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Two-dimensional imaging of tumour control probabilities and normal tissue complication probabilities

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ABSTRACT

Aim: To create a presentation method of TCP and NTCP distributions calculated based on dose distribution for a selected CT slice.

Materials and methods: Three 24-bit colour maps – of dose distribution, delineated structures and CT information – were converted into m-by-n-by-3 data arrays, containing intensities of red, green, and blue colour components for each pixel. All calculations were performed with Matlab v.6.5. The transformation function, which consists of five linear functions, was prepared to translate the colour map into a one-dimensional data array of dose values. A menu-driven application based on the transformation function and mathematical models of complication risk (NTCP) and treatment control probability (TCP) was designed to allow pixel-by-pixel translation of colour maps into one-dimensional arrays of TCP and NTCP values.

Results: The result of this work is an application created to visualize the TCP and NTCP distribution for a single CT scan based on the spatial dose distribution calculated in the treatment planning system. The application allows 10 targets (PTV) and 10 organs at risks (OaR) to be defined. The interface allows alpha/beta values to be inserted for each delineated structure. The application computes TCP and NTCP matrices, which are presented as colour maps superimposed on the corresponding CT slice. There is a set of parameters used for TCP/NTCP calculations which can be defined by the user.

Conclusion: Our application is a prototype of an evaluation tool. Although limited to a single plane of the treatment plan, it is believed to be a starting point for further development.

1. Introduction

For many years radiation therapy has been considered as a curative treatment in which the relatively high risk of complication was in balance with the tumour control probability.[1]

Therefore, for many years, the goal of radiotherapy development concerned constant improvement of the dose distribution conformity and normal tissue sparing in order to reduce treatment toxicity.[2] Dosimetric characteristics have significantly improved since intensity-modulated radiation therapy (IMRT) entered clinical practice. In particular, the

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advantages of IMRT over conventional, conformal technique were noticeable in tumours in close proximity to critical structures or of irregular shape, when safe delivery of a high dose to the planning volume was challenging.[3–6] Further development of IMRT technique has led to image-guided treatment planning (IG IMRT) which additionally decreases the risk of geometric uncertainties caused by organ movements.[7]

The advent of the IMRT era has led to non-uniform organ irradiation significantly reducing the direct relation between the physical dose delivered to the treated volume and normal tissue reaction. Higher doses are proved to correlate with higher tumour control probability, while, simultaneously, escalating the dose in healthy tissue increases the risk of injury.[8] Nevertheless, the response to irradiation is shown to be a diverse and complex process affected by many radiobiological factors and no longer can be characterized by a simple relationship between the prescribed dose and observed toxicity.[9,10] It may lead to the conclusion that predicting radiotherapy outcomes have become demanding.

Further development in radiotherapy planning seems to be targeted at biologically based optimizations and biological evaluation of the radiotherapy plan.[11–14] Alternative fractionation schedules are becoming more and more popular in modern radiotherapy, which explains the increased significance of evaluation of the biological response of tissue to radiotherapy.

Treatment plan evaluation tools provided by commercial software for treatment planning are mostly based on the dose-to-volume relation, which reduces the spatial dose distribution to two-dimensional graphs[15] and neglects the biological effect of the delivered dose.[16]

Calculations based on the dose-to-volume relation provide the same TCP and NTCP values when different spatial dose distributions result in the same dose-volume histogram (DVH). However, there is no evidence that different dose distributions characterized by the same DVH parameters may lead to different clinical outcomes.[17]

Software for estimation of the results of radiotherapy is not widely accessible; it is still considered as an insignificant tool in clinical practice and is not delivered with commercial treatment planning systems.[13]

Thus, will flexible and convenient tools for TCP and NTCP calculations benefit future treatment planning practice? We believe that TCP and NTCP maps calculated based on the spatial dose distribution assist plan evaluation and provide additional information about the spatial location of the "volume at risk" where low-local TCP or high-local NTCP may result in treatment failure or increased toxicity.

Computer applications for translation of the spatial dose distribution into TCP and NTCP maps will help make the decision for the plan more successful and allow the use of different radiobiological parameters and mathematical models.

2. Materials and methods

Mathematical models for simulation of tumour control probability (TCP) and normal tissue complication probability (NTCP) are widely reported in the literature.[8] One of the most frequent mathematical models for NTCP calculations is the Lyman model and an alternative method with Kutcher-Burman reduction algorithm.[18–20] Those methods are usually based on the dose-volume histogram representing the dose distribution inside irradiated volumes. Available algorithms are based on parameters concerning a homogeneous dose distribution (effective volume) and estimated probabilities ($TD_{5/5}$ and $TD_{50/5}$). Even though reduction methods are used to translate an inhomogeneous distribution into an equivalent dose delivered homogeneously to the whole volume, Kutcher et al. underline the limited value of this method.[20,15]

Additionally, opposite to the dose response of healthy tissue which is similar in the group of patients irradiated to the same dose level, tumour reaction is much more complex and determined by many factors that influence the tumour response. Little is known about the repopulation, reoxygenation or number of clonogenic cells and how those factors contribute to the complex response to irradiation.[10] All those circumstances made the TCP evaluation difficult and challenging. Thus, the method proposed in this work is based on the relative TCP levels, expressed as a reference TCP in relation to the total dose delivered in 2 Gy fractions. Our method reduces the number of biological parameters under discussion. Additionally, presentation of the results as TCP/NTCP colour maps does not require any reduction method to translate non-uniform dose distribution into homogeneous coverage of the target volume.

