combined photon-electron). It is imperative for future studies to abide by clear and scientifically based approaches when designing the dosimetric aspect of the proposed approach.

Conclusions

As expected, photon-only plans demonstrated the highest target coverage and total lung V20 Gy. The superiority of electron-only beams, in terms of decreasing lung dose, is set back by the dosimetric hotspots associated with such plans making them inappropriate for this body region. Combined photon-electron supraclavicular nodal irradiation was demonstrated as a feasible and easy to implement technique in the treatment of patients with breast cancer and results in adequate nodal target coverage, acceptable dosimetric hotspots, and slightly reduced lung dose while avoiding the complexity typically associated with inverse-IMRT plans.

Acknowledgment

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Supplementary Materials

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.meddos.2014.12.001.

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