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Comp Plan: A computer program to generate dose and radiobiological metrics from dose-volume histogram files

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ABSTRACT

Treatment planning studies often require the calculation of a large number of dose and radiobiological metrics. To streamline these calculations, a computer program called Comp Plan was developed using MATLAB. Comp Plan calculates common metrics, including equivalent uniform dose, tumor control probability, and normal tissue complication probability from dose-volume histogram data. The dose and radiobiological metrics can be calculated for the original data or for an adjusted fraction size using the linear quadratic model. A homogeneous boost dose can be added to a given structure if desired. The final output is written to an Excel file in a format convenient for further statistical analysis. Comp Plan was verified by independent calculations. A lung treatment planning study comparing 45 plans for 7 structures using up to 6 metrics for each structure was successfully analyzed within approximately 5 minutes with Comp Plan. The code is freely available from the authors on request.

Introduction

Radiotherapy treatment planning studies have been undertaken for many different treatment techniques and many different clinical sites.[1–3] Treatment planning studies allow several treatment options to be compared for a single patient dataset. Within these studies, a large number of dose and radiobiological metrics may be used as a surrogate for patient outcome.

Dose metrics are indicators providing a single value to represent the physical dose distribution, *e.g.*, the use of V20 and mean lung dose for assessing likely lung toxicity.[4] Radiobiological metrics incorporate parameters representing the tissue concerned as well as physical dose. Radiobiological metrics include equivalent dose models, such as that proposed by Niemerko and colleague,[5,6] and outcome probability models. Outcome probability models attempt to predict the likelihood of a given dose distribution resulting in the eradication of all tumor cells for tumor control probability (TCP)[7–10] or a given clinical end point for normal tissue complication probability (NTCP).[11,12]

Calculation of dose and radiobiological metrics can be time-consuming. For a given treatment planning study, there may be a large number of metrics per structure, structures per treatment plan, and treatment plans per patient. It is often necessary to modify planning parameters and repeat these calculations several times.

There are a number of programs that have been published to calculate dose and radiobiological metrics,[5,13–16] with the selection of metrics and input data format specific to each program. Bioplan[14] and Calc_NTCP[16] require dose-volume histogram (DVH) data, whereas CERR[17] and DREES[13] use radiotherapy dicom datasets. The program described here provides another option for calculating and comparing dose and radiobiological metrics. The unique features of this computer program, called Comp Plan, are its ability to use DVH data to adjust the fraction size according to the linear quadratic model, to use a simple program structure so that additional models could be added, and to export results in a manner easily used for statistical analysis.

Materials and Methods

The metrics considered in this program together with parameters required for calculations, references for the models, and references containing parameter values where available are detailed in Tables 1–4. Each of these metrics can be calculated with or without conversion to standard effective dose (SED).[18] SED is also known as biological effective dose (BED)[19] and fraction size–equivalent dose (FED),[20] and when the conversion is to 2-Gy fractions it is equivalent to EQD2[21] and normalized tolerance dose (NTD).[22] Within the parameters for the SED calculation, a saturation SED limit can also be set, such that if the SED is determined to be above this value, then it is replaced by the saturation SED value. This accounts for the possibility of an isoeffect threshold beyond which any further damage has no further clinical significance.[23] For each of the structures considered a homogeneous boost dose, of a specified total dose and fraction number, can also be added. In most circumstances, it is expected that the SED conversion will be used with the boost option to account for changes in fractionation.

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Table 1
SED, EUD, and logitEUD models used in the Comp Plan program

Model name and description	Equation(s)	Parameters required	References
SED This model uses the linear quadratic model to determine the equivalent dose values in a given fraction size. All models within Comp Plan can be calculated for SED instead of physical dose if chosen by the user	$SED = \frac{D(1+(D/n)/(\alpha/\beta)}{(1+X/(\alpha/\beta)}$	α/β = tissue parameter, as described by the linear quadratic model D = the dose matrix for the given structure X = the standard dose per fraction n = the number of fractions	For the model: 18 For parameter values: 26
EUD This model generates an equivalent dose from DVH data representing a uniform dose that leads to the same probability of injury as the given inhomogeneous distribution	$EUD = \left(\sum_i \left(v_i D_i^a\right)\right)^{1/a}$	v_i = the normalized volume for the voxel or dose bin being considered D_i = the dose to the voxel or dose bin being considered a = a parameter related to the considered structure determining the behavior of the EUD-based model	For the model: 5,6 For the parameters: 5
LogitEUD A logit dose-response model, using EUD values. This can be used for both TCP and NTCP	$\mathrm{Pr}obability = \frac{1}{1+\left(\frac{D_{50}}{EUD}\right)^{4\gamma_{50}}}$	D_{50} = dose for 50% control or complication γ_{50} = slope of the dose response curve	For the model: 5 For the parameters: 5, 27

Comp Plan structure

Comp Plan was written using MATLAB R2007a (The MathWorks, Natick, MA) and designed so that the user can choose multiple dose and radiobiological metrics for each treatment plan and structure. Separate functions for each metric were written so that additional metrics can be added easily.

The structure of Comp Plan is detailed in Fig. 1. Comp Plan reads the plan, structure, and metric details, which are specified by the user in a text file, opens the appropriate DVH file formatted in Excel as a column of dose and volume data, calculates DVH variations, and then calculates each of the required metrics. For each structure, if the structure string starts with "boostDXny_", a homogeneous boost dose with a prescription dose of X Gy delivered in y fractions is added to the DVH. In a similar fashion for each metric, if the metric string starts with "SED_", the dose is first converted to a chosen standard fractionation before calculation of the metric. Once the metrics for each structure are determined, the metric results are exported to an Excel spreadsheet.

Comp Plan requires details of a "base directory" containing the text files described above (see Fig. 1) and the DVH files are placed into a directory structure according to plan and structure names. The user specifies the format of DVH data, *e.g.*, cGy or Gy and cumulative or differential volume data. To allow calculation of the different metrics, all dose data are converted to Gy and differential and cumulative as well as absolute and normalized volume matrixes are calculated.

For each of the radiobiological models, a related function was written to read in parameter values. This function scans the text file to find the appropriate structure name and returns the parameter values for that structure. These parameter files are stored in the base directory as seen in Fig. 1. Once these files are established, they could be used for many treatment planning studies. Individual functions were written for each of the metrics and can also be used independently of the overarching program. The resulting spreadsheet contains a new sheet for each structure. Within each sheet, the name of the plan is given in the left column, and the names of the metrics are given in the top row (Fig. 2).

Verification of data input into the program can be achieved with a number of options in the main script. First, the parameter verification option can be selected. In this situation, the parameters used for the calculation of each metric for each plan and structure are printed in a corresponding worksheet in the resulting spreadsheet. Second, each of the DVHs generated, including the absolute and normalized as well as cumulative and differential for each structure, can be plotted in the main structure spreadsheet together with dose *vs.* SED when this conversion has been used. As the verification options slow down calculation time, they can be selected to be on or off.

Table 2
Dose metrics used in the Comp Plan program

Model name	Model description
Max	Maximum dose delivered to the structure considered
Min	Minimum dose delivered to the structure in question
Mean	Mean dose delivered to the structure in question
Median	Median dose delivered to the structure in question
Vol	Volume of the normal structure in question
Vy	Volume of the organ receiving at least the dose yGy
isoX	The volume receiving dose above %X of the prescription dose (*i.e.*, the volume encompassed by the X% isodose line)

Program Verification

To ensure Comp Plan was calculating metrics correctly, an example dataset was tested. For each of the metrics, the Comp Plan calculated data were compared with independent calculations. These calculations were undertaken using Excel or by manual observation for simple metrics, as detailed in Table 5. First, dose data were converted to Gy. Second, normalized and absolute, as well as differential and cumulative volume data were generated. These datasets were then used to calculate each of the values. Simpson's rule was used to approximate the integral in the TCP Poisson linear quadratic (LQ) values with α distribution; other values were calculated without approximations.

A lung treatment planning study undertaken in our department[24] comparing 45 plans and 7 structures and requiring calculation of up to 6 metrics per structure was used to investigate the performance of this program in a realistic environment. Factors affecting the time required for the initial data to be set up for calculation and for recalculation of metrics were noted for this dataset.

Results

Comp Plan ran successfully on MATLAB version 2007a and 2010b. It is anticipated that it would also run effectively on other versions of MATLAB; however, this has not been confirmed. All plan files, structure and metric files, and DVH files were read successfully. Figure 2 shows a screen capture of the exported excel file.

Program verification

The conversion to SED of the dose matrix was verified when the metric label specified SED. Each of the SED values for the sample dataset was compared with the values from Comp Plan, showing agreement with at least 4 significant figures. The addition of the boost dose was also verified, comparing a sample dataset with values from Comp Plan showing agreement to at least 4 significant figures. The verification results for each of the metrics together with the method of verification are given in Table 5. Only the TCP Poisson, LQ values with α distribution showed a minor discrepancy as a result of using Simp-

Table 3
TCP models used in the Comp Plan program

Model name and description	Equation(s)	Parameters required	References
TCP Poisson, LQ values (TCPpossionLQ) This model uses a Poisson distribution with the linear quadratic model to predict the probability of tumor control	$BED_i = D_i\left(1 + \frac{D_i/n}{\alpha/\beta}\right)$ $TCP(\alpha) = \prod e^{-\rho v_i \exp(-\alpha BED_i)}$	$\alpha\beta$ and α are tissue parameters, as described by the linear quadratic model D = the dose matrix for the given structure v_i = the normalized volume for the voxel or dose bin being considered ρ = the cell density n = the number of fractions	For the model: 9,28,29 For parameter values: 26
TCP Poisson, LQ values with α distribution (TCPpossionLQadist) This model considers the model above also incorporating a distribution of radiosensitivity values, represented by either a normal or lognormal distribution	Where f(α) can either be a normal distribution: $TCP = \int_0 f(\alpha)\prod e^{-\rho V_i \exp(-\alpha BED_i)} d\alpha$ Where f(α) can either be a normal distribution: $f(\alpha) = \frac{1}{\sigma_\alpha^N\sqrt{2\pi}}\exp\frac{-(\alpha-\alpha_0^N)^2}{2(\sigma_\alpha^N)^2}$ Or a lognormal distribution: $f(\alpha) = \frac{1}{\alpha s\sqrt{2\pi}}\exp\frac{-(\ln\alpha - m)^2}{2s^2}$ $m = In\left[\frac{(\alpha_0^L)^2}{\sqrt{(\alpha_0^L)^2 + (\sigma_\alpha^L)^2}}\right]$ $s = \sqrt{\ln\left[(\sigma_\alpha^L/\alpha_0^L)^2 + 1\right]}$ Or a lognormal distribution:	v_i, D_i, α, α/β, n, and BED_i = as above $\alpha^N{}_0$ = the mean *a* value for the normal distribution $\sigma^N{}_\alpha$ = the standard deviation for the normal distribution α^{L0} = the mean *a* value for the log normal distribution $\sigma^L{}_\alpha$ = the standard deviation for the log normal distribution	For the model: 6,9,29 For the parameters: 9
TCP Possion based, D50 and γ50 (TCPd50) A tumor control probability model based on Possion statistics, using D50 and γ50 to describe the response	$TCP = \left(\frac{1}{2}\right)^{\sum v_i \exp[e\gamma_{50}(1 - D_i/D_{50})]}$	D_{50} = dose for 50% control or complication γ_{50} = the slope of the dose response curve v_i = the normalized volume for the voxel or dose bin being considered D_i = the dose to the voxel or dose bin being considered	For the model: 8 For the parameters: 10,27
TCP logit (TCPlogit) A tumor control probability model based on the logit model	$TCP\text{logit} = \prod\left[\frac{1}{1 + \left(\frac{D_{50}}{D_i}\right)^{4\gamma_{50}}}\right]^{v_i}$	D_{50} = the dose for 50% control γ_{50} = the slope of the dose response curve v_i = the normalized volume for the voxel or dose bin being considered D_i = the dose to the voxel or dose bin being considered	For the model: 8 For the parameters: 30
TCP probit (TCPprobit) A tumor control probability model based on the probit model	$TCP = \frac{1}{2}\prod\left\lfloor 1 - erf\left[\sqrt{\pi\gamma}\left(1 - \frac{D_i}{D_{50}}\right)\right]\right\rfloor^{v_i}$	D_{50} = the dose for 50% control γ_{50} = the slope of the dose response curve v_i = the normalized volume for the voxel or dose bin being considered D_i = the dose to the voxel or dose bin being considered	For the model: 8 For the parameters: 27

son's rule. It is noted that this verification testing verifies the accuracy of the algorithm implementation and that uncertainties caused by parameter selection and other issues should still be considered carefully.

Input parameters showed no discrepancy with those output on the parameter verification worksheet, demonstrating correct use of parameters. Comp Plan–converted DVH formats also showed no discrepancy from those determined in Excel.

This program was effectively used for a clinical treatment planning study. The time required for the initial setup of the DVH data files into the directory structure was dependent on the time required to extract the DVH data from the treatment planning system and will vary between centers and treatment planning systems. Setup for files containing plan, structure, metric, and parameter information required was dependent on the number of metrics entered by the user. Editing these files once they were set up—to change metrics, plans, or parameters—was a minor task.

For the considered planning study, a number of metrics were investigated before the final metrics for analysis were determined. This program allowed multiple combinations of metrics and metric parameters to be calculated for all plans within approximately 5 minutes, dependent on the exact parameters chosen. The metric values as output in the Excel spreadsheet were analyzed using standard statistical software (SPSS, Inc., Chicago, IL).

Discussion

This program has been shown to calculate a large number of metrics for a large number of treatment planning datasets in an efficient manner, allowing for comparison of models and parameters. The resulting data output was placed in an Excel spreadsheet that can be used for further analysis in statistical software.

The DVH files used as input for the program are formatted as 2 columns in Excel or 2 columns in a text file. This format can be exported from Focal (CMS-Elekta, St. Louis, MO). Other text DVH formats as exported from other treatment planning systems could be formatted in Excel manually or with a script. If the text file structure is understood, this could be scripted with minimal programming knowledge in either MATLAB or another programming language capable of output to Excel or a delimited file.

Compared with similar programs available, Comp Plan uses a simple program structure such that the user can incorporate additional metrics without impact on the remainder of the program. This program allows all metrics to be calculated for the given physical dose or for a SED. The SED could be used when the fractionation schedule from which the parameter set was derived varies from the data for which the comparison is being undertaken. Use of SED can also generate other parameters. SED used with equivalent uniform dose (EUD) will generate EUBED,[25] also named equivalent survival dose (ESD).[23] Although dose distributions cannot be added together, because of the

Table 4
Normal tissue complication probability models used in the Comp Plan program

Model name and description	Equation(s)	Parameters required	References
Lyman, Kutcher Burman NTCP (NTCPlkb) A normal tissue complication probability model determined by a fit to the clinical data	$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t}\exp(-t^2/2)dt$ $t = \frac{D - D_{50}(V_{eff})}{m}D_{50}(V_{eff})$ $D_{50}(1) = D_{50}(V_{eff})\cdot V^{-n}$ $V_{eff} = \sum D_i^{1/n}v_i$	v_i = the normalized volume for the voxel or dose bin being considered D_i = the dose to the voxel or dose bin being considered m and n = tissue parameter values obtained by fitting tolerance doses for uniform whole and partial organ irradiation	For the model: 11,12 For parameter values: 12
Relative Seriality NTCP(NTCPrs) A normal tissue complication probability model based on the concept of structures being either serial or parallel or a combination of the two options	$NTCP = (1 - \prod[1 - P((D_i)^s)]^{v_i})^{1/s}$ $P_{M=0} = 1 - (1 - P_{FSU})^N$ $P(D_i) = \left(\frac{1}{2}\right)^{\exp[e\gamma_{50}(1 - D_i/D_{50})]}$	v_i = the normalized volume for the voxel or dose bin being considered D_i = the dose to the voxel or dose bin being considered D_{50} = the dose for 50% control or complication γ_{50} = the slope of the dose response curve s = the seriality parameter	For the model: 6 For the parameters: 6
Critical Volume NTCP (NTCPcv) An NTCP model considering functional subunits of structures considering the probability of a given number of subunits surviving and the impact this has on the structure	$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t}\exp(-x^2/2)dx$ $t = \frac{M - NP_{fsu}^{eff}}{\sigma_{fsu}}$ $\sigma_{fsu} = \sqrt{NP_{fsu}(1 - P_{fsu}^{eff})}$ $P^{eff}{}_{FSU} = \sum v_i P^i(D_i)$ $P_{fsu}^i = (1 - e^{-\alpha BED})^k$ $BED_i = D_i\left(1 + \frac{D_i/n}{\alpha/\beta}\right)$	α/β, α = tissue parameters as described by the linear quadratic model v_i = the normalized volume for the voxel or dose bin being considered D_i = the dose to the voxel or dose bin being considered n = the number of fractions N = the number of functional subunits M = the number of functional subunits which must be depleted for the organ to lose its functionality k = the number of cells per function subunit	For the model: 31 For the parameters: 32

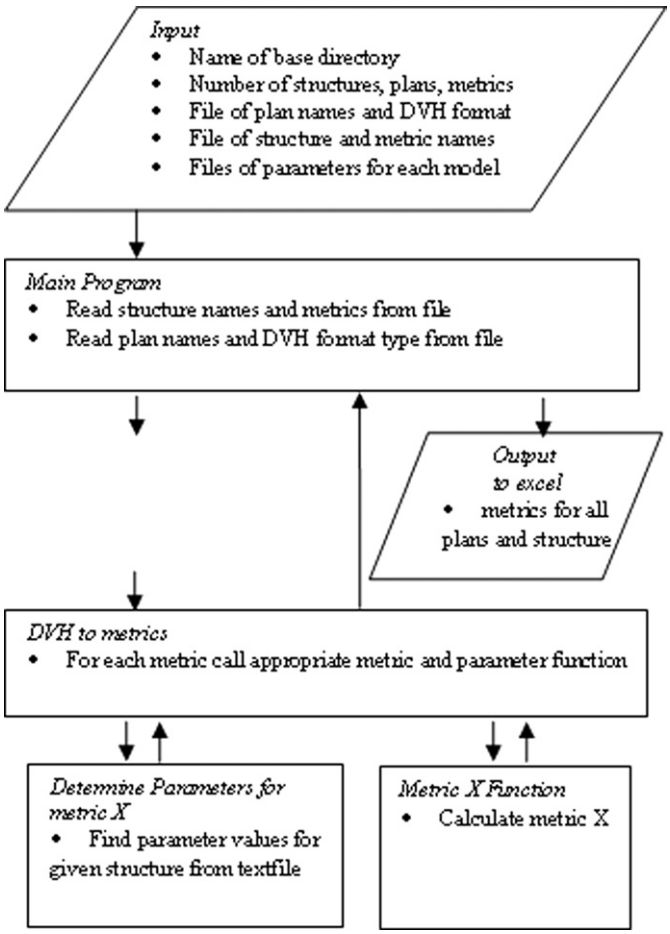
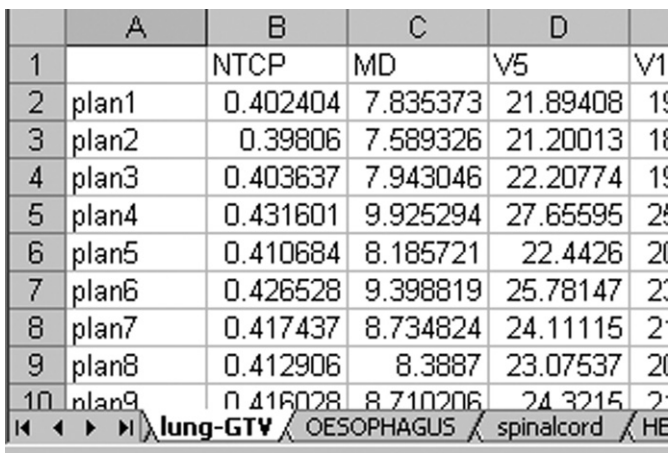


Fig. 1. Flow chart of Comp Plan program, showing input and output data and functions.

need for a complete dose matrix, which is beyond the scope of this program, simple homogeneous boost doses can be added to consider changes in metrics with additional fractionation schedules. Comp Plan does not provide a list of parameter values, although suggested references for parameter values are given. The user is required to determine these for the structure and metric that will be considered. This should be undertaken cautiously considering the conditions under which the parameters were determined.

This program provides the opportunity for a comparison between metrics and parameters to be easily undertaken in a treatment planning study environment. The flexibility to assess many metrics across multiple structures and treatment plans will add value to treatment planning studies and improve understanding of the difference between metrics and parameter choices. The structure of Comp Plan allows users to customize the program and incorporate new models,



	A	B	C	D	
1		NTCP	MD	V5	V1
2	plan1	0.402404	7.835373	21.89408	19
3	plan2	0.39806	7.589326	21.20013	18
4	plan3	0.403637	7.943046	22.20774	19
5	plan4	0.431601	9.925294	27.65595	25
6	plan5	0.410684	8.185721	22.4426	20
7	plan6	0.426528	9.398819	25.78147	23
8	plan7	0.417437	8.734824	24.11115	21
9	plan8	0.412906	8.3887	23.07537	20
10	plan9	0.416028	8.710206	24.3215	22

lung-GTV | OESOPHAGUS | spinalcord | HE

Fig. 2. Screen captures of the excel file containing the resulting metrics.

Table 5
Verification technique and results for models used in the Comp Plan program

Model name	Verification technique	Absolute difference between Comp Plan and verification results	Percentage difference between Comp Plan and verification results
EUD	Algorithm set up in Excel	0.0000	0.0000
LogitEUD	Algorithm set up in Excel	0.0000	−0.0001
Max	Manual observation of data	0.0000	0.0000
Min	Manual observation of data	0.0000	0.0000
Mean	Algorithm set up in Excel	0.0000	0.0000
Median	Algorithm set up in Excel	0.0000	0.0000
Vol	Manual observation of data	0.0000	0.0000
Vy	Algorithm set up in Excel	0.0000	0.0000
isoX	Algorithm set up in Excel	0.0000	0.0000
TCP Poisson, LQ values (TCPpossionLQ)	Algorithm set up in Excel	0.0000	0.0000
TCP Poisson, LQ values with α distribution (TCPpossionLQadist)	Algorithm set up in Excel	0.0019	0.0032
TCP Possion based, D50 and γ50 (TCPd50)	Algorithm set up in Excel	0.0000	0.0000
TCP logit (TCPlogit)	Algorithm set up in Excel	0.0000	0.0000
TCP probit (TCPprobit)	Algorithm set up in Excel	0.0000	0.0000
Lyman, Kutcher Burman NTCP	Algorithm set up in Excel	0.0000	0.0000
Relative seriality NTCP	Algorithm set up in Excel	0.0000	0.0000
Critical volume NTCP	Algorithm set up in Excel	0.0000	0.0000

as well as provide a convenient means for comparing the various models and metrics available.

Conclusion

Comp Plan provides an efficient calculation of dose and radiobiological metrics for a large number of patient datasets, treatment plans, and structures. Accuracy of the program has been verified and performance proven in a realistic setting, showing effective and efficient function. Comp Plan can be easily edited to incorporate additional models and is freely available from the authors on request.

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