The approach to TCP/NTCP distribution desires "pixel-by-pixel" transformations of spatial dose distributions into spatial biologically equivalent doses.

Point-by-point calculations demand dose values collected in the form of a 2D matrix. We were unable to obtain directly from the planning system dose values in the file format required for further processing.

With this concept, dose maps for a selected, transverse CT scan, acquired directly from treatment planning systems, were stored as 24-bit colour maps, and converted into an m-by-n-by-3 data array that defines red, green, and blue colour components for each individual pixel. All calculations were performed with Matlab v. 6.5, where graphics file formats store RGB images as 24-bit images, where the red, green, and blue components are 8 bits each.

The colour of each pixel is determined by the combination of the red, green, and blue intensities stored in each colour plane at the pixel's location. The three colour components for each pixel are stored along the third dimension of the data array. For example, the red, green, and blue colour components of the pixel (10,5) are stored in RGB (10,5,1), RGB (10,5,2), and RGB (10,5,3), respectively.

Three channels are red, green and blue components in treatment planning system (TPS) Eclipse/Helios (Varian) colour maps. Intensity of each component may change independently but in Eclipse two of the components are constant when the third component changes its value from 0 to maximum or from maximum to zero.

The mathematical model to translate the colour map into one-dimensional data array of dose values assumes five linear functions characterized by coefficients a and b, and defined in the range d (Fig. 1).

The model assumes that coefficient "a" is defined by the relation H/d, where H is the maximal intensity of the colour

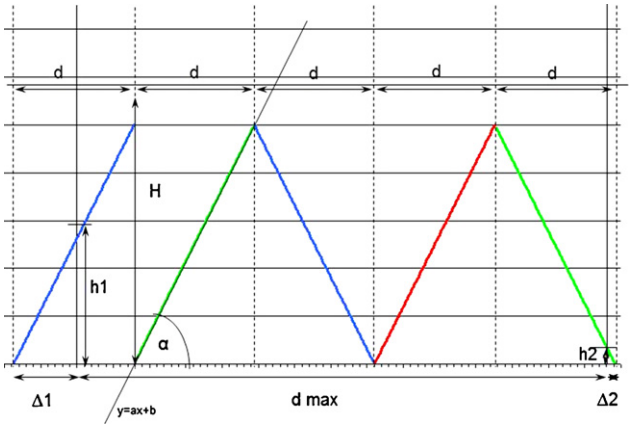

Fig. 1 – Transformation function which translates colour range of the bitmap colour pallet into dose range. Five linear functions describe changes of the intensities of each colour component of RGB space. Linear functions were defined in five dose ranges of equal size. 0 Gy corresponds to h1 value of blue component and maximal dose corresponds to h2 value of green component. Changes of colour intensity range from 0 to *H*. d_{max} is the maximum dose for a dose distribution.

component and coefficients "*b*" differ for each linear function and are determined geometrically.

$b_1 = h_1$
$b_2 = -(H - h_1)$;
$b_3 = 2H - h_1$;
$b_4 = -(3H - h_1)$;
$b_5 = (4H - h_1)$

where d is described by the expression:

$$d = \frac{\Delta 1 + d_{max} + \Delta 2}{5}$$

To verify the precision of this method, a function was applied to the dose distribution calculated for a phantom and for a single radiation photon's beam of 6 MV. Phantom size was 40 cm × 40 cm × 40 cm and field size was 10 cm^2. In the treatment planning system localizations of the marker points were defined according to the dose values they represent (Fig. 2) in order to correlate colour with dose.

Bit maps of the phantom distribution were analyzed in the graphical software in order to define RGB values for pixels which correspond to marker point localizations. RGB values predicted by the transformation function and those sampled with the eyedropper tool were compared. The correlation coefficient was 0.999.

Matlab m-files, which contain the transformation function, were designed to allow pixel-by-pixel translation of colour maps from Eclipse into one-dimensional dose arrays. A simple Matlab application was created to facilitate calculations. A menu-driven application operates with 24-bit coloured maps of dose wash, structure wash and corresponding CT scan. At each level of application colour maps are transformed into a data array of double precision so as to enable mathematical operations on the values of matrix cells. First, the dose colour map is transformed into a dose matrix and stored in a workspace. Then, the structure colour map is translated into a data array which contains information about structure type (PTV or OaR). The data array, which controls structure definitions, is required for further analysis.

