Dose coverage evaluation for lung cancer radiation therapy

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Key words: *lung cancer, conformal radiotherapy, target.*

Summary. *Purpose of the study was to evaluate adequacy of target volume coverage with conventional two-dimensional radiotherapy; and to estimate potential of three-dimensional conformal radiotherapy for increasing dose to the target.*

Material and methods. Analysis was performed for 34 lung cancer patients referred for curative intend two-dimensional radiation therapy. For the same patients two independent specialist teams created conventional two-dimensional plans according to "gold standard" radiotherapy and three-dimensional conformal plans. Evaluation of target coverage adequacy and normal tissue complication probability parameters was performed on two-dimensional isodose distributions overlay over outlined clinical target volumes. Maximum total dose for three-dimensional conformal radiotherapy was estimated keeping normal tissue complication probability on the same level as for two-dimensional plans. Conformity was evaluated.

Results. For two-dimensional planning maximum target dose was on average 52 Gy (3 Gy 1 standard deviation). Clinical target volumes coverage was poor for most plans; 95% isodose surface covers 57%. This percentage was consistent with 1 standard deviation of 10–17%. Minimum target dose was low – 5–10% of prescribed dose.

Three-dimensional conformal radiotherapy allows increasing dose to clinical target volume with elective nodes irradiation up to 68–72 Gy and up to 78–90 Gy without it. Conformity of clinical target volume coverage was acceptable for all patients; 95% isodose surface covered on average 95% of target.

Conclusion. Three-dimensional conformal radiotherapy allows increasing of total dose to the target keeping tolerable dose to functional tissues for most patients. However, only combinations of modern imaging, planning and delivery techniques enable providing adequate and homogeneous clinical target volume coverage with therapeutically significant dose for lung tumors.

Introduction

Most lung cancers are non-small cell lung cancers (NSCLC). In Lithuania, this disease is a leading cancer in males and makes up to 25% of all male cancers. In NSCLC, results of standard treatment are poor in all but the most localized cancers. Therefore, all newly diagnosed patients with NSCLC are candidates for studies evaluating new forms of treatment. Surgery is the main potentially curative therapeutic option for this disease; radiation therapy can produce cure in a small minority and palliation in the majority of patients; chemotherapy in advanced-stage disease, offers modest improvements in median survival although overall survival is still poor.

The statistical data for 2002 show that approximately one third of lung cancer patients in Lithuania have at the time of diagnosis stage I–II disease. About 40% of these patients are treated at Oncology Institute of Vilnius University (OI VU). These patients should be considered for curative treatment. There is no statistically reliable data on what proportion of these patients receive surgery as the first line treatment. However, many patients treated surgically subsequently develop regional or distant metastases. Therefore, patients should be considered for entry into clinical trials evaluating adjuvant treatment with chemotherapy or radiation therapy following surgery. In addition, there is large proportion of patients with inoperable (locally advanced or with other medical contraindications) stage I–II disease and with

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sufficient pulmonary reserve, which should be considered for radiation therapy as a primary treatment with curative intent. The term locally advanced non-small cell lung cancer (LA-NSCLC) is used to describe disease that is too extensive for primary surgical resection, is limited to the thorax, and technically allows the inclusion of the entire tumor within a reasonable radiation field.

Both groups of patients until recently were receiving conventional two-dimensional (2D) radiation therapy (1). However, in view of the poor rate of local control following conventional radiation therapy, there is a clear need for methods to improve its efficacy. Radiation dose escalation could enhance local disease eradication but if conventional techniques were utilized the resulting normal tissue effects would probably cause prohibitive toxicity (2–5).

The aim of this study was employing now available modern imaging and planning techniques:

1. To evaluate the adequacy of target volume coverage with conventional two-dimensional radiotherapy (2D RT), and
2. To estimate the potential of three-dimensional conformal radiotherapy (3DCRT) for increasing target dose and improving dose homogeneity while keeping lung toxicity within acceptable level.

Material and methods

The rationale for applying 3DCRT to lung cancer is based on the frequency of failure to eradicate gross tumor with conventional approaches. It may therefore be appropriate to ignore subclinical or microscopic extensions when designing a clinical target volume, thereby restricting target volume size and allowing dose escalation. When the clinical target volume is expanded to a planning target volume, an optimized margin would result in homogeneous irradiation to the highest dose feasible within normal tissue constraints. To arrive at such optimized margins, multiple factors, including data acquisition, data transfer, patient movement, treatment reproducibility, and internal organ and target volume motion, must be considered (6, 7).

