Clinical aspects of normal tissue complication probability

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Summary

Purpose: To review medical literature data on tolerance doses for a number of radiosensitive organs and put forward some proposals of how to evaluate a treatment plan in terms of the normal tissue complications or how to estimate it in every-day clinical practice.

Material and methods: Studies assessing the relationship between a dose (dose distribution) and radiation injuries of the heart, liver, lung, rectum and parotid gland have been selected for the review.

Results: The Lyman model with Kutcher's reduction algorithm and a relative seriality model proposed by Källman as well as the literature data for the heart, liver, lung, rectum and parotid gland are presented. The parameters of the most often used mathematical models describing the normal tissue complication probability are invoked. The authors' proposals for simple quantitative parameters to be used in clinical practice are put forward.

Conclusion: Mathematical radiobiological models should be applied with special caution. Up-to-date three dimensional CT treatment planning in radiotherapy makes it possible to collect data for more precise assessment of the relationship between dose and injuries of sensitive organs.

Key words: injury of normal tissue, radiobiological models, treatment planning.

Aspekty kliniczne NTCP

Streszczenie

Cel: Dokonano przeglądu literatury pod kątem danych dotyczących dawek tolerancji dla kilku narządów promieniowrażliwych. Zaproponowano, jak można w stosunkowo prosty sposób oceniać jakość planu leczenia z punktu widzenia dawek zaabsorbowanych przez narządy promieniowrażliwe.

Materiał i metody: Publikacje naukowe zostały przeanalizowane z punktu widzenia zamieszczonych danych opisujących zależność pomiędzy rozkładem dawki i prawdopodobieństwem uszkodzenia dla serca, wątroby, płuc, rektum i ślinianek przyusznych.

Wyniki: Przedstawiono model radiobiologiczny zaproponowany przez Lymana i Kutchera oraz model opublikowany przez Källmana. Przytoczono liczbowe wartości parametrów modeli Lymana-Kutchera i Källmana. Zaproponowano proste metody oceny jakości planu leczenia w oparciu o rozkłady dawki w narządach promieniowrażliwych.

Wnioski: Modele radiobiologiczne opisujące zależność dawka-efekt dla narządów promieniowrażliwych powinny być stosowane ze szczególną ostrożnością. Współczesne przestrzenne systemy planowania leczenia umożliwiają gromadzenie danych, w oparciu, o które możliwe jest bardziej precyzyjne określenie zależności pomiędzy dawką i prawdopodobieństwem uszkodzenia narządów promieniowrażliwych.

Słowa kluczowe: uszkodzenie tkanek zdrowych, modele radiobiologiczne, planowanie leczenia.

Introduction

The results of many reports have demonstrated that local control of different malignancies increases with a radiation dose. By increasing the prescribed dose, the risk of developping complications to normal structures also become greater. For each radiosensitive organ, the normal tissue complication probability (NTCP) depends in a very complex way on the dose and the irradiated volume. Determination of the relationship between the NTCP as well as the tumour control probability (TCP) and the dose distribution has been the subject of many research papers over the past few years. Several mathematical models describing the NTCP and the tumour control probability (TCP) have been proposed [1,2,3]. Yet, they, were seldom used for quantitative plan evaluation. It is still common practice to evaluate

and choose the best plan based upon a limited number of dosimetric endpoints, target dose uniformity and maximum critical organ doses. This practice generally results from the lack of reliable mathematical models of TCP and NTCP and the lack of the commercially available treatment planning systems, that enabled us to quantitatively evaluate treatment plans. Even if a given model is accepted, the values of the parameters used by the model are often put to question. It is difficult to acquire good clinical data that may be used for the calculation of these parameters. However, one may expect that a more common use of CT, based 3D treatment planning systems will allow us to develop reliable models of normal tissue response to radiation or, if the models already proposed are acceptable, to estimate more accurately the parameters used in these models.

The purpose of this presentation is to discuss tools for quantitative evaluation of a treatment plan, especially for the calculation of the normal tissue complication probability. Simple parameters describing the quality of a plan will be proposed. My presentation is based on a literature review with respect to radiation injury of the rectum, liver, heart, lung and salivary glands.

Methods

Mathematical models for NTCP calculations

There are two most often used models: the Lyman model with Kutcher's reduction algorithm and a relative seriality model proposed by Källman [4,5]. There are three other models by Fenwick, Jackson: a parallel architecture model and the Niemierko equivalent uniform dose model [6,7,8]. The former two ones will be discussed in detail.

The Lyman model

This model aims at estimating a homogenous dose distribution in an organ at risk. Based on this model, the NTCP can be expressed by the following equations:

$$NTCP(v,D) = \frac{1}{\sqrt{2 \cdot \Pi}} \int_{-\infty}^{t} exp\left(-\frac{x^2}{2}\right) dx \quad (1)$$

$$t = \frac{D - TD_{50}^{v}}{m \cdot D_{50}^{v}} \quad (2)$$

$$TD_{50}^{v} = TD_{50} \cdot v^{-n} \quad (3)$$

$$v \quad \frac{V}{V_{ref}} \quad (4)$$

V is the volume of the organ, receiving the dose D,
TD_{50} is the tolerance dose for 50% of the population when

the fraction volume is equal to V_{ref}; (usually V_{ref} represents the whole organ),
m is the slope parameter which affects the steepness of the S-shaped dose-response curve,
n is the parameter which represents the "volume effect"; (n is close to 1 for an organ in which a small volume may be damaged without a significant effect on the function of the whole organ, such organs are referred to as a parallel organ; n is close to 0 for an organ in which damaged of a small volume may cause dramatic consequences, such organs are referred to as a serial organ).

For a heterogeneous dose distribution the reduction algorithm of the DVH to one step DVH is applied. The influence of the fraction dose on the cells' survival is also applied. Instead of the fraction volume, the following equation helps to calculate the effective volume:

$$v_{eff} = \sum_{i} \Delta v_{i} \cdot \left(\frac{\lambda_{i} \cdot D_{i}}{\lambda_{max} \cdot D_{max}}\right)^{1/n} \quad (5)$$

$$\lambda_{i} = \frac{\frac{\alpha}{\beta} + \frac{D_{i}}{N_{fr}}}{\frac{\alpha}{\beta} + d_{2Gy}} \quad (6)$$

Δv_{i} is the subvolume of the organ at risk, receiving the total dose D_{i},
D_{max} is the maximum dose absorbed by the organ,
α/β is the parameter of the linear-quadratic model (LQ),
N_{fr} is the number of fractions,
n is the parameter of relative seriality of the organ/tissue,
d_{2Gy} is the fraction dose of 2 Gy.
The basic idea underlying above the model is that if the v_{eff} fraction volume of the organ at risk is irradiated with the dose D_{max}, the NTCP would be the same as that for the real heterogeneous dose distribution. This reduction scheme was proposed by Kutcher [4].

The relative seriality model

This model of a homogenous dose distribution in the organ at risk expresses the NTCP by the following equations [5]:

$$NTCP = \left[1 - \prod_{i=1}^{n} \left[1 - P\left(\lambda_{i} \cdot D_{i}\right)^{s}\right]^{\Delta V_{i}}\right]^{1/s} \quad ,and \quad (7)$$

$$P(D_{i}) = 2^{-e \cdot \gamma^{(1 - D_{i}/D_{50})}} \quad (8)$$

Δv_{i}, D_{i}, D_{50}, and λ_{i} have the same meaning as that in the Lyman model.
γ is the slope parameter which has an effect on the steepness of the S-*shaped* dose-response curves is a parameter of relative seriality of the organ/tissue (serial organ: s = 1, parallel organ s =0).

Results

Assessment of heart injury

Close attention has been drawn to heart injury as a consequence of irradiation when it became clear that the increase in survival in a group of irradiated breast cancer patients may be lost because of cardiac mortality due to an excessive dose to the heart [9,10]. In this group of patients, the question whether radiation can injure the heart has been discussed for many years, because the risk of the adverse effect is relatively small, of the order of several percent, and the injury remains latent for about 15 years. In order to settle this long-lasting issue a study would be needed in that would include thousands of patients so as to produce statistically significant results.