Input parameters for this application consist of alpha/beta coefficient, overall treatment time (OTT), repopulation time

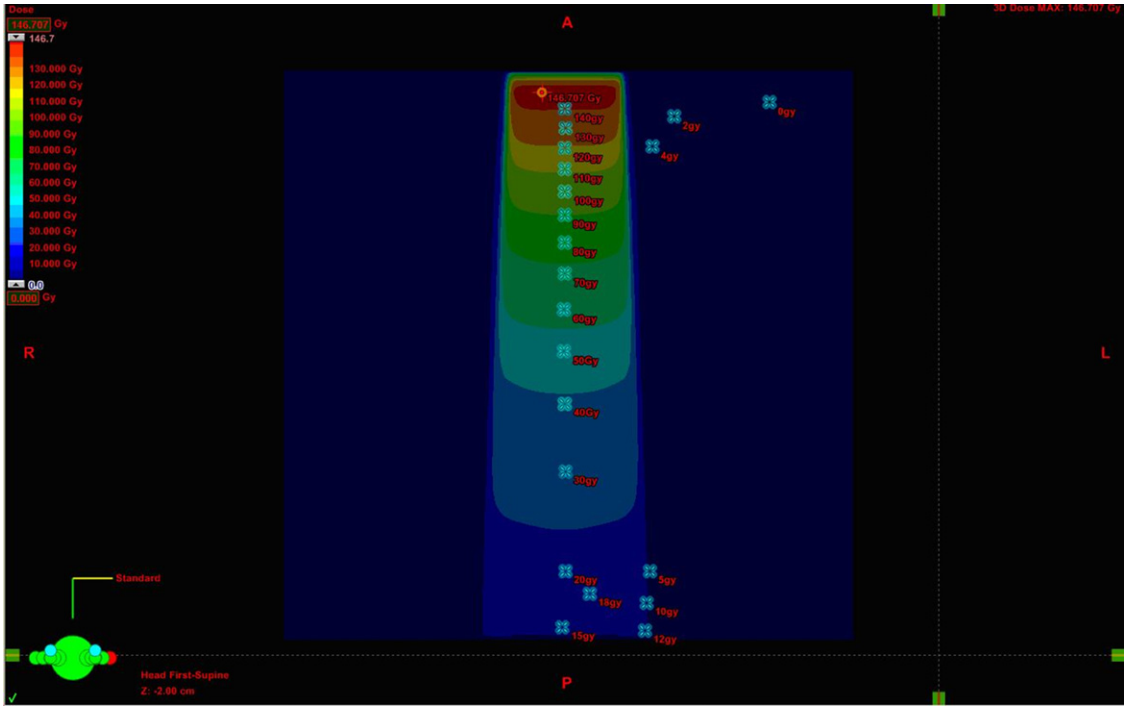

Fig. 2 – 24 bitmap which presents dose distribution for a single beam calculated in a water-based phantom. Marker points were inserted to define the localization of the selected dose values.

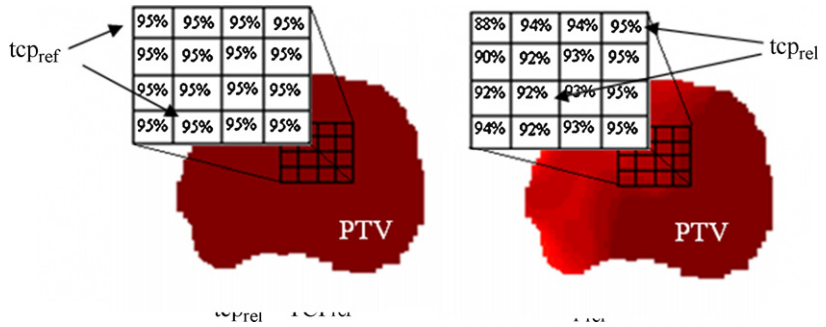

Fig. 3 – Calculation formalism assumes that reference TCP (TCP_{ref}) is produced by the tcp_{ref} which is a result of homogeneously distributed reference biological dose (NTD_{ref}). Relative TCP calculated for each point of the dose map presents local changes of TCP with respect to TCP produced with a certain therapeutic scheme.

(t_{rep}) (start of accelerated repopulation), effective dose (D_{eff}) and fraction number (n). These parameters can be edited and modified by the user. The resulting TCP/NTCP map is presented as an image, and is stored as a one-dimensional data array which finally is converted into a three-dimensional matrix and superimposed on the corresponding CT slice.

In this section we will describe an attempt to convert a physical dose distribution to a TCP and NTCP distribution, translating, at first, physical dose values into a biologically equivalent dose in 2 Gy fractions.

2.1. *Physical models*

2.1.1. *Biologically effective dose*

To convert a physical dose to a biologically equivalent dose (BED) we apply the linear-quadratic (LQ) model

$$\ln(SF) = -\alpha D - \beta D^2 \tag{1}$$

where α and β are parameters characteristic of tissue types.[15] The general expression of BED derived from the LQ model can be defined by the formula:

$$BED = -\frac{\ln(SF)}{\alpha} \tag{2}$$

In our study the LQ formula was employed to calculate the therapeutic isoeffectiveness of the tested regime of dose fractionation and reference scheme related to the dose delivered in 2 Gy fractions (normalized total dose (NTD)):

$$NTD_{2\,Gy} = D \cdot \left[\frac{\alpha/\beta + d}{\alpha/\beta + 2}\right] \tag{3}$$

where D is the total dose delivered with fraction size d.

In this paper, Eq. (3) was expanded by including additional parameters which characterize the treatment scheme, such as: overall treatment time (OTT), accelerated repopulation time (t_{rep}) and dose delivered to compensate accelerated repopulation (d_{rep}).[21,22] Modification of formula (3) leads to an expression which combines radiobiological parameters of tissue radiosensitivity and parameters of the treatment scheme (Eq. (4)).[23]

$$NTD_{2\,Gy} = D \cdot \left[\frac{\alpha/\beta + d}{\alpha/\beta + 2}\right] - (OTT - t_{rep}) \cdot d_{rep} \tag{4}$$

TCP and NTCP calculations required structure localization and definition. Bitmaps of coloured structures delineated in the TPS are translated into one-dimensional data arrays which store information about structure type (PTV type or OaR) and alpha/beta values for each tissue type (Fig. 3). Three matrices – dose matrix, PTV/OaR definition matrix and alpha/beta matrix – defined for a single plan are used for TCP/NTCP calculation.

2.1.2. *TCP and NTCP models*

For the purpose of this study relative TCP and NTCP models were used for analysis.[21] Models are based on the doses which result in reference TCP/NTCP values. Reference doses are established based on clinical experience and data collected for the specific radiotherapy regime. The relative model is based on the Poisson statistic where $TCP = e^{(-N \cdot p)}$. N is the total number of tumour cells and p is survival probability for a single cell after irradiation to dose D. Probability p for a multi-target model is expressed by the equation $p = m \cdot e^{(-D/D_{eff})}$ where m is the number of hits required for cell killing. Thus, $TCP = e^{-N \cdot m \cdot e(-D/D_{eff})}$. Finally, relative TCP (tcp_{rel}) and NTCP ($ntcp_{rel}$) models are expressed by the formulas:

$$tcp_{rel} = e^{\ln(TCP_{ref}) \times e[(NTD_{ref} - D_{rel})/D_{eff}]} \tag{5}$$

similarly

$$ntcp_{rel} = e^{\ln(NTCP_{ref}) \times e[(NTD_{ref} - D_{rel})/D_{eff}]} \tag{6}$$

where D_{ref} is the total biologically effective dose delivered to obtain assumed TCP_{ref} or $NTCP_{ref}$. Effective dose D_{eff} is the dose which reduces survival to $e^{(-1)}$ for the particular fractionation pattern.[24]

Reference probabilities (TCP_{ref} and $NTCP_{ref}$) relate to the reference NTD values which, when delivered homogeneously to the whole PTV or OaR, are assumed to produce a certain biological effect. We assume that the reference dose delivered homogeneously to the PTV or OaR results in reference TCP (tcp_{ref}) or NTCP ($ntcp_{ref}$) values at each point of the irradiated volume (Fig. 3).

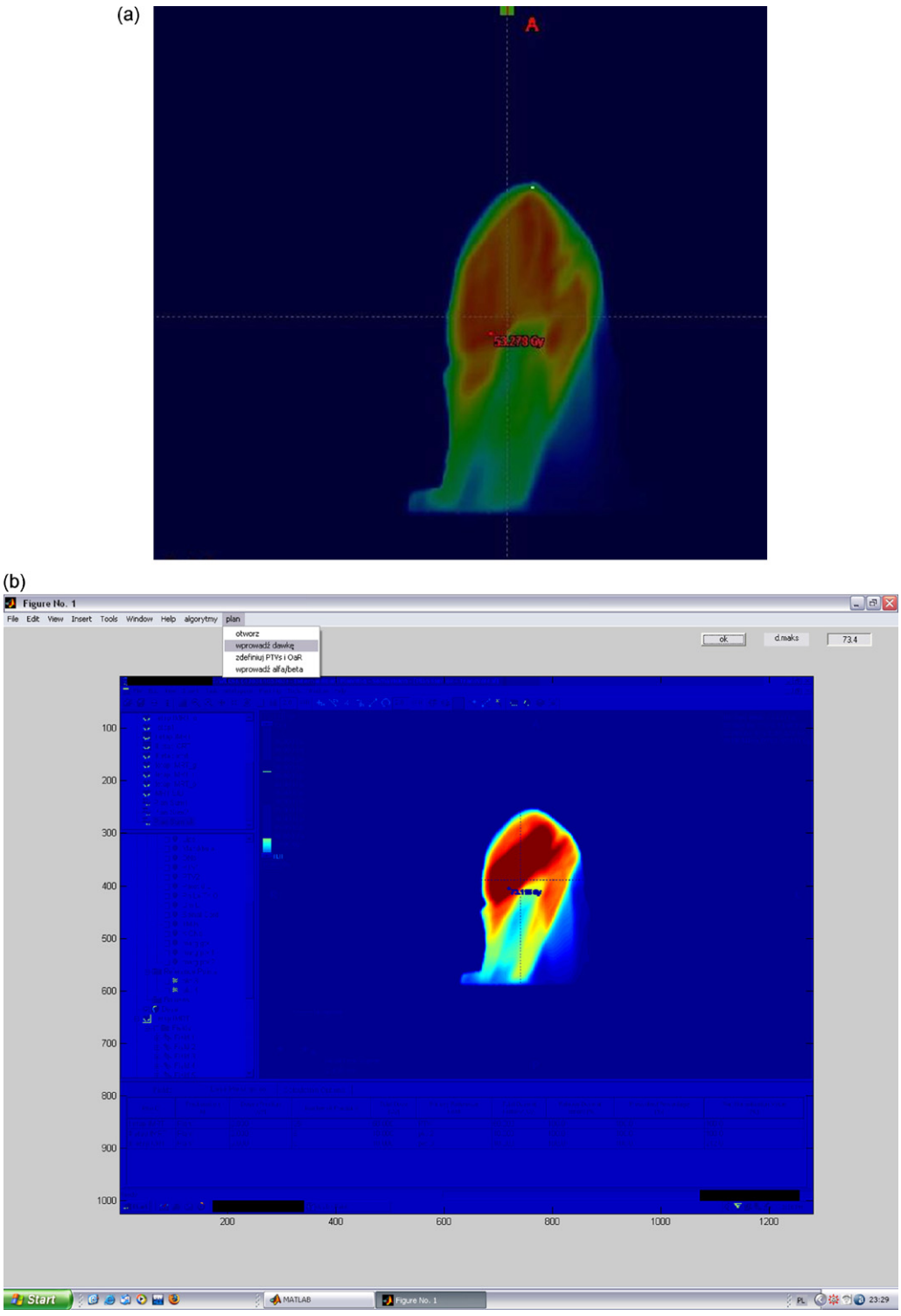

Fig. 4 – (a) Dose distribution for selected CT scan (preferred scan) calculated in Varian Eclipse treatment planning system presented in colourwash mode. The range of the dose values is from 0 Gy to 73.4 Gy. Maximal dose is searched not only on the preferred scan, but also in the whole calculated volume. It is important for definition of the range of the transformation function, which converts the colour scale into the dose scale. The dose distribution, as it is presented above, is stored as a 24 bitmap. Hounsfield units' information was discarded to obtain a pure colour map of the dose distribution. (b) Application interface presenting the dose matrix as a colour map and edit window for maximal dose input. Maximal dose value entered by the user is used to specify transformation function range. Dose values in each matrix cell were calculated based on the 24-colour bitmap acquired from treatment planning systems and transformation function which converts RGB values into dose values.