3DCRT is a mode of high precision radiotherapy which accurately conforms the isosurface of a given radiation dose to the anatomical boundaries of the tumor in its entire three-dimensional configuration (8). Technical analysis for lung cancer demonstrates that 3DCRT had the potential to enhance delivery of high dose radiation with a reduction in dose to normal tissues (9, 10). These phenomena suggested that 3DCRT might improve the therapeutic ratio of radiation therapy for locally advanced non-small cell lung cancer. This was the basis for the clinical utilization of 3DCRT for lung cancer.

Radiotherapy department of OI VU now possesses a unique possibility to use modern treatment planning and delivery to clinically evaluate 3DCRT for lung cancer.

Data acquisition

Patients are immobilized supine for treatment planning computed tomography (CT) scan, treatment plan verification and treatment delivery with the arms placed above the head. This position allows selection of oblique treatment fields. Initial simulation was not performed; instead following planning CT procedure; virtual simulation was applied using either Advantage Sim or XimaVision systems. This achieves significantly better accuracy in treatment field set-up. During planning CT procedure the track of the three alignment lasers on the patient are marked with radio opaque markers which are taped to the skin and will then be visible on CT slices, and the point of intersection of these three marks indicates the transverse location of the initial isocenter if it were projected to that particular cephalo-caudal position. Also, a marker is placed on the sternum of the patient inside of scanning interval to ensure a stable reference point for treatment planning. Eventually, the CT scan is used as the basis for subsequent planning and the final plan will usually involve designation of a new isocenter, which can be identified by a process of translation from the initial isocenter. Utilizing virtual simulation for initial simulation, we eliminate errors relating to position change of the patient during transfer between initial simulation and acquisition of planning CT.

CT slices are labeled with a *y*-value indicating how many centimeters they are superior to the origin/isocenter (*y* has a positive value) or inferior to it (*y* has a negative value). CT slices are taken at 1.0 cm intervals. The CT should extend from the bottom of the larynx to the bottom of the second lumbar vertebra to include all lung parenchyma. This ensures that dose-volume histograms can include all relevant normal structures of interest.

Choice of treatment volumes

Because established pathways of primary lung tumor spread follow lymphatic flow from tumor to hilum, mediastinum, and supraclavicular lymph nodes, traditional radiation volumes include the primary lesion, ipsilateral hilum, bilateral mediastinum, and

often ipsilateral supraclavicular region. Elective nodal irradiation has been commonplace of the traditional practice (11). It was believed that survival of patients treated with no elective nodal radiotherapy (RT) was inferior to those who did.

However, there is a recent movement to limit the size of the RT fields to include gross primary and only known nodal disease, as defined by thoracic CT scans. Because larger RT field sizes have limited total dose and have been related to increased acute and late toxicity, several investigators have delivered thoracic RT to the gross tumor only, reporting no compromise in loco regional control or survival (11, 12).

There are good reasons now to suggest that treatment of patients with T1-2N0 lesions to small volumes encompassing the primary tumor without elective nodal irradiation may be an appropriate option. It should be recognized that this represents a choice between leaving possible microscopic nodal disease rather than under treating known disease at the primary site. Success of such a strategy will rely on there being a steep dose-control relation in the range of dose escalation facilitated by elimination of nodal irradiation. So long as local failure rates are high, the survival benefits to be gained by increasing the treatment volume to include suspected sub clinical mediastinal disease are likely to be small. The ability of 3D treatment planning to design effective plans for delivery of high doses to the target volume is hampered as target volume increases. Than a reasonable research strategy will be to escalate doses to a limited target volume. For patients with clinical T1-2N1 disease, there is no good data supporting treatment of restricted volumes, and the mediastinum should probably be irradiated in these patients.

Imaging

The imaging resolution of CT is itself a source of inaccuracy in the process of defining the gross target volume (GTV) and normal structures. Appearance of the CT image used for delineation of the GTV can be varied by CT window display settings.

A detailed discussion and description of imaging procedures for accurate outlining of different structures of thorax is the subject of separate publication. In essence, we use lung settings when outlining the GTV for a peripheral tumor and use soft tissue windows as most appropriate for imaging of central structures such as mediastinal nodes.

Tumor-induced atelectasis can make it impossible to determine the extent of macroscopic disease. If the combined radiological appearance of tumor and atelectasis is too massive to be encompassed in a tolerable radiation field, then the patient is not suitable for treatment with 3DCRT. If, on the other hand, the entire radiological abnormality can be encompassed in a tolerable radiation field then the entire abnormality can be regarded as gross tumor volume. Such a patient can be treated with 3DCRT.

After CT is obtained, the target volumes are outlined according to International Commission on Radiation Units and Measurements (ICRU*)* 50 and 62 (14, 15). Contours for normal structures of interest, including skin, lungs, esophagus, spinal cord and heart, are also outlined. We may usually distinguish two main types of CTVs (clinical target volumes) suited for 3DCRT; CTV with elective nodal irradiation (ENI) and CTV without ENI.

Clinical target volumes with elective nodal irradiation

When ENI is to be included there are two CTVs. CTVl inc1udes both gross disease and microscopic (radiologically invisible) and is prescribed to receive 50 Gy in 25 fractions. CTV2 is reduced to include the gross disease only and after it receives 50 Gy as part of CTVl it is continued to 68–72 Gy in conventional fractionation. Such a simple scheme needs to be modified to take into account the fact that some lymph nodes may be visible and be smaller than 1 cm. At that size, they may or may not be involved. If these lymph nodes are involved, they should be included in CTV2 and if not, they should only be in CTV1. There are no strict rules available as to how such a situation should be hand1ed. At or institute we decided to use the following scheme: if there are no visible nodes in a lymph node station then that station should be in CTVl only; if the station contains visible node(s), of any size, then the station should be included in CTV2.

Clinical target volumes without elective nodal irradiation

As there is only one target volume, it is simply designated as the CTV and is prescribed to a radical dose, e.g. 68–72 Gy with conventional fractionation. In regard to the visible CT scans nodes of less than or equal to 1 cm we use the following scheme: if the nodes within a station are not visible then that station is excluded from the GTV. If a single node is less than or equal to 1 cm size in maximum dimension then it alone (not its entire station) is included in the GTV. If there is more than one node in the station which is less than or equal to 1 cm in maximum size or if one (or more) node is greater than 1 cm then the entire station should be included in the GTV.

The planning target volume delineation and irradiation techniques

After the CTV was defined either by clinician or, as in our institution is most common, with the assistance of clinical radiologist, the planning target volume (PTV) is created on 3D virtual simulation workstation by adding a margin to the CTV. The margin added to the CTV accounts for variations and uncertainties in the execution of treatment, including patient movement and set-up displacements as well as organ movement and variations in size and shape of the CTV. Generally, those uncertainties are specific for particular clinic and cannot be adapted automatically from other institutions practice or from literature. Most of these uncertainties and variations were carefully investigated and incorporated into the margin definition procedure. The margin to account for technical inaccuracies was found to be almost constant and equal to 0.5–0.6 cm in all directions.

The internal margin, however, which accounts for internal organ movements can vary very much depending on the size, location and shape of the CTV. This margin can be different in different directions and falls in interval from 0.5 cm to 1.2-cm. Therefore, combined margin is specific for each patient and may vary in size and direction from 0.7 to 1.3 cm.

Dose planning was performed utilizing fully 3D treatment planning system and volume images imported from virtual simulation. 15 MV X-rays beam with multi-leaf collimation (MLC) was used in all cases. In addition, in some cases for large patient and/or large planning volume 25 MV X-rays beam was employed to achieve better dose homogeneity throughout the treatment volume. Standard three field conformal technique with open or wedged beams was used in most cases. For highly irregular PTVs, split target technique (two field levels) with exact mach achieved by applying half beam block for each level was used. Total prescribed doses ranged from 64 Gy given in 2 Gy fractions (50 Gy to the large ENI volume and than boost of 14 Gy to GTV) to 72 Gy of conventional fractionation delivered to "small" CTV without ENI.

Retrospectively 34 patients were evaluated. For each patient digitally reconstructed radiographs (DRRs) produced from volume CT image were used as substitute of conventional radiographs for traditional 2D RT plans (Perez et al) (13). These plans were created by experienced radiation therapist and medical physicist. For the same patients target volumes were delineated by the team of diagnostic radiologist and different radiotherapist. The dose matrix of conventional RT plan was than combined with volumetric PTV and than adequacy of target coverage was estimated for each patient. The volumes of 95% isodose, mean and minimum target doses were chosen as simple parameters for this evaluation. The mean lung dose and volume of normal lung receiving dose above 30 Gy (V30) were chosen as parameters for lung complication probability estimation.

Next step was creation of 3D conformal radiotherapy plans for these patients according to the approach early described. The maximum possible total dose to the target was estimated as dose to the target, which does not exceed the lung complication probability of correspondent 2D plan.

Results and discussion

Out of 34 patients included in this study – stage I–II lung cancer, 23 patients (68%) were treated with ENI and 11 patients (32%) were treated according to the scheme without ENI. Below are demonstrated two representative cases of these respective patients groups.

First example is the typical case of inoperable lung tumor. The patient was referred to curative intend radiotherapy. Because of high risk of microscopic lymph nodes invasion the treatment was proceeded according to irradiation with ENI scheme. The outline in red (Fig. 1) shows large ENI volume to be irradiated up to 50–54 Gy of total dose, which is minimum necessary dose to likely eradicate the positive lymph node metastases. The small volume in green (CTV and PTV) inside of large red volume is tumor volume to be irradiated to the higher (boost) dose.

2D treatment plan was created according to the "gold standard" conventional clinical practice (13) based on DRRs as substitute for simulator radiographs. 8MV X-rays were used for this treatment. Posterior-anterior (PA) radiation field was tilted by 20 degree to spare as much as possible of the spinal cord; wedge was used for anterior-posterior (AP) field to produce homogeneous dose distribution through out irradiated volume. Customized blocks were used to avoid unnecessary lung irradiation. As a second stage, the CTV was "blindly" outlined by a different radiation oncologist. This CTV was overlaid with isodose distribution for 2D treatment plan. Unfortunately, the target coverage was poor for this plan, which is clearly seen on the CTV isodose surface color wash (Fig. 2).

Part of the target volume was not included in the radiation field at all. Therefore, only 58% of the CTV has received 95% of the prescribed dose; mean target

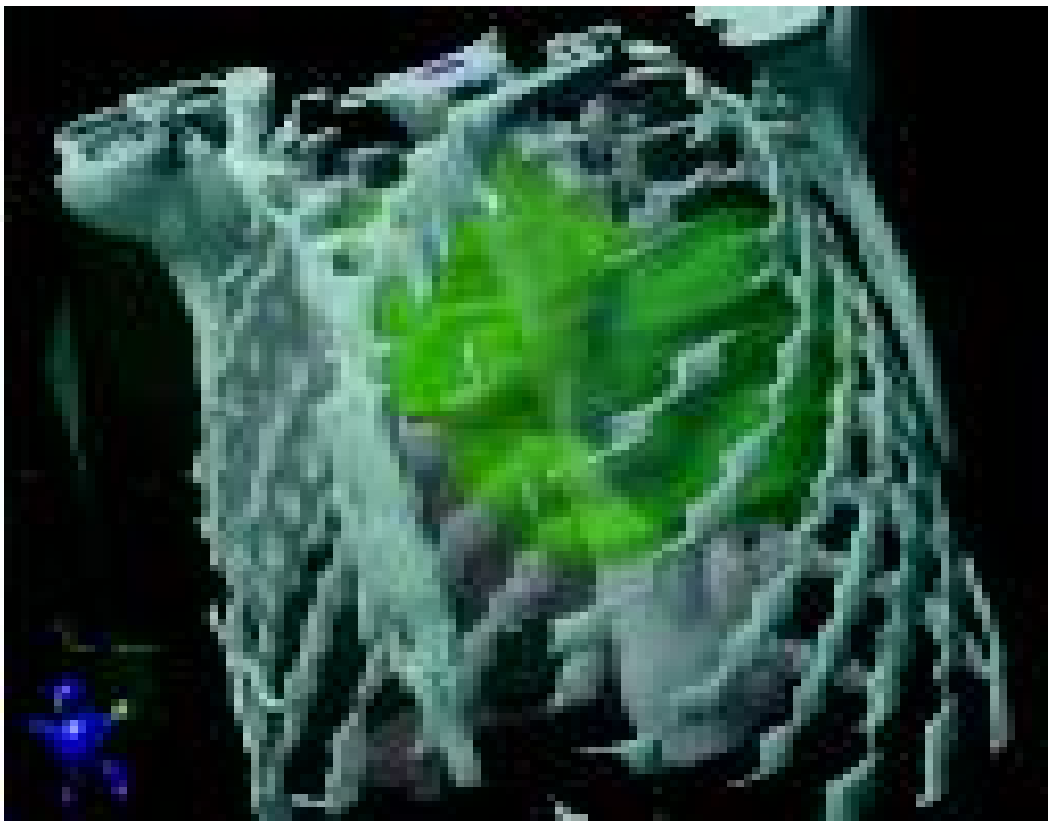

Fig. 1. **Clinical target volume and clinical target volume boost for patient irradiation with ENI (CTV is shown in red and CTV boost is shown in green)**

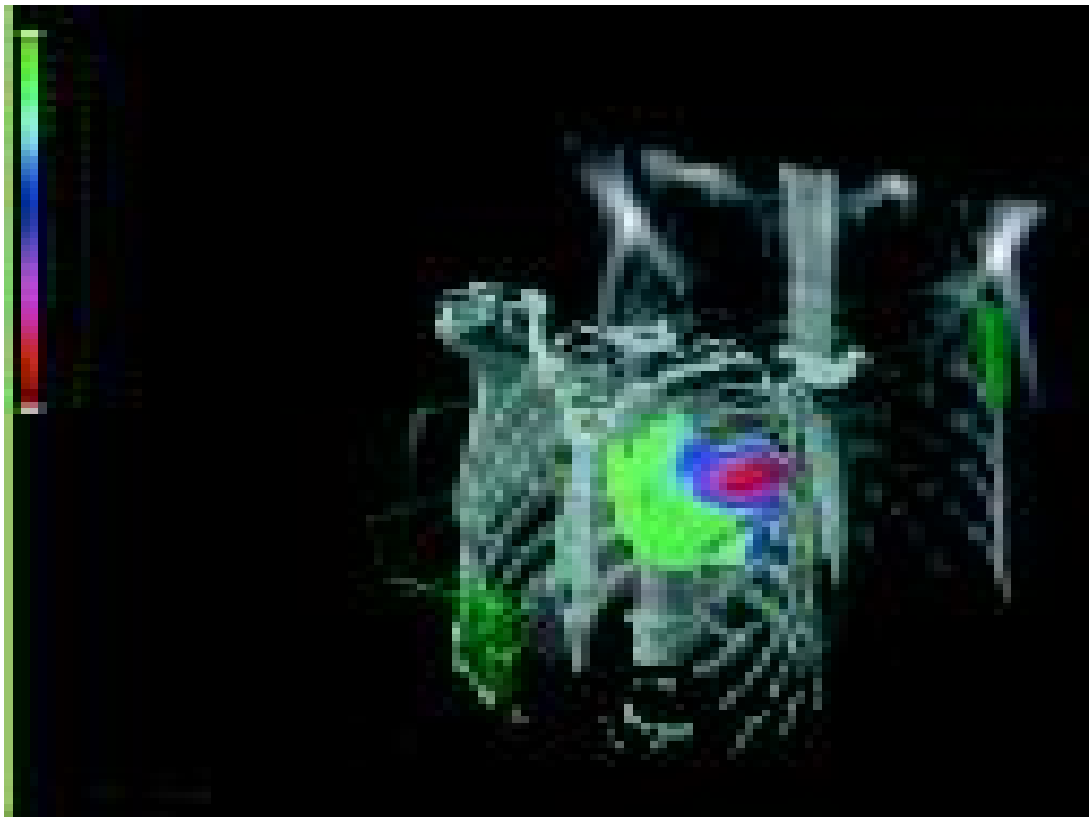

Fig. 2. **Clinical target volume with ENI isodose surface color wash for 2D conventional treatment plan**

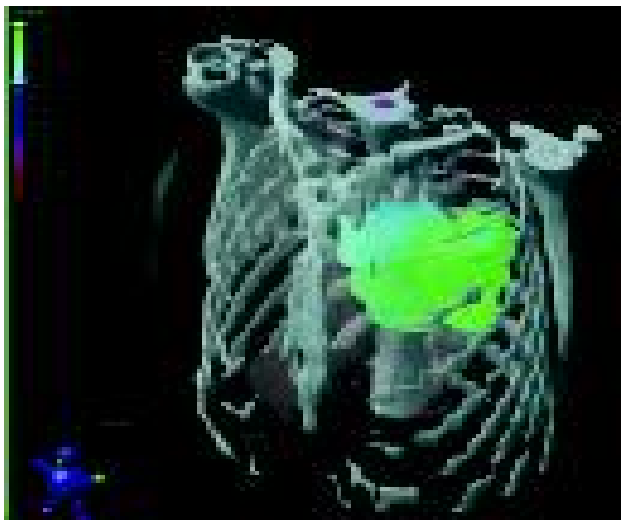

Fig. 3. **Clinical target volume with ENI isodose surface color wash for 3DCRT treatment plan**

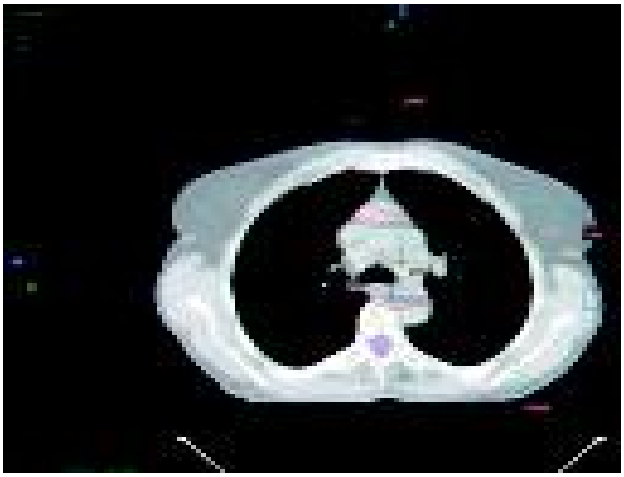

Fig. 6. **Field arrangement and isodose distribution for 3DCRT plan. Irradiation without ENI**

Fig. 4. **2D conventional treatment plan for the irradiation of clinical target volume without ENI (CTV is shown in red)**

dose was 89% and minimum target dose was only 5%. It is apparent that the main total dose-limiting factor for conventional plans is the dose to the spinal cord. In this case, it was 85% from the dose prescribed to the ICRU point. Therefore, it was possible to deliver maximum of 54 Gy in 2 Gy fractions to the prescription point.

The calculated mean lung dose for this plan was 21% (11.3Gy) and V30 was 16%, which was quite acceptable. Probability of grade II radiation pneumonitis should not exceed 5% level.

3DCRT plan produced for this patient allows to deliver 95% of 54 Gy prescribed dose to 100% of CTV with maximum dose of 104.3% and consequent boost to the GTV up to 70Gy of total dose. The dose to the spinal cord is still kept within 46 Gy and V30 for lung is 21%. The illustration of the CTV (volume with EN) and GTV (boost volume) coverage is presented in Fig. 3.

The next presented case is typical for 32% of the evaluated patients. For these patients the CTV was defined as GTV with correspondent safety margin. Normally, this CTV is considerably smaller than CTV with elective nodes. For such cases, traditional 2D planning is still limited by presence of spinal cord in the radiation fields for centrally located tumors and by the volume of lungs irradiated for peripheral tumors. The highest achievable prescribed dose in this case for 2D planning and field arrangement is around 60 Gy. The CTV (in red), a beams configuration and dose distribution for selected patient is shown in Fig. 4.

The 95% isodose surface covers only 61% of the outlined by independent radiotherapist CTV. The minimum target dose was 58% and mean target dose was 96%. The dose to the spinal cord was below 46 Gy. For the lung V30 was 21% and mean lung dose was 24% (14.4 Gy) of the prescribed dose. The correspondent dose volume histograms (DVH) of CTV (red), spinal cord (light blue) and lungs (dark blue) are presented in Fig. 5.

The fields arrangement and dose distribution of 3DCRT plan for this patient is shown in Fig. 6.

For this plan 95% isodose surface covers 95% of the CTV. The minimum target dose was 78.5% and mean target dose was 100.2% with maximum being 104.4%. It was possible to increase prescribed dose up to 88Gy for this patient. The maximum dose to the spinal cord was 48 Gy and V30 for lung was only 16%. The corresponding DVH for CTV (red), spinal cord (light blue) and lungs (dark blue) are shown in Fig. 7.

Retrospective statistical evaluation of 2D conventional treatment plans (see Table 1) for lung patients reveals that all patients can be distinguished according to the maximum possible prescribed to the target dose ($p=0.014$; 95% confidence interval being 0.85–0.98) in two groups: lower lung tumors and middle-upper lung tumors. The maximum achievable target dose is in average 52 Gy (3 Gy 1SD) for the massive tumors located in the lower lung. The CTV coverage was poor for most of these plans; 95% prescribed isodose surface covers only 57% of the CTV. Surprisingly this percentage was very consistent with 1SD of 10%. Consequently, the minimum target dose was low – 5–10% of the prescribed dose. Analysis of 2D conventional treatment plans for irradiation of smaller tumor volumes located in the middle and upper lung shows somewhat better result. The average achievable target dose was 59 Gy with 5 Gy of 1SD. Target coverage was marginally better; 95% isodose surface covered in average 63% of CTV with large 1SD of 17%.

Some investigators (10) concluded that the dose required to achieve 50% of lung tumor control probability (TCP) at three years is in order of 85 Gy. However, considering the fact that TCP parameters in most studies are based on conventional radiotherapy clinical experience, where the origins of recurrence either in or outside of radiation field were not well documented, these conclusions are very questionable. This study shows that inadequate target coverage (not the low prescribed dose) is the main reason for failures

Table 1. **Dose parameters related to the conventional 2D treatment planning for lung cancer patients. Maximum possible prescribed dose estimation is based on spinal cord dose limited by 48 Gy and volume of lung receiving more than 30Gy (V30) limited by 22%**

Patients' groups	Number of patients	Average CTV coverage (95% isosurface)	Average minimum dose for CTV	Average maximum prescription dose to CTV
Lower lung tumors	16 (47%)	57%	8.7%	52 Gy
Middle and upper lung tumors	18 (53%)	63%	12%	59 Gy

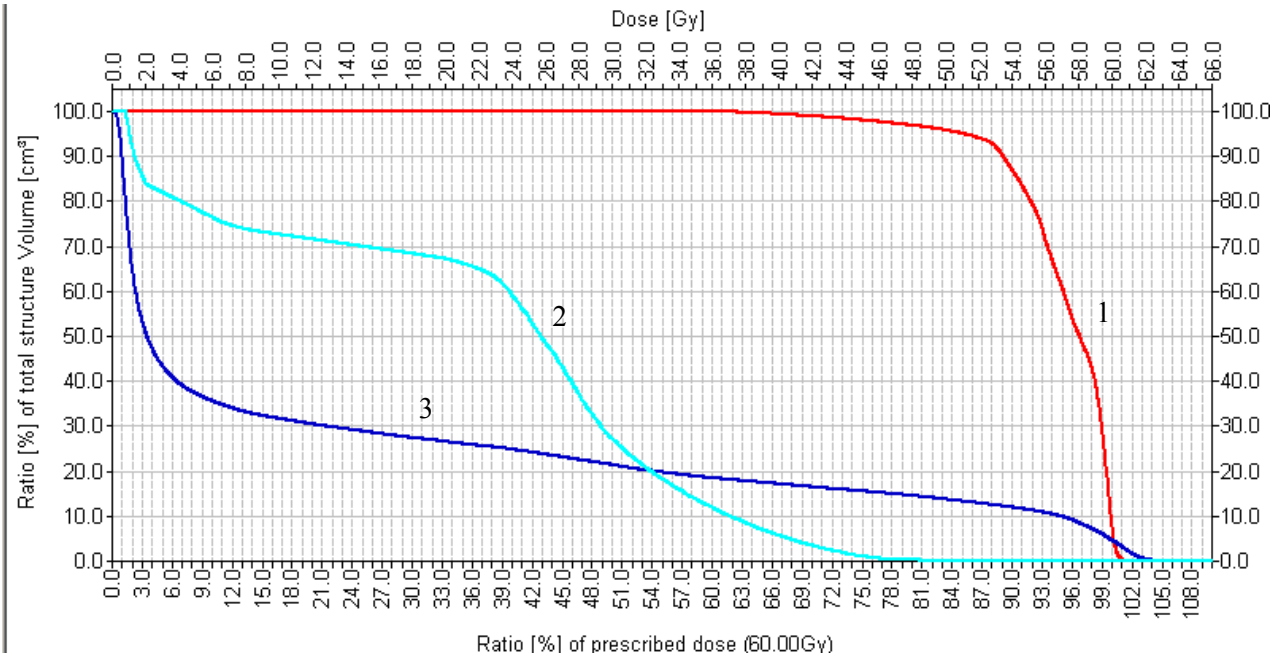

Fig. 5. **Dose volume histograms of CTV and critical structures for 2D treatment plan of CTV without ENI irradiation (DVH of CTV-line 1, of spinal cord-line 2 and of lungs-line 3)**

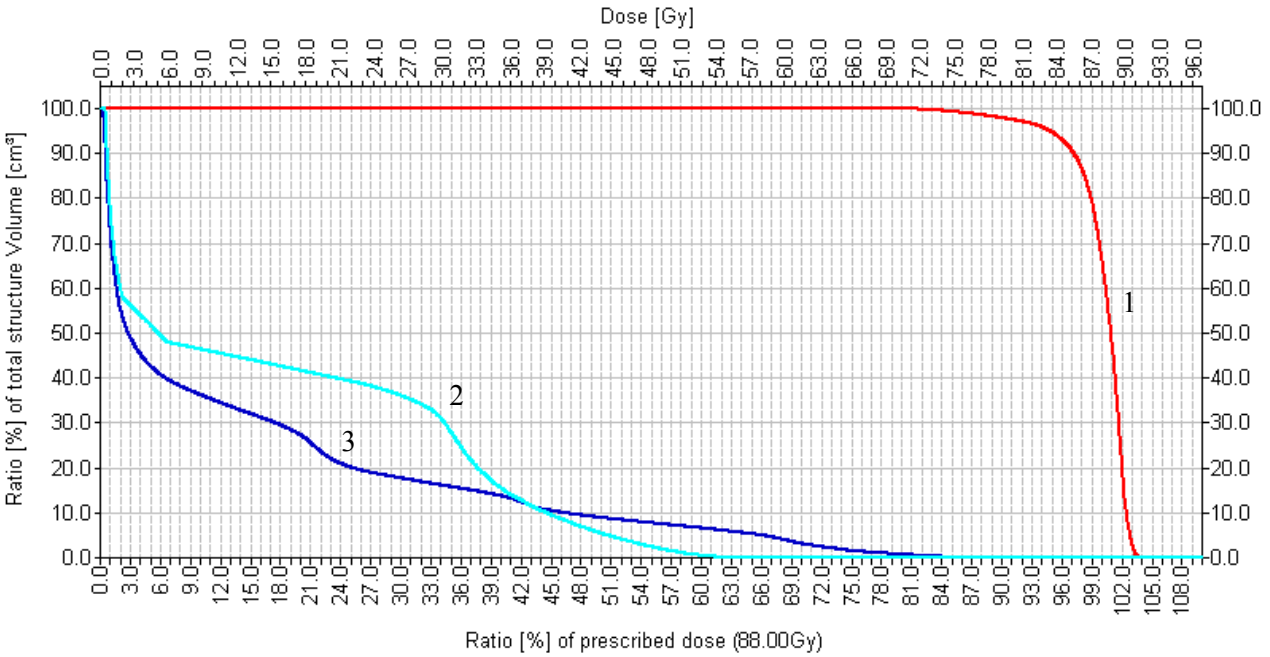

Fig. 7. **DVH of CTV without ENI and critical structures for 3DCRT treatment plan (DVH of CTV-line 1, of spinal cord-line 2 and of lungs-line 3)**

in conventional 2D radiotherapy of lung tumors.

Precise, conformal methods of dose planning and delivery produce dose distributions such as to keep doses to the critical organs (lungs and spinal cord) well below tolerance levels and at the same time to increase dose to the target volumes. The 3DCRT allow increasing prescribed dose to the CTV with ENI up 68–72 Gy and to the CTV without ENI up to 78–90 Gy (Table 2). The conformity of CTV volume coverage was acceptable for all patients; 95% isodose surface covered in average at least 95% of the CTV volume. The maximum dose always located inside of CTV volume and did not exceed 105% of the prescribed dose.

Table 2. **Dose parameters for 3DCRT planning of lung patients. Maximum possible prescribed dose estimation is based on spinal cord dose limited by 48 Gy and volume of lung receiving more than 30Gy (V30) limited by 22%**

Patients' groups	Number of patients	Average CTV coverage (95% isosurface)	Average minimum dose for CTV	Average maximum prescription dose to CTV
CTV with ENI	23(68%)	96%	81%	69 Gy
CTV_{tumor}		93%	72%	52 Gy
$CTV_{limph\ nodes}$				
CTV without ENI	11(32%)	96%	84%	83 Gy

Conclusion

In conclusion, it can be pointed out that careful planning of 3DCRT allow to increase total dose to the target while keeping dose to the functional tissues within the tolerance for most of the lung cancer patients. However, probably, most important is the fact that only combinations of modern imaging, planning and delivery techniques enable to provide adequate and homogeneous clinical target volume coverage with therapeutically significant dose for lung tumors. The previous clinical radiation therapy experience and results should be applied for the designing of new clinical protocols for 3DCRT and intensity modulated radiotherapy treatments of lung cancer with very careful consideration.

Dozės padengimo įvertinimas plaučių vėžio spindulinėje terapijoje

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Raktažodžiai: plaučių vėžys, konforminė radioterapija, taikinys.

Santrauka. *Darbo tikslas* – įvertinti dviejų ir trijų dimencijų konforminės radioterapijos galimybes padidinti dozę į taikinį ir pagerinti jos homogeniškumą neviršijant plaučių audinio toleravimo ribos.

Medžiaga ir metodai. Analizuoti 34 plaučių vėžiu sergantys pacientai, kuriems skirta radikali dviejų dimencijų spindