Analysis of outcomes in radiation oncology: An integrated computational platform

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Radiotherapy research and outcome analyses are essential for evaluating new methods of radiation delivery and for assessing the benefits of a given technology on locoregional control and overall survival. In this article, a computational platform is presented to facilitate radiotherapy research and outcome studies in radiation oncology. This computational platform consists of (1) an infrastructural database that stores patient diagnosis, IMRT treatment details, and follow-up information, (2) an interface tool that is used to import and export IMRT plans in DICOM RT and AAPM/RTOG formats from a wide range of planning systems to facilitate reproducible research, (3) a graphical data analysis and programming tool that visualizes all aspects of an IMRT plan including dose, contour, and image data to aid the analysis of treatment plans, and (4) a software package that calculates radiobiological models to evaluate IMRT treatment plans. Given the limited number of general-purpose computational environments for radiotherapy research and outcome studies, this computational platform represents a powerful and convenient tool that is well suited for analyzing dose distributions biologically and correlating them with the delivered radiation dose distributions and other patient-related clinical factors. In addition the database is web-based and accessible by multiple users, facilitating its convenient application and use. © 2009 American Association of Physicists in Medicine. [DOI: [10.1118/1.3114022](https://doi.org/10.1118/1.3114022)]

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I. INTRODUCTION

Radiotherapy is one of the most technologically advanced fields in modern medicine. Radiotherapy research and outcome studies have recently become a focus of much attention because many sophisticated technologies from image diagnosis to dose delivery are widely used in cancer clinics.^{1,2} Intensity modulated radiation therapy (IMRT) is an advanced form of three-dimensional (3D) conformal radiotherapy, with the ability to conform the treatment volume to complicated tumor shapes.³ Another recent advancement in treatment planning and delivery is image-guided radiotherapy (IGRT). IGRT can be used to measure and correct target and critical structure positional errors immediately prior to or during treatment delivery.⁴ Both IMRT and IGRT have wide spread applications in most aspects of radiation oncology. However, quantifying the clinical benefits of applying these technologies is far from maturity.⁵ One of the most pertinent metrics of the benefit of a new technology is treatment outcome. Two radiobiological models, tumor control probability (TCP) and normal tissue complication probability (NTCP), are used extensively to predict comprehensive measures of the possible outcomes in clinics.^{6–16} The model parameters of TCP/NTCP for different organs were systematically introduced by Emami and co-workers in 1991.^{7,8} These parameters were based on data from the 1980s when conventional large field treatments were used in the clinic. How these parameters are

applicable to current three-dimensional conformal treatment and IMRT is an unanswered question and requires further investigation.

Many computational tools have been designed and developed to assist radiotherapy research and outcome analysis.^{17–23} Examples include CERR,¹⁷ DICOM_RT Toolbox,¹⁸ MMCTP,¹⁹ MINERVA,²⁰ EUCLID,²¹ BIOPLAN,²² TCP NTCP CALC,²³ etc. While these applications have several useful features for outcome analysis, they are limited in that many of them require access to third-party software packages, use interpreted and slow language tools,^{17–19,21} or lack advanced dose calculation capabilities (e.g., Monte Carlo).^{22,23} Moreover, apart from CERR, none of these software tools utilize databases to facilitate large-scale studies. An infrastructural database is crucial to radiotherapy research since radiotherapy outcomes are highly dependent on a variety of factors including patient, tumor, pathological differentiation, and radiotherapy techniques. A well designed database is essential to collect and manage clinical data.^{24–28}

The computational platform presented herein provides a framework for biologically analyzing dose distributions and correlating them with the delivered radiation dose distributions and other patient-related clinical factors. This facilitates the understanding of the relationship between dose distributions and clinical outcomes with the support of large-scale clinical data stored in the infrastructural database.

FIG. 1. The architecture of the computational environment for radiotherapy research and outcomes study.

II. METHODS AND MATERIALS

The functional modules of the computational platform consist of a web-based infrastructural outcome-study database, an interface tool for data exchange among different treatment planning systems, a calculator for radiobiological models, and a visualization and programming software package for IMRT planning data. The outcome-study database serves as a key component to identifying study populations and storing medical information in the computational platform. IMRT plans are imported and converted by the interface tool, and are then analyzed using the visual graphical user interface within the platform. Biological dose parameters (metrics) are computed from dose distributions in the form of dose-volume histograms (DVH). The biological dose metrics include biologically effective dose (BED), equivalent uniform dose (EUD), TCP, and NCTP, among others. Patient treatment planning image datasets, as well as long-term follow-up image data, are imported and stored in the database for correlation of observed outcomes with dose distributions. The general architecture of the computational platform is shown in Fig. 1.

II.A. Infrastructural outcome-study database

The infrastructural outcome-study database serves as a key component of the computational platform. All patient medical information, including demographic, social, diagnostic, treatment, and follow-up information are collected and stored in the database. The treatment information includes records of the multidisciplinary modalities of cancer care, including surgery, chemotherapy, radiotherapy, radiosurgery, and other ongoing experimental therapies. Information regarding a specific patient is related by a uniquely assigned medical record number for that patient. Sample data elements of the database are shown in Table I. In addition to the basic operations of a database, such as adding, editing, and/or deleting records, the database also has a general search engine and a function for automatically generating a narrative from diagnosis, treatment, and follow-up informa-

tion. The general search engine allows users to custom search statements by specifying search fields, conditions, values, and logical relationships. Automatic narrative generation makes it convenient to trace a patient's course from the stage of diagnosis to follow up and evaluate treatment outcome using all available information in the databases.

The database is open-structured and web-based and is integrated with our department record-and-verify system (ARIA, Varian Medical Systems, Palo Alto, CA) and the global hospital database, currently to retrieve information (in a "passive" manner), and in the future, more generally in an active way to help guide clinical decisions prospectively. The open-structured design provides flexibility for future expansion and data exchange with other existing databases. The web-based design allows data access from various platforms (PC-compatible, Macintosh, and UNIX workstations) anywhere within the Henry Ford Health System intranet.

TABLE I. Data elements for patient information database objects.

Database objects/table	Data elements
Social information	MRN, Name, Birth date, Gender, Race, Address, Referring Dr, Referring hospital
Diagnosis information	Dx type, Dx code, Dx description, Site, Histology, Stage, Stage group, KPS
Tx: Surgery	Site, Surgery type, treatment date
Tx: Chemotherapy	Drug, Treatment date
Tx: Radiotherapy	Site, Dose, Fraction, Technique, Treatment dates, DVH, Plan metrics
Tx: Radiosurgery	Site, Subsite, Dose, Fraction, Target volume, Target size, Beam number, Treatment date, DVH, Plan metrics
Follow-up information	Follow-up date, Radiological date, Clinical, KPS, Pain, Tumor response, Death, Toxicity acute, Toxicity late

Note: MRN=medical record number; Dx=diagnosis; KPS=Karnofsky performance status; Tx=treatment

TABLE II. Biological dose metrics for plan evaluation.

Dose metrics	Formulas	Ref.
Biological effective dose (BED)	$BED = Nd_i \left(1 + \frac{d_i}{\alpha/\beta} \right)$ <p>N is the number of fractions, d_i is the dose per fraction in bin i of the DVH, and α and β supposedly a measure of the relative damage from single hit and two-hit events respectively.</p>	Fowler 1989 (Ref. 29)
Generalized equivalent dose (gEUD) for TCP	$gEUD = (\sum_{i=1}^N v_i D_i^a)^{1/a}, \quad TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{gEUD} \right)^{4\gamma_{50}}}$ <p>TCD_{50} is the tumor dose to control 50% of the tumors when the tumor is homogeneously irradiated and γ_{50} is a unitless model parameter that is specific to the tumor and describes the slope of the dose response curve.</p>	Niemierko 1999 (Ref. 30), Wu 2002 (Ref. 31)
Lyman-Kutcher-Burman model for NTCP	$NTCP = \frac{1}{2} \left(1 + \operatorname{erf} \left(\frac{t}{\sqrt{2}} \right) \right)$ while $t = \frac{EUD - TD_{50}}{m \cdot TD_{50}}$ <p>TD_{50} represents the dose (or relative damaged volume) for a complication rate of 50%, and m is the slope parameter.</p>	Lyman 1985 (Ref. 32), Kutcher 1989 (Ref. 33), Niemierko 1991 (Ref. 11), Seppenwoolde 2003 (Ref. 34)
Relative seriality model for NTCP	$NTCP = \{ 1 - \prod_{i=1}^n (1 - P(D_i)^{v_i})^{1/s} \}$ <p>$P(D_i)$ is the NTCP of the organ homogeneously irradiated with dose D_i, v_i is the volume ratio, and s is the seriality of subunits.</p>	Kallman 1992 (Ref. 10)
Dose-volume relationship $V_{D_{th}}$	<p>Dose-volume relationship $V_{D_{th}}$ is the volume of lung receiving more than a threshold value.</p>	Graham 1999 (Ref. 35), Hernando 2001 (Ref. 36), Armstrong 1997 (Ref. 37)
Effective volume DVH reduction V_{eff}	$V_{eff} = \sum \left\{ v_i \times \left(\frac{D_i}{D_{ref}} \right)^{1/n} \right\}$ <p>v_i is the various subvolumes homogeneously irradiated with dose D_i, D_{ref} is the reference (maximal) dose in the organ, and n is a volume-effect parameter.</p>	Kutcher 1991 (Ref. 38)

Note: TCP=tumor control probability; NTCP=normal tissue complication probability; DVH=dose-volume histogram

The outcome-study database was developed using commercial software as a basis. The portable desktop database management system, MICROSOFT ACCESS (Microsoft Corporation, Redmond, WA), was used to manage and store medical information. The adapted MICROSOFT ACCESS-based system was integrated with structured query language (SQL), one of the most popular computer languages used to create, modify, retrieve, and manipulate data from relational database management systems, and also with statistical analysis software (SAS) (Cary, NC), a widely used program for analyzing clinical outcome data. The architecture of the outcome-study database follows browser/server mode to enable web and multiuser access. Active server page (ASP), a server-wide technology for dynamically generated web pages, was used to process client requests on the server end.

II.B. Interface tool for data exchange

Since most popular planning and treatment machine systems support the DICOM standard and its radiotherapy extensions, DICOM RT protocols, a set of routines to parse patient information, CT, radiotherapy plan parameters, and dose distributions in DICOM RT format was implemented in the interface tool. Other data formats, for example, AAPM/RTOG (America Association of Physicists in Medicine and Radiation Therapy Oncology Group, respectively) and MATLAB binary data files are also supported in order to be com-

patible with other computational environments for radiotherapy research.

II.C. Software tool for evaluating plan metrics

IMRT has widespread applications in most aspects of radiation oncology because of its ability to differentially target dose to multiple targets and multiple avoidance structures, as well as to weight targets and avoidance structures according to their importance. However, the complicated design of IMRT plans makes the task of plan evaluation, in terms of physical dose, complex. A software tool was developed to assist IMRT plan evaluation in terms of radiobiological models. Physical dose distributions are converted to biologically equivalent dose. Several biological dose parameters (metrics) can be analyzed, including, generalized equivalent uniform dose (gEUD), TCP, and NCTP. Details on these biological dose metrics are found in Table II.

II.D. Visualization tool for IMRT treatment plans and dose analysis

A visualization tool was developed to import, analyze, modify, and/or optimize IMRT plans. The software tool was implemented using VISUAL STUDIO.NET (Microsoft Corporation, Redmond, WA) and OPENGL (Silicon Graphics, Inc., Sunnyvale, CA). VISUAL STUDIO.NET is an advanced inte-

(a)

(b)

FIG. 2. A comprehensive software tool for importing, analyzing, modifying, and/or optimizing IMRT plans. (a) Visualization of CT images with the thumbnail viewer of CT images (①); (b) Visualization of structure sets and dose distributions with the axial viewer (②), the sagittal viewer (③), and the coronal viewer (④) of the CT images with dose distributions and structure sets, and the indices for the structure sets (⑤).

grated development environment for the design of graphical user interfaces. OpenGL is a standard specification defining a cross-language cross-platform API for writing applications that produce 2D and 3D computer graphics. Visualizing diagnosis images with dose distributions and analyzing IMRT plans are fundamental to retrospective dose calculation and recorelation of dose with outcome.

The visualization tool interface is illustrated in Fig. 2. The CT scan data, contours, and dose distributions were illustrated in the axial, sagittal, and coronal views. As an ex-

ample, a prostate IMRT plan with 72 slices (512×512 pixels per slice), and nine structures, required approximately 30 s for loading and visualization on a desktop PC (single 2.8 GHz Pentium IV CPU with 2.0 Gbit memory).

II.E. Overall data flow

The database is currently integrated within the routine clinical workflow in a passive way, i.e., information is trans-

Stereotactic Database Thursday, December 18, 2008

Home Tumor Board Patient Diagnosis Treatment Follow-up Tools Logout

Tumor Board Information

Insert Patient Record into Board Date From 12/14/2008 To 12/20/2008 Go Edit Print Tumor Board

No.	MRN	Name	Date	Note	Description
1			12/17/2008	Not Noted	
2			12/17/2008	Not Noted	
3			12/17/2008	Not Noted	
4			12/16/2008	Not Noted	
5			12/17/2008	Not Noted	
6			12/17/2008	Not Noted	
7			12/17/2008	Not Noted	

1/1

(a)

Stereotactic Database Thursday, December 18, 2008

Home Tumor Board Patient Diagnosis Treatment Follow-up Tools Logout

Tumor Board Information

Insert Patient Record into Board Date From 12/14/2008 To 12/20/2008 Go Edit Print Tumor Board

MRN	Name	Date of Birth	Sex	Race	Referring Dr	Referring Hospital

Diagnosis Information

No.	Date	Diagnosis Type	Site	Sub Site	Histology	Diagnosis Description
1	8/15/1984	Primary Tumor	colon			dx'd at another hospital
2	6/15/1987	Primary Tumor	prostate			dx'd at another hospital

Radiotherapy Tx

No.	Date	Diagnosis Type	Site	Sub Site	Dose	Description
1	8/15/1987	Primary Tumor	Prostate			Brachytherapy

Surgery Tx

No.	Date	Diagnosis Type	Site	Sub Site	Surgery Type	Description
1	8/15/1984	Primary Tumor	colon		colon resect	at another hospital
2	6/15/1996	Primary Tumor	Prostate		Salvage prostatectomy	For rising PSA

Chemotherapy Tx

No.	Date	Diagnosis Type	Drug	Description
1	6/15/2003	Primary Tumor	Lupron, Casodex	On and off till 2007

Follow-up Information

No.	Date	Tumor Response	Description

(b)

FIG. 3. The practical use of the SRS database for weekly “tumor board” meetings. (a) Weekly “tumor board” schedule; (b) the narrative of a specific patient including demographic (①), diagnostic (②), treatment (③) and follow-up (④) information.

ferred from the hospital system and/or ARIA to the database without altering the information or transferring it back to these clinical databases. Future work will be focused on integration of the database with the clinical systems in an “active” manner to help guide clinical decisions prospectively. This process will involve careful quality assurance (QA) of

the entire process to verify the integrity of patient data during the transfer of information between the outcomes and clinical databases.

The computational platform is used in clinical studies and/or protocols by first developing the data fields necessary for the particular study. Different cancer types and modalities

FIG. 4. Regional distributions of spinal metastases from prostate carcinoma.

used to treat these cancers will require different data fields, which are customized within the database. The concept of polymorphism (in object-oriented programming) was used here to implement the open-structured design since not all data fields are different between the studies. The open-structured design of the database facilitated customization of the data fields. The next step involves data collection and maintenance. The patient's initial record, including demographic and social information is populated in the outcome-study database by the respective physician during patient referral and patient consultation. The diagnostic information is added by the physician. The physician, nurse, and other staffs such as dosimetrists, physicists, and therapists are responsible for collecting relevant information at the stages of simulation, treatment planning, and treatment delivery. A data manager, hired to verify clinical data transfer for protocol studies, is responsible for collecting follow-up information documented during follow-up visits. The data manager also works with the clinical team (nurse and physician) to perform QA on patient data to ensure information consistency and integrity. Several programming techniques were also implemented to improve data consistency; for example, asynchronous JavaScript and XML (AJAX) is used to determine whether the patient record already exists when users attempt to create a record for the patient. QA of patient data during the transfer process is an imperative step toward generating proper outcome information. The concerted effort of the entire clinical team is necessary for minimizing errors in the transfer of patient data to and from the database.

III. ILLUSTRATIVE EXAMPLES

In addition to being used as a platform for archiving and retrieving patient information for large-scale retrospective studies,³⁹ the integrated environment incorporates functionality for analysis of dose-volume-outcome data,⁴⁰ TCP/NTCP calculation, and maximum likelihood estimation for TCP/NTCP parameters based on correlation of dose with outcome data.

III.A. Clinical application of the outcome-study database

Currently outcome-study database systems have been implemented in our department for stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT). The SRS database includes patient medical information as well as data relevant to the patient's treatment plan and dose distributions. Thus far approximately 800 SRS/SBRT patients' medical records and treatment information have been populated into the SRS database. In addition to the use of the database for research and outcome studies for SRS, it is also used to acquire pertinent patient information during weekly "spine tumor board" meetings, which requires multidisciplinary input from various specialties including radiation oncology, diagnostic radiology, neurosurgery, and pathology. Figure 3 provides an illustration of how the SRS database is used for weekly spine tumor board meetings. The patients are listed according to the weekly schedule [Fig. 3(a)] and the narrative for a specific patient [Fig. 3(b)], including demographic,

FIG. 5. Average dose-volume histograms of the spinal cord according to the prescribed dose. (a) 16 Gy. (b) 18 Gy.

diagnostic, treatment, and follow-up information, are displayed upon selection of the patient's medical record number (MRN). The SBRT database contains over 200 hundred lung SBRT patient medical records, including treatment and follow-up information.

III.B. A case study for radiosurgery for spinal metastases

Each year, 5% of patients with cancer, or approximately 61 000 persons, will develop spinal metastases. The cancers

most often metastasizing to the spine include breast, lung, prostate, and multiple myeloma.⁴¹ Single-fraction SRS is increasingly used to treat patients with spinal metastases. A recent review about SRS for spinal metastases reported that as of August 2007 many publications on SRS have been found in PubMed, but only a few publications investigated dosimetric parameters important to outcome studies.⁴² In this example we demonstrate how such information can be efficiently accessed from our SRS patient population using the database. The database is first searched to find all prostate

FIG. 6. Biologically effective dose (BED) conversion using the LQ model.

cancer patients with spinal cord metastases [“patient’s diagnosis site (search field 1) equal (condition) ‘prostate’ (value 1) and (logical relationship) radiosurgery treatment site (search field 2) equal ‘spine’ (value 2)”]. The search result returned 44 patients with 69 lesions from a current total of 831 radiosurgery patient records in the database. From the search results, one can also find that symptomatic lesions occur more frequently in the thoracic and lumbar regions (62/69) than in the sacral and cervical segments (Fig. 4). Given the median radiosurgery dose of 16 Gy (range: 12–24 Gy) in a single fraction prescribed to the 90% isodose line, the calculated median tumor BED was 37 Gy _{$\alpha/\beta=10$} and the spinal cord maximum BED was 61 Gy _{$\alpha/\beta=3$} . Other plan/dose metrics, such as TCP/NTCP, D100, D90, V100, and V95, also were computed. Figure 5 shows the average dose-volume histograms of the spinal cord according to the prescribed doses of 16 and 18 Gy, respectively. Follow-up information mainly focusing on pain relief as an endpoint was finally analyzed to establish the correlation between plan/dose metrics and clinically observed outcome.

III.C. Analysis of outcome data for patients with central lung lesions treated with SBRT

Although the use of hypofractionated SBRT is becoming a more well-established modality for the treatment of early stage, peripheral lung lesions,^{43,44} the data on the role of SBRT in the treatment of central lung lesions are scant.

In the following example, we illustrate the use of the database in extracting novel outcomes information on patients with central lung lesions who have been treated at our institution using SBRT. Twenty one patients with central lesions treated with SBRT (12 Gy/fraction $\times$ 4 fractions to the 95% isodose line) between the dates of 2002 and 2008 were chosen from our lung SBRT database. The central lesions were defined as tumors within a 2 cm zone of the proximal bronchial tree.

DVHs for seven of these patients were extracted from the database and were analyzed for demonstration purposes. The computation module of the database was used to convert all physical doses into BEDs using the LQ model with an α/β

FIG. 7. The simulated clinical complications using NTCP based on mean lung dose.

ratio of 3.0 Gy (Fig. 6). The computed mean lung dose (MLD) was 13.06 Gy (range: 9.24–15.84 Gy). NTCP calculations using the Lyman–Kutcher–Burman model^{32,33} as a function of MLD are plotted in Fig. 7. Simulated clinical complications ranged from 10.96% to 32.78% and are in agreement with a previous study (from another institution) in which the one year grade 3–5 toxicity rate was 25% for centrally located lesions treated with SBRT.⁴⁵ However, no grade 3–5 toxicity was actually observed in our clinical experience of treating more than 20 patients with SBRT for central lesions. These data are currently anecdotal, and a much larger cohort of patients is required to better understand the dose–effect relationships for patients with central lung lesions undergoing SBRT. Nonetheless, the example illustrates that the database is capable of extracting novel outcomes information in a convenient and effective manner.

IV. CONCLUSION

The overall goal of this study was to develop a flexible computational platform with the aim of integrating new patient-specific treatment planning with clinical factors suitable for multivariable dose–response studies. We have applied the database to access outcome data for two large patient populations and have found it to be an effective tool, with wide ranging utility, including in such venues as weekly tumor board meetings. The advantages of applying the computational platform in radiotherapy research include the acquisition and storage of comprehensive information related to the patient’s treatment and outcomes, the streamlining of data capture and analysis, and hence the reduction in time and effort for outcomes studies. Future work includes refining the dose–effect relationships, by optimizing biological model parameters based on our own patient outcome data (local tumor control and observed normal tissue complications) using maximum likelihood recursion methods.

This computational platform represents tens of thousands of lines of computer code developed in seven languages (C++, OPENGL, MATLAB, JAVA, ASP, HTML, and SQL). The source code of the web-based database and the DVH-based calculator for plan metrics is available upon request.

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¹ A. B. Jani, L. W. Davis, and T. H. Fox, “Integration of database for radiotherapy outcomes analysis,” *J. Am. Coll. Radiol.* **4**(11), 825–831 (2007).

² W. T. McGivney and S. J. Perkel, “Oncology: Practice guidelines and outcomes measurement,” *Ambul. Outreach Spring*, 1998 (unpublished), pp. 17–19.

³ J. M. Galvin *et al.*, “Implementing IMRT in clinical practice: A joint document of the American Society for Therapeutic Radiology and Oncology and the American Association of Physicists in Medicine,” *Int. J. Radiat. Oncol., Biol., Phys.* **58**(5), 1616–1634 (2004).

⁴ L. A. Dawson and M. B. Sharpe, “Image-guided radiotherapy: Rationale,

benefits, and limitations,” *Lancet Oncol.* **7**(10), 848–858 (2006).

⁵ C. C. Ling, E. Yorke, and Z. Fuks, “From IMRT to IGRT: Frontierland or Neverland?,” *Radiother. Oncol.* **78**, 119–122 (2006).

⁶ J. O. Archambeau and R. M. Shymko, “Tissue population configuration as a modifier of organ dose response,” *Int. J. Radiat. Oncol., Biol., Phys.* **15**(3), 727–734 (1988).

⁷ C. Burman, G. J. Kutcher, B. Emami, and M. Goitein, “Fitting of normal tissue tolerance data to an analytic function,” *Int. J. Radiat. Oncol., Biol., Phys.* **21**(1), 123–135 (1991).

⁸ B. Emami, J. Lyman, A. Brown, L. Coia, M. Goitein, J. E. Munzenrider, B. Shank, L. J. Solin, and M. Wesson, “Tolerance of normal tissue to therapeutic irradiation,” *Int. J. Radiat. Oncol., Biol., Phys.* **21**(1), 109–122 (1991).

⁹ A. Jackson, G. Kutcher, and E. Yorke, “Probability of radiation-induced complications for normal tissues with parallel architecture subject to non-uniform irradiation,” *Med. Phys.* **20**(3), 613–625 (1993).

¹⁰ P. Kallman, A. Agren, and A. Brahme, “Tumour and normal tissue responses to fractionated nonuniform dose delivery,” *Int. J. Radiat. Biol.* **62**(2), 249–262 (1992).

¹¹ A. Niemierko and M. Goitein, “Calculation of normal tissue complication probability and dose-volume histogram reduction schemes for tissues with a critical element architecture,” *Radiother. Oncol.* **20**(3), 166–176 (1991).

¹² A. Niemierko and M. Goitein, “Modeling of normal tissue response to radiation: The critical volume model,” *Int. J. Radiat. Oncol., Biol., Phys.* **25**(1), 135–145 (1993).

¹³ T. E. Schultheiss, C. G. Orton, and R. A. Peck, “Models in radiotherapy: Volume effects,” *Med. Phys.* **10**(4), 410–415 (1983).

¹⁴ H. D. Thames and J. H. Hendry, *Fractionation in Radiotherapy* (Taylor & Francis, London, 1987).

¹⁵ H. R. Withers, J. M. Taylor, and B. Maciejewski, “Treatment volume and tissue tolerance,” *Int. J. Radiat. Oncol., Biol., Phys.* **14**(4), 751–759 (1988).

¹⁶ A. B. Wolbarst, “Optimization of radiation therapy II: The critical-voxel model,” *Int. J. Radiat. Oncol., Biol., Phys.* **10**(5), 741–745 (1984).

¹⁷ J. O. Deasy, A. I. Blanco, and V. H. Clark, “CERR: A computational environment for radiotherapy research,” *Med. Phys.* **30**(5), 979–985 (2003).

¹⁸ E. Spezi, D. G. Lewis, and C. W. Smith, “A DICOM-RT-based toolbox for the evaluation and verification of radiotherapy plans,” *Phys. Med. Biol.* **47**, 4223–4232 (2002).

¹⁹ A. Alexander, F. DeBlois, G. Stroian, K. Al-Yahya, E. Heath, and J. Seuntjens, “MMCTP: A radiotherapy research environment for Monte Carlo and patient-specific treatment planning,” *Phys. Med. Biol.* **42**, N297–N308 (2007).

²⁰ J. Lehmann *et al.*, “Monte Carlo treatment planning for molecular target radiotherapy within the MINERVA system,” *Phys. Med. Biol.* **50**, 947–958 (2005).

²¹ O. Gayou, D. Parda, and M. Miften, “EUCLID: An outcome analysis tool for high-dimensional clinical studies,” *Phys. Med. Biol.* **52**, 1705–1719 (2007).

²² B. Sanchez-Nieto and A. E. Nahum, “BIOPLAN: Software for the biological evaluation of radiotherapy treatment plans,” *Med. Dosim.* **25**, 71–76 (2000).

²³ B. Warkentin *et al.*, “TCP-NTCP estimation module using DVHs and known radiobiological models and parameter sets,” *J. Appl. Clin. Med. Phys.* **5**, 50–63 (2004).

²⁴ P. C. de Groen, J. A. Barry, and W. J. Schaller, “Applying world wide web technology to the study of patients with rare diseases,” *Ann. Intern. Med.* **129**(2), 107–113 (1998).

²⁵ E. E. Westberg and R. A. Miller, “The basis for using the internet to support the information needs of primary care,” *J. Am. Med. Inform. Assoc.* **6**(1), 6–25 (1999).

²⁶ M. R. Mahoney, D. J. Sargent, M. J. O’Connell, R. M. Goldberg, P. Schaefer, and J. C. Buckner, “Dealing with a deluge of data: An assessment of adverse event data on North Central Cancer Treatment Group Trials,” *J. Clin. Oncol.* **23**(36), 9275–9281 (2005).

²⁷ M. G. Herman, “Computer networking and information systems in radiation oncology,” AAPM Refresher Course (1999).

²⁸ R. A. Dahl, “Radiation oncology information systems,” *Med. Phys.* **29**(6), 1364 (2002).

²⁹ J. F. Fowler, “The linear-quadratic formula and progress in fractionated radiotherapy,” *Br. J. Radiol.* **62**, 679–694 (1989).

- ³⁰A. Niemierko, "A generalized concept of equivalent uniform dose (EUD)," *Med. Phys.* **26**(6), 1100 (1999).
- ³¹Q. Wu, R. Mohan, A. Niemierko, and R. Schmidt-Ullrich, "Optimization of intensity-modulated radiotherapy plans based on the equivalent uniform dose," *Int. J. Radiat. Oncol., Biol., Phys.* **52**, 224–235 (2002).
- ³²J. T. Lyman, "Complication probability as assessed from dose volume histograms," *Radiat. Res.* **8**, S13–S19 (1985).
- ³³G. J. Kutcher and C. Burman, "Calculation of complication probability factors for non-uniform normal tissue irradiation: The effective volume method," *Int. J. Radiat. Oncol., Biol., Phys.* **16**(6), 1623–1630 (1989).
- ³⁴Y. Seppenwoolde *et al.*, "Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability," *Int. J. Radiat. Oncol., Biol., Phys.* **55**, 724–735 (2003).
- ³⁵M. V. Graham, J. A. Purdy, B. Emami, W. Harms, W. Bosch, M. A. Lockett, and C. A. Perez, "Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC)," *Int. J. Radiat. Oncol., Biol., Phys.* **45**(2), 323–329 (1999).
- ³⁶M. Hernando *et al.*, "Radiation induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer," *Int. J. Radiat. Oncol., Biol., Phys.* **51**(3), 650–659 (2001).
- ³⁷J. G. Armstrong *et al.*, "Promising survival with three-dimensional conformal radiation therapy for non-small cell lung cancer," *Radiother. Oncol.* **44**, 17–22 (1997).
- ³⁸J. G. Kutcher *et al.*, "Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations," *Int. J. Radiat. Oncol., Biol., Phys.* **21**, 136–146 (1991).
- ³⁹D. Liu, J. Jin, S. Ryu, F. Siddiqui, B. Movsas, and I. J. Chetty, "An integrated software platform for treatment documentation and outcome analysis for stereotactic radiosurgery and hypo-fractionated stereotactic body radiotherapy," *Med. Phys.* **35**(6), 2639 (2008).
- ⁴⁰I. J. Chetty, I. Ouyang, N. Wen, D. Liu, Q. Chen, D. Babij, I. Aref, B. Movsas, and M. Ajlouni, "Assessment of target volumes and dose coverage in 4D imaging and planning of lung cancer patients treated with stereotactic body radiotherapy (SBRT)," *Radiother. Oncol.* **88**, S30 (2008).
- ⁴¹B. Georgy, "Metastatic spinal lesions: State-of-the-art treatment options and future trends," *AJNR Am. J. Neuroradiol.* **29**, 1605–1611 (2008).
- ⁴²A. Sahgal, D. Larson, and E. Chang, "Stereotactic body radiosurgery for spinal metastases: A critical review," *Int. J. Radiat. Oncol., Biol., Phys.* **71**(3), 652–665 (2008).
- ⁴³D. Song, B. Kavanagh, S. Benedict, and T. Schefter, "Stereotactic body radiation therapy: Rationale, techniques, applications, and optimization," *Oncology* **18**(11), 1419–1430 (2004).
- ⁴⁴R. Timmerman and B. Kavanagh, "Stereotactic body radiation therapy," *Curr. Probl Cancer* **29**(3), 120–157 (2005).
- ⁴⁵R. Timmerman *et al.*, "Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer," *J. Clin. Oncol.* **24**(30), 4833–4839 (2006).