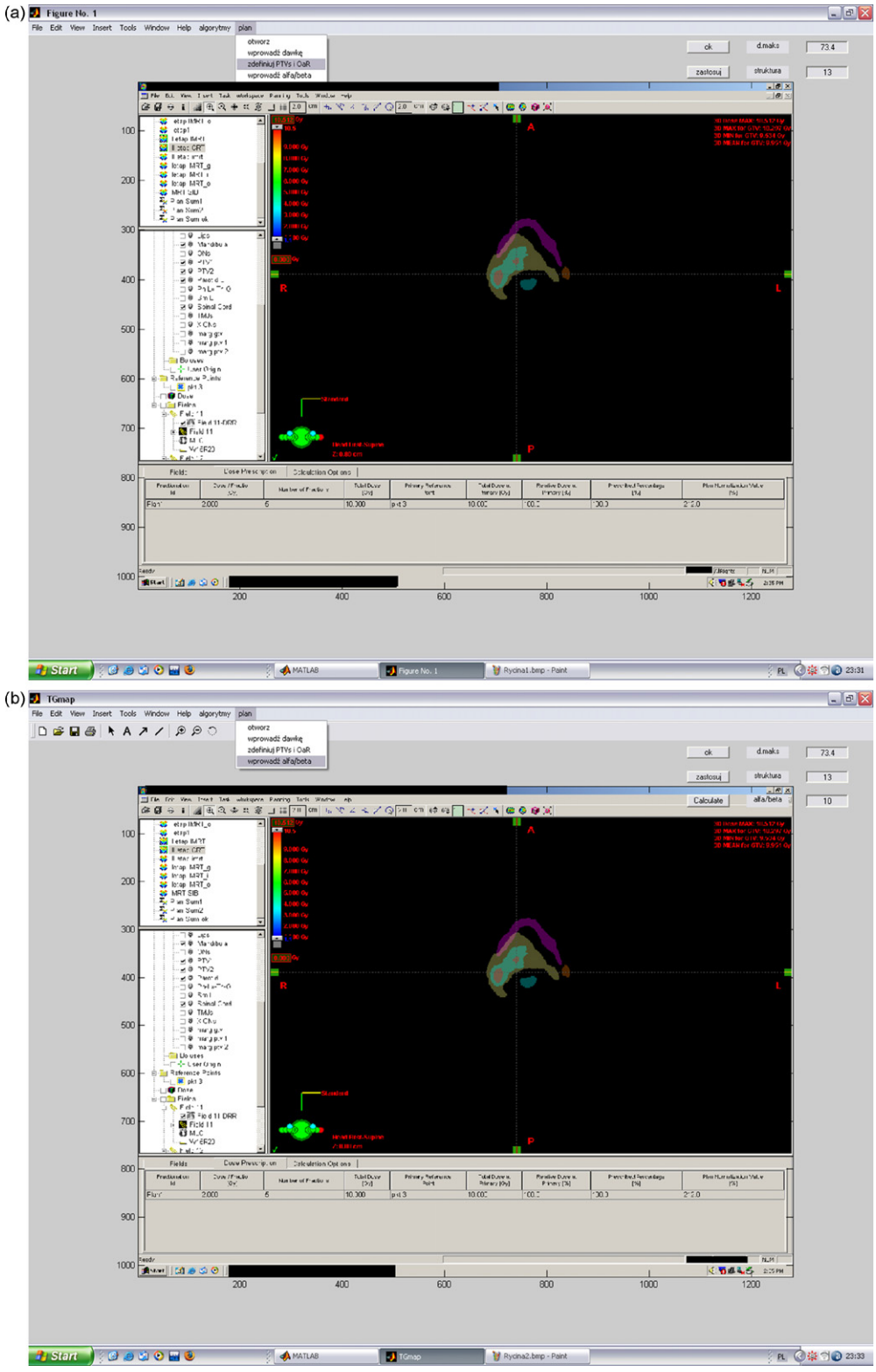

Fig. 5 – Application interface presenting bitmap with structures delineated in the contouring mode of TPS. (a) In the dialogue box, the user inputs a value from 1 to 20 and selects a structure in an image. RGB values of the selected colour which describe the structure's area turn into a single value defined by the user. It allows the bitmap with structures to be converted into a single matrix of values which encode information about the structure type. Values from 1 to 10 identify volumes planned for treatment (PTV, GTV, CTV) and from 11 to 20 for organs at risk (OaR). (b) In the alpha/beta dialogue box the user defines alpha/beta ratio and selects structure in the image. The defined alpha/beta value is connected with the structure and used for calculations.

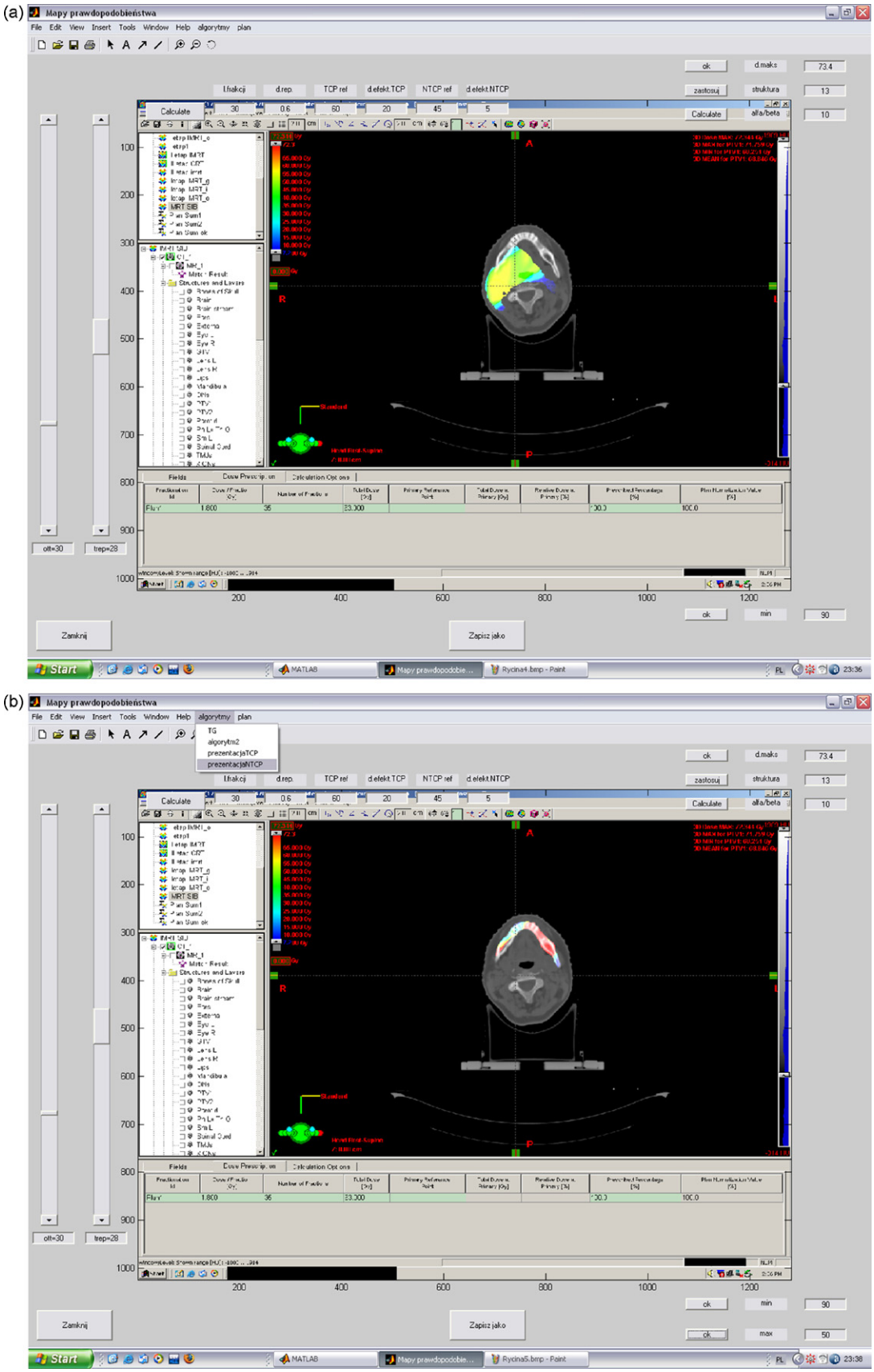

Fig. 6 – The resultant (a) TCP and (b) NTCP colour maps superimposed on the CT slice. TCP and NTCP ranges can be entered for better visualization of the TCP and NTCP distributions and differences.

Relative TCP and NTCP (tcp_{rel} and $ntcp_{rel}$) are local values which describe the biological effect at the relevant points of the transverse CT scan when the dose delivered to this point will change in respect to the assumed value. tcp_{rel} and $ntcp_{rel}$ illustrate gain or loss in tcp_{ref} or $ntcp_{ref}$. Calculated probabilities refer to the single points in the transverse CT scan. In this paper total TCP (NTCP), which is a global response of the irradiated organ and a result of the inhomogeneous dose distribution, was not evaluated.

2.2. *Input parameters*

The set of bitmaps from TPS and model parameters implemented to our application comprise the data input for calculations. The list of parameters which state the user can enter for calculations consists of alpha/beta ratio, overall treatment time, accelerated repopulation time, dose for compensation, effective dose and reference values for TCP and NTCP.

2.3. *Output parameters*

Matrices which contain TCP and NTCP values were calculated for each colour in dose bitmaps. Data matrices were transformed into colour maps and superimposed on the corresponding CT slice.

3. Results

The result of this work is a simple application created specifically to visualize the TCP and NTCP distribution for a single CT scan based on the spatial dose distribution calculated in the TPS. The application requires input of the dose colour map stored as a 24-bit map. First, the transformation function is rescaled to adjust colours to the dose range. For adjustment, maximal dose recorded for the treatment plan should be entered for calculation.

TCP and NTCP calculation requires definition of the irradiated volumes. The application allows 10 targets and 10 organs at risks to be defined. The number in the dialogue box, from 1 to 10, identifies volume recognized as TCP volume. In this area TCP will be calculated in further steps of the algorithm. NTCP volumes are characterized by the numbers 11–20 (Fig. 4). Alpha/beta ratio can also be prescribed by the user. The interface allows one to insert alpha/beta values for each delineated structure. Both volume and alpha/beta definition require the structure map and structures presented as a colour wash (Figs. 4 and 5).

After data input the application computes TCP and NTCP matrices, which are presented as colour maps on the corresponding CT slice. A few parameters used for TCP/NTCP calculations have default values but at this stage can be re-entered or accepted by the user (Fig. 6).

4. Discussion

The computer application which converts the dose distribution into a TCP/NTCP map is based on a mathematical model which predicts the results of therapy with some degree of uncertainty, which is why the application has to be flexible for the user and accessible for further development. Our application allows for a wide range of model parameters entered by the user, while models are still a subject of intensive studies.

The TCP/NTCP map calculated with the pixel-by-pixel transformation method leads to mutually independent values of probabilities at each point of the TCP/NTCP map. Such analysis neglects the volume effect, which influences the total value of TCP or NTCP. The authors of the delta TCP method underline that the voxel-by-voxel method is inaccurate for TCP calculations. However, the weight of volume influence seems to be still under consideration. That is why our method is rather a visualization technique of a probability data matrix and a pure, basic structure for TCP analysis. We treat our TCP/NTCP distribution as a starting point for further analysis such as volume influence or statistics. A simple probability map can be material for any mathematical operations or models because the two-dimensional data structure can be easily converted into a cumulative result and provide flexible material for investigation.

5. Conclusions

Our application is a simple prototype of a tool for radiobiological evaluation of the delivered dose distribution. Different radiotherapeutic schemes can be compared with respect to local TCP and NTCP values. TCP and NTCP maps are updated immediately after modification of treatment parameters and radiobiological coefficients. It allows evaluation of the influence of the model's parameters on tumour control and normal tissue complication probabilities expressed as spatial maps.

Although still limited to a single plane of the treatment plan, it is believed to be a starting point for radiobiological estimation modules which use a spatial dose distribution.

That is why it seems reasonable to visualize probabilities in a two-dimensional manner, which can be easily converted into a one-dimensional plot if necessary.

To create a flexible and convenient tool our application is still under development, and additional new functionalities and models are considered to be implemented.

REFERENCES

1. Deasy JO, El Naqa I. TCP and NTCP important: tools or toys? *Radiother Oncol* 2006;**78**(S1):S20–1.
2. De Kruijf JM, Heijmen Ben JM, Levendag PC. Quantification of trade-off between parotid gland sparing and planning target volume underdosages in clinically node-negative head-and-neck intensity-modulated radiotherapy wilhelmus. *Int J Radiat Oncol Biol Phys* 2007;**68**(1):136–43.
3. Chau MC, Teo PML, Kam MKM, Leung SF, Cheung KY, Chan ATC. Dosimetric comparison between 2-dimensional radiation therapy and intensity modulated radiation therapy in treatment of advanced T-stage nasopharyngeal carcinoma: to treat less or more in the planning organ-at-risk volume of the brainstem and spinal cord ricky. *Med Dosim* 2007;**32**(4):263–70.
4. Grzadziel A, Grosu AL, Kneschaurek P. Three-dimensional conformal versus intensity-modulated radiotherapy dose planning in stereotactic radiotherapy: application of

standard quality parameters for plan evaluation. *Int J Radiat Oncol Biol Phys* 2006;**66**(4):S87–94.
5. Lamers-Kuijper E, Schwarz M, Rasch C, Mijnheer B. Intensity-modulated vs. conformal radiotherapy of parotid gland tumors: potential impact on hearing loss. *Med Dosim* 2007;**32**(4):237–45.
6. Lawson JD, Elder E, Fox T, Davis L. Quantification of dosimetric impact of implementation of on-board imaging (OBI) for Imrt treatment of head-and-neck malignancies. *Med Dosim* 2007;**32**(4):287–94.
7. Kim Y, Tomé WA. Risk-adaptive optimization: selective boosting of high-risk tumor subvolumes. *Int J Radiat Oncol Biol Phys* 2006;**66**(5):1528–42.
8. Feng – Ming (Spring) K, Pan Ch, Eisbruch A, Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity. *Semin Radiat Oncol* 2007;**17**:108–20.
9. Wilson GD. Cell kinetics. *Clin Oncol* 2007;**19**:370–84.
10. Yaromina A, Krause M, Thames H, Rosner A, Krause M, Hessel F, et al. Pre-treatment number of clonogenic cells and their radiosensitivity are major determinants of local tumour control after fractionated irradiation. *Radiother Oncol* 2007;**83**:304–10.
11. Tai A, Erickson B, Khater KA, Li XA. Estimate of radiobiologic parameters from clinical data for biologically based treatment planning for liver irradiation. *Int J Radiat Oncol Biol Phys* 2008;**70**(3):900–7.
12. Brahme A. Individualizing cancer treatment: biological optimization models in treatment planning and delivery. *Int J Radiat Oncol Biol Phys* 2001;**49**(2):327–37.
13. Sanchez-Nieto B, Nahum A, Bioplan E. Software for the biological evaluation of radiotherapy treatment plans. *Med Dosim* 2000;**25**(2):71–6.
14. Peñagarícano JA, Papanikolaou N, Wu C, Yan Y. An assessment of biologically-based optimization (Bort) in the IMRT era. *Med Dosim* 2005;**30**(1):12–9.
15. Bodey RK, Evans PM, Flux GD. Application of the linear-quadratic model to combined modality radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;**59**:228–41.
16. Sanchez-Nieto B, Nahum AE. The Delta-Tcp concept: a clinically useful measure of tumor control probability. *Int J Radiat Oncol Biol Phys* 1999;**44**(2):369–80.
17. Gay A, Niemierko A. A free program for calculating Eud-based Ntcp and Tcp in external beam radiotherapy. *Hiram Phys Med* 2007;**23**:115–257.
18. Xu ZY, Liang SX, Zhu J, Zhu XD, Zhao JD, Lu HJ, et al. Prediction of radiation-induced liver disease by lyman normal-tissue complication probability model in threedimensional conformal radiation therapy for primary liver carcinoma. *Int J Radiat Oncol Biol Phys* 2006;**65**(1):189–95.
19. Söhn M, Yan D, Liang J, Meldolesi Carlos Vargas E, Alber M. Incidence of late rectal bleeding in high-dose conformal radiotherapy of prostate cancer using equivalent uniform dose-based and dose-volume-based normal tissue complication probability models. *Int J Radiat Oncol Biol Phys* 2007;**67**(4):1066–73.
20. Kutcher GJ, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. *Int J Radiat Oncol Biol Phys* 1989;**16**:1623–30.
21. Ślosarek K, Zajusz A, Szlag M. Comparison of traditional and simultaneous IMRT boost technique basing on therapeutic gain calculation. *Med Dosim* 2008;**33**(4):299–302.
22. Steel EG. *Basic clinical radiobiology*. Edward Arnold Publishers; 1993. p. 57.
23. Koukourakis MI, Abatzoglou I. Biological dose volume histograms during conformal hypofractionated accelerated radiotherapy for prostate cancer. *Med Phys* 2007;**34**(1).
24. Halperin EC, Perez CA, Brady LW. *Perez and Brady's principles and practice of radiation oncology*. Williams & Wilkins, Lippincott; 2007.