Medical Dosimetry 39 (2014) 23–30

Medical Dosimetry

journal homepage: www.meddos.org

Critical dose and toxicity index of organs at risk in radiotherapy: Analyzing the calculated effects of modified dose fractionation in non–small cell lung cancer

Piernicola Pedicini, Ph.D.,[*] Lidia Strigari, Ph.D.,[†] Marcello Benassi, Ph.D.,[‡] Rocchina Caivano, Ph.D.,[*] Alba Fiorentino, M.D.,[§] Antonio Nappi, M.D.,[‖] Marco Salvatore, M.D.,[¶] and Giovanni Storto, M.D.[‖]

[*]*Service of Medical Physics, I.R.C.C.S. Regional Cancer Hospital C.R.O.B, Rionero in Vulture, Italy;* [†]*Laboratory of Medical Physics and Expert Systems, Regina Elena National Cancer Institute, Rome, Italy;* [‡]*Service of Medical Physics, Scientific Institute of Tumours of Romagna I.R.S.T., Meldola, Italy;* [§]*U.O. of Radiotherapy, I.R.C.C.S. Regional Cancer Hospital C.R.O.B., Rionero in Vulture, Italy;* [‖]*U.O. of Nuclear Medicine, I.R.C.C.S. Regional Cancer Hospital C.R.O.B., Rionero in Vulture, Italy; and* [¶]*U.O. of Nuclear Medicine, I.R.C.C.S. SDN Foundation, Naples, Italy*

ARTICLE INFO

Article history:
Received 26 February 2013
Accepted 14 August 2013

Keywords:
DVH
SIB-IMRT
Dose fractionation
BED
LQ model

ABSTRACT

To increase the efficacy of radiotherapy for non–small cell lung cancer (NSCLC), many schemes of dose fractionation were assessed by a new "toxicity index" (*I*), which allows one to choose the fractionation schedules that produce less toxic treatments. Thirty-two patients affected by non resectable NSCLC were treated by standard 3-dimensional conformal radiotherapy (3DCRT) with a strategy of limited treated volume. Computed tomography datasets were employed to re plan by simultaneous integrated boost intensity-modulated radiotherapy (IMRT). The dose distributions from plans were used to test various schemes of dose fractionation, in 3DCRT as well as in IMRT, by transforming the dose-volume histogram (DVH) into a biological equivalent DVH (BDVH) and by varying the overall treatment time. The BDVHs were obtained through the toxicity index, which was defined for each of the organs at risk (OAR) by a linear quadratic model keeping an equivalent radiobiological effect on the target volume. The less toxic fractionation consisted in a severe/moderate hyper fractionation for the volume including the primary tumor and lymph nodes, followed by a hypofractionation for the reduced volume of the primary tumor. The 3DCRT and IMRT resulted, respectively, in 4.7% and 4.3% of dose sparing for the spinal cord, without significant changes for the combined-lungs toxicity ($p < 0.001$). Schedules with reduced overall treatment time (accelerated fractionations) led to a 12.5% dose sparing for the spinal cord (7.5% in IMRT), 8.3% dose sparing for V_{20} in the combined lungs (5.5% in IMRT), and also significant dose sparing for all the other OARs ($p < 0.001$). The toxicity index allows to choose fractionation schedules with reduced toxicity for all the OARs and equivalent radiobiological effect for the tumor in 3DCRT, as well as in IMRT, treatments of NSCLC.

Introduction

Radiobiology is currently experiencing a phase in which pre clinical research efforts are being made to increase the understanding of the biological response to radiation, with the aim of improving the outcome of radiotherapy.[1,2]

In the past, radiobiological studies were more focused on finding the dose fractionation by using the linear quadratic (LQ) model describing the phenomenological aspects of lethal and potentially lethal damage.[3] However, dose fractionation still plays an important role in radiation therapy, and understanding the phenomena of cellular recovery[4] has led to more biologically effective fractionation schedules.[5]

In particular, this is true for radiotherapy of lung disease in which the limited dose to the target volume depends on the simultaneous presence of organs at risk (OARs) serial and parallel (*i.e.*, the spinal cord and lungs). The literature provides several dose fractionations for this kind of pathology, from continuous accelerated hyper fractionations to severe hypofractionations, often with conflicting results.[6–8]

At our institution, the lung disease, when selected for 3-dimensional conformal radiotherapy (3DCRT), is treated by a combination of radiation solutions with a first phase of reduced damage for the lungs followed by a second phase with sparing for the spinal cord. Based on this solution, we have explored the

Reprint requests to: Piernicola Pedicini, Ph.D., Department of Radiation Oncology, IRCCS CROB, 1 Padre Pio Street, Rionero in Vulture, Potenza 85028, Italy. Tel.: +39 320 818 9883; fax: +39 097 2 72 3509.
E-mail: ppiern@libero.it

0958-3947/$ – see front matter Copyright © 2014 American Association of Medical Dosimetrists
http://dx.doi.org/10.1016/j.meddos.2013.08.009

possibility to modify the dose fractionation: in the first phase, where the serial organ is penalized, as well as in the second phase where the parallel organs are penalized.

This resulted in a new radiobiological method that allowed to handle the nonuniform irradiation of healthy organs, without a reduction of dose-volume histogram (DVH) as done with several standard radiobiological models.[9–12]

In this work, the method was employed to study a possible reduction of toxicity not only for the patients planned by 3DCRT, but also for patients treatable by simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT). Therefore, computed tomography (CT) datasets were used to re plan by SIB-IMRT adopting similar solutions to those developed in 3DCRT. However, our intent was not to define a new model to change the clinical practice solely on the basis of a computational study, but to demonstrate the general effects that could be considered for many specific treatment situations or to launch new clinical studies.

Methods and Materials

Volumes

The volumes were outlined on the CT dataset for each patient. The gross tumor volume (GTV) was defined by the planning physician as known gross disease from the treatment planning CT. The gross tumor typically included the primary tumor (GTVT) and all lymph nodes (GTVN) measuring 2.0 cm on the CT scan. The clinical tumor volume for primary tumor (CTVT) was defined as a 0.7-cm 3D expansion of the GTVT (median 110 cm^3), to account for microscopic extension. CTV for lymph node (CTVN) was equivalent to GTVN (median 124 cm^3). The overall CTV (CTVT + N) was equivalent to CTVT + CTVN (median 393 cm^3).[13] The planning target volumes (PTVs) for tumor and lymph nodes (PTVT + N) were obtained as 15 mm uniform expansion of CTVs (CTVT + N) to compensate for any variability in the internal target motion due to respiration as well as any variability in the patient setup.

3DCRT planning

The 3DCRT plans were developed with a first phase (P1) up to 50 Gy to PTV related to the overall CTV (PTVT + N), 25 fractions (fr), 2 Gy/fr. Then a second phase (P2) to PTV related only to CTVT (PTVT) with additional 20 Gy, 2 Gy/fr (Table 1).

In the phase P1, a classical technique of irradiation with anteroposterior/posteroanterior fields (0° and 180°) conforming with the PTVT + N up to about 30 to 34 Gy (Phase P1A) was adopted (Fig. 1A). Subsequently, the posterior field (180°) was replaced by 2 rear oblique fields (around 120° and 240°) (Fig. 1B) until the full prophylactic dose (50 Gy) was delivered (Phase P1B).

Thus, the Phase P1A involved the spinal cord with the entire prescribed dose, but the combined lungs were relatively spared. The Phase P1B mainly involved the lungs, but the dose for the spinal cord was greatly reduced. The overall solution allowed an acceptable PTVT + N coverage but at doses very close to tolerances for both the spinal cord and the combined lungs.

In the Phase P2, a boost of dose was delivered using a number of beams and individual beam orientations chosen to produce the optimal conformal dose distribution on PTVT.

IMRT planning

The same CT datasets used for 3DCRT plans were used to re plan by SIB-IMRT technique to study similar solutions to those developed in 3DCRT. The optimization was set on 2 phases: the first (P1) with a greater saving for the combined lungs (high priorities and severe constraints for combined lungs) and the second (P2) with a greater saving for the spinal cord (high priorities and severe constraints for the spinal cord).

The overall goal was to deliver 50 Gy on PTVT + N (30 Gy in P1 and 20 Gy in P2) and 70 Gy on PTVT (42 Gy in P1 and 28 Gy in P2) with SIB technique (Table 1).

Table 1
Doses prescribed for primary tumor and lymph nodes with respect to the different phases of treatment.

Technique	First phase (P1)		Second phase (P2)
	P1A	P1B	
3DCRT	T + N (30 to 34 Gy)	T + N (50 Gy)	T (70 Gy)
IMRT	N (30 Gy) + T (42 Gy)		N (50 Gy) + T (70 Gy)

The plan optimization and analysis process principally took into account the spinal cord (serial organ, tolerance dose: $D_{max} = 46$ Gy) and combined lungs with exclusion of GTV (parallel organs, tolerance dose: $V_{20} < 25\%$).[14]

All IMRT plans were developed with 9 fixed fields (1 every 40°) by Varian Trilogy equipped by MLC Millennium 120 with a sliding window technique (Fig. 1C and D).

Radiobiological analysis

The radiobiological models based on the LQ model have mainly been used to describe the surviving fraction S of cells in the tissue exposed to a total radiation dose D.[15] The cell survival probability is given by S as follows:

$$S = \exp(-E)$$

and the biological effect of radiation effect E can be expressed as follows:

$$E = n \cdot d \cdot (\alpha + \beta \cdot d),$$

where α and β are the parameters describing the cell radiosensitivity, the doses, d, represent the dose per fraction, n is the number of fractions, and the biological effective dose, that is commonly used in clinical practice, can be found by dividing both sides by α.

The changes brought about in dose fractionation for different organs, were evaluated directly on the DVH, transforming it into biological equivalent DVH (BDVH).

The BDVH was obtained from a new index I (we call it the "*toxicity index*"), defined for each OAR exposed to radiation, as the ratio between the effects in modified and standard fractionations:

$$I = \frac{E(d_m, m, \alpha/\beta_o)}{E(d_s, n, \alpha/\beta_o)} \tag{1}$$

Here α/β_o refer to the OAR, the doses, d_m and d_s, represent the dose per fraction, and m and n are the number of fractions in modified and standard fractionations, respectively.

Because in Eq. (1) both the effects were evaluated by the LQ model with the condition of equivalent effect on the target volume,[15] the index I may be written as follows (Appendix A):

$$I = \frac{(\alpha/\beta_t + d_s)}{(\alpha/\beta_t + d_m)} \cdot \frac{(\alpha/\beta_o + d_m)}{(\alpha/\beta_o + d_s)} \tag{2}$$

where α/β_t refers to the target and α/β_o to the OAR.

Dose values indicating an increase of toxicity for the OAR ($I > 1$) occur when

$$(\alpha/\beta_t - \alpha/\beta_o) \cdot (d_m - d_s) > 0 \tag{3}$$

This inequality is satisfied if the factors have the same sign.

Then, if α/β_t is greater than α/β_o ($\alpha/\beta_t - \alpha/\beta_o > 0$), the toxicity increases in the case of hypofractionation ($d_m > d_s$) and decreases for hyper fractionation ($d_m < d_s$). Inversely, if α/β_t is lower than α/β_o, the toxicity decreases in the case of hypofractionation and increases with hyper fractionation.

This simple analysis only refers to the value of the prescribed dose in modified and standard fractionation. However, to describe the behavior of OARs irradiated with nonuniform dose distribution, we define a generalized index I_i for each value of dose d_i correspondent of ith bin of volume v_i.

As each d_i is a fraction of d_s,

$$d_i = f_i \cdot d_s \tag{4}$$

the toxicity index for each d_i will be

$$I_i = \frac{(\alpha/\beta_t + d_s)}{(\alpha/\beta_t + d_m)} \cdot \frac{(\alpha/\beta_o + f_i \cdot d_m)}{(\alpha/\beta_o + f_i \cdot d_s)}, \tag{5}$$

whereby, there will be an increase of toxicity when (see Appendix B):

$$(f_i \cdot \alpha/\beta_t - \alpha/\beta_o) \cdot (d_m - d_s) > 0 \tag{6}$$

This inequality highlights the existence of a critical theoretical dose value d^*, such as $I^* = 1$, for every scheme of fractionation. Excluding the banal solution ($d_m = d_s$), I^* will be equal to 1 when

$$f^* \cdot \alpha/\beta_t - \alpha/\beta_o = 0 \tag{7}$$

i.e., when

$$d^* = \frac{\alpha/\beta_o}{\alpha/\beta_t} \cdot d_s \tag{8}$$

and for overall treatment

$$D^* = \frac{\alpha/\beta_o}{\alpha/\beta_t} \cdot D_s \tag{9}$$

where $D^* = n_s \cdot d^*$, $D_s = n_s \cdot d_s$, and n_s is the number of fractions in the standard fractionation.

The fraction, f^*, only depends on the ratio, $\alpha/\beta_o|\alpha/\beta_t$, and not on the chosen fractionation or the volumetric parameters, and it is automatically defined for each OAR, irrespective of its nonuniform dose distribution. However, the critical dose, D^*, does not depend on the dose distribution and it is defined for each OAR when the prescription dose is defined. However, their usefulness is expressed when applied