The risk of the excess of late cardiac mortality has usually been calculated with the use of a relative seriality model [11]. The parameters of the model used by Gagliari are D50=52.4 Gy, γ=1.28, s=1. In the paper two organs at risk were drawn in CT slices separately: the heart and myocardium. As the authors stated: "The cranial limit of the heart included the infundibulum of the right ventricle, the right atrium and the right atrium auricule and excluded the pulmonary trunk, the ascending aorta and the superior cava. The myocardium was defined with the same external contour as the heart. The wall thickness of the left ventricle was assumed to be between two and three times that of the right ventricle. The volume of the myocardium thus defined was of the order of about 65% of the heart…" As usual, physical doses were converted to biologic doses by means of a linear-quadratic model with α/β value of 3 Gy. For typical treatment of breast cancer with two tangential beams, with a prescribed dose of 50 Gy, 2 Gy/fraction, the mean estimated excess of the long-term cardiac mortality was about 5%. In another work by Hurkmans the correlation between the Maximum Heart Distance (MHD) for a tangential technique and the NTCP was calculated [12]. The MHD is the maximum distance of the heart contour to the medial field end, as can be seen in the beam's eye view (in the simulator radiograph) of the medio-lateral tangential field. For a tangential technique the NTCP values were less than 2% for the MHD smaller than 2 cm. If the MHD exceeds 2 cm the NTCP increases by about 2% for each 1 mm increase in the MHD. The results for the dose-volume dependence for the heart injury and the prediction ability of models should be treated with high caution. The parameters of these mathematical models were estimated on the basis of a small number of mortalities events so the error limits are high.

Assessment of liver injury

Radiation-induced liver disease (RILD) is a dose-limiting complication of liver irradiation. The prospective dose-vo-

lume analysis of the RILD for the largest series of 203 patients was performed by a group from Ann Arbor [13]. Nineteen patients developed of grade 3 or 4 RILD according to the Radiation Therapy Oncology Group. For the NTCP calculations, the DVH was obtained in the normal liver (liver minus gross tumour). The physical dose values were converted to normalized iso-biologic effective dose at 1.5 Gy /fraction using the LQ model with α/β =2 Gy. The mean dose to the normal liver was also calculated. Using the maximum likelihood method parameters of the LKB model were estimated. The calculated value of TD50, m and n being 43.3 Gy, 0.18 and 1.1, respectively. It should be emphasized that these values are different from the original data published by Burman [14]. The large value of the n parameter suggesst that the liver responds as a typical parallel organ, so a strong correlation between the RILD and the mean liver dose may be expected. It was concluded that below the mean dose of 30 Gy no patient developed the RILD, and that the NTCP increases approximately by 4% for on increment of 1 Gy of the mean dose. The first conclusion is very important for the practice of radiotherapy. When planning a treatment, if the treated volume includes parts of the liver, the biological mean dose should be kept below 30 Gy. It is worth reminding that in the paper by Dawsan the physical doses were converted to normalized biological doses at 1.5 Gy/fraction using α/β =2 Gy [13]. The authors also confirmed Jackson's results [15]. When the irradiated volume of the liver is kept below the threshold volume, the risk of the RILD is estimated as being close to 0 regardless of the dose delivered to this volume. If approximately one-third of the whole liver is irradiated with a dose larger than 80 Gy the risk of RILD is negligible.

Assessment of lung injury

For many sites within the chest, the lungs limit the total dose delivered to the target. This problem was seen as particularly important for breast patients and for patients undergoing dose escalation protocols for lung cancer. Many papers have been published, but the data substantiating conclusions were questionable. The improvement in mathematical models of photon beams and CT-based treatment planning made it possible to obtain a better data collection. Some interesting articles concerning this problem have been published in the last few years. The early effect associated with radiation energy absorbed by the lungs is radiation pneumonitis observed over a period of 1-8 months after radiotherapy. The symptoms include fever, dyspnoea, cough or even death from respiratory failure. The late sequel is fibrosis appearing 6 months later. Fibrosis causes a reduction in pulmonary function. The clinical diagnosis of normal tissue complications is generally based on whole-organ toxicity classified very often according to the Southwest Oncology Group criteria. Grade 1 (mild) radiation pneumonitis applies when radiographic changes are observed (diagno-

sis based on chest X-rays or CT), Grade 2 (moderate) is assigned when steroids are required, Grade 3 (severe) when oxygen is needed, and Grade 4 (life threatening), assisted ventilation is required. The whole-organ toxicity is usually mathematically described by means of the Lyman model or by the relative seriality model. Another approach is to model local changes in function. The cumulative effect of these changes on both lungs represents a whole-lung change in function. For example, the diffusing capacity of carbon monoxide is used as an objective index of the pulmonary function [16,17,18].

With regard to the problem of lung injury, a methodological question arises, whether to treat both lungs as a single organ or the left and right lung as separate organs. Both answers have their merit, however more often the lungs are treated as a single organ. In all the recently published papers physical dose distributions were corrected for fractionation, using a linear quadratic model, with an α/β ratio of 2.5 - 3.0 Gy. The mean dose to the normal lungs was also calculated. Using the maximum likelihood method parameters of the LKB model were estimated [19]. The calculated TD50, m and n were 30.8 Gy, 0.37 and 0.99, respectively. These values are different from the original data published by Burman. The value of the n parameter of almost 1 supports the idea that the lungs may be considered as a parallel organ. As for the liver, a strong correlation between the radiation pneumonitis and the mean dose to the lungs was observed. If this dose is smaller than about 15 Gy (using normalized biological doses) the incidence of Grade 3 or higher radiation pneumonitis is near nil. Another single parameter may be used as a predictor for the incidence of lung injury, which is the volume of the lung receiving more than the threshold dose. In the paper of Seppenwoolde and Gopal, the volume of the lungs receiving a dose exceeding 13 Gy (using normalized biological dosse) is strongly associated with lung injury [20]. In the paper written by Graham et al., very often cited by other authors, the strongest correlation was found for the volume of lungs received more than 20 Gy [21]. This paper describes the investigation based on the physical dose so both results might not differ greatly. Gagliari et al. applied the relative seriality model for lungs injury. In her study both lungs were treated as separate organs [17]. The parameters of the model were determined with the maximum likelihood method. The log likelihood was even a little higher for this model than for the Lyman model applied by Seepenwoolde, for which parameters were D50=30.1 Gy, γ=0.97, s=0.01.

Assessment of parotid gland injury

The salivary glands are highly sensitive to radiation [22]. The secretion of the saliva is significantly reduced following 10-15 Gy delivered to the largest part of the gland. If the dose is smaller than about 30-40 Gy, some recovery of the function of the salivary glands is possible. The precise mea-

surement of the influence of the radiation dose on the saliva secretion is difficult and very time consuming. The relationship between the 3D dose distributions in the parotid glands and the production of saliva was determined in the work of the group from Ann Arbor [23]. The parotid glands appeared as a typical parallel organ, for which the mean dose is a very good predictor of injury. If, the glands receive a mean dose below 24-26 Gy, a substantial preservation of flow rates is observed. If this is the case, a lasting improvement is observed over time. The authors' data revealed very high degree of steepness of the NTCP. Glands receiving a mean dose higher than 26 Gy produced little saliva with no recovery over time. The parameters of the NTCP Lyman model were TD50=28.4 Gy, n=1 and m=0.18. These parameters were fitted to the clinical data that were converted into binary values of "severe complications" or "no complications" for each gland. The authors have defined severe complication as a reduction of stimulated salivary output to less than 25% of the pre-radiotherapy output. This is grade 4 parotid gland toxicity according to the RTOG/EORTC Late Effects Consensus Conference. Recently, much more promising data for patients irradiated in the head-and-neck region were published by Roesnik et al. [24]. Their results confirmed that the parotid gland is a parallel organ. They showed that one year after completion of the treatment the NTCP for the parotid gland is not a very steep curve with TD50=39 Gy and m=0.45.

Assessment of rectum injury

Several papers have dealt with the problem of injury to the rectum and bladder after external beam irradiation. Assessment of the adverse effects was mostly based on the RTOG/EORTC or SOMA/LENT scales [24,25]. Late radiation effects were also assessed by a mailed questionnaire completed by patients. The NTCP were calculated using the DVHs of the whole rectum including the cavity and the rectal wall using the Lyman-Kutcher model and the parameters published by Burman and his colleagues – n=0.12, m=0.15, D50(1)=80 Gy [14,26]. It must be emphasized that the parameters apply for endpoints specified as "Severe proctitis/necrosis/fistula/stenosis". Absolute rectal and bladder volumes were investigated additionally, irradiated to various dose levels in correlation with the observed actuarial incidence of the gastrointestinal (GI) and genitourinary (GU) complications. The review of the literature does not give a clear answer concerning the dose-volume relationship for the rectum and bladder [27,28,29,30,31]. There is general agreement that the Lyman-Kutcher model with parameters published by Burman does not estimate the probability of developing GU and GI complications reliably. For the bladder it can be explained by a very unreliable dose distribution. The bladder volume depends directly on the amount of urine it contains. For the rectum it is explained by different endpoints used by Burman and

the authors of other articles. In several articles the correlation between late rectal injuries, e.g. bleeding, and the partial volume of the rectum receiving a dose higher then D - VD were investigated. Storey et al. found that there is a significant increase in late rectal complications when more than 25% of rectum received 70 Gy or greater [32]. Very recently similar results were obtained by two Italian groups. Cozzarini and coworkers showed that the V50 is very predictive for late bleeding [33]. In their study if V50 is less than 63% there were only 7% of late bleeding (Grade 2-3), if larger than 63% the late bleeding increased to more than 25%. Fiorino and the others showed that if V50 is less than 60-65% it enables to keep the rate of rectal bleeding (Graden2-3) below 10% [34].

Conclusions

The NTCP for each organ results from a complex interaction between the dose and the irradiated volume. Moreover, the probability of injury to a normal tissue may depend in each patient on many individual factors. One should always keep in mind that the uncertainty of the quantitative evaluation of the irradiation risk based on the published data may be quite high. In clinical practice, it means that the quantitative evaluation of the treatment plan based on radiobiological models should be handled with particular caution.

It must be strongly emphasized that in almost all the latest publications, the physical DVHs are converted to the equivalent biological dose (EBD) by means of a linear-quadratic model. On one hand there is no doubt that cell survival depends on the dose per fraction, so this effect should be accounted for but on the other hand the recalculation of the DVHs to the EBD is an additional source of uncertainty in the NTCP calculations (it is easy to notice that for all normal organs the same α/β value is taken into calculations). Another problem is that there is no commercially available treatment planning system which enables the EBD calculations. In most cases, however, it is possible to export the data to a spread sheet, such as Microsoft Excel^{TM}, and convert physical data to biological data.

The lack of reliable, quantitative data on normal tissue pro-bability results mainly from the lack of a precise 3-D dose distribution based on CT calculation and from the lack of reliable clinical data. It seems that the first problem is slowly disappearing due to increased accessibility of CT 3-D treatment planning. The other one still remains serious because of the lack of good clinical practice regarding data acquisition. There is an urgent need of a good and precise follow up. Simple forms of injury records, based on interna-

Table 1. The tolerance doses (proposals).

organ	dose	single quantitative parameter - tolerance dose	radiobiological model	remarks
heart		there is no good single parameter	relative seriality model; TD50=52.4 Gy, γ=1.28, s=1	the model should be used with special caution
	for tangential technique the NTCP values were smaller than 2% for the MHD less than 2 cm; if the MHD exceeds 2 cm than the NTCP increases by about 2% for each 1 mm increase of the MHD			
lung	the equivalent biological dose (EBD) at 2 Gy dose per fraction α/β=2.5-3 Gy	the mean EBD < 15 Gy	LKB model TD50=30.8 Gy, n=0.99, m=0.37	most often the lung is treated as a single organ
		the volume of the lung receiving more than EBD=13 Gy < 30%		
liver	the EBD at 1.5 Gy dose per fraction α/β=3 Gy	the mean EBD < 30 Gy	LKB model TD50=43.3 Gy, n=1.1, m=0.18	NTCP increases of about 4% for 1 Gy increase over the mean EBD=30 Gy
rectum	the physical dose	the volume of the rectum receiving more than 50 Gy < 35-50%, 70 Gy < 25%	there were no reliable data for any model	the data were acquired for the treatment with 2 Gy dose per fraction; many articles but give inconsistent conclusions
salivary glant	the physical dose	the mean dose < 30 Gy	LKB model TD50=39 Gy, n=1.0, m=0.45	only few data in the literature

tionally accepted scales should be used in each radiotherapy centre.

Table 1 shows the author's proposals for a simple evaluation of the NTCP, the aim of which is to introduce dose distribution parameters that would make the NTCP evaluation available to all who have access to a 3-D CT based treatment planning system with DVH calculation capabilities. Up-to-date 3D CT treatment planning of radiotherapy enables collecting the data for more precise assessment of dose relationship for sensitive organs injuries.

I call these "my proposition" not because I want to get all the credit. Quite the contrary: I would like them to be considered in confrontation with other propositions, especially those published in highly regarded journals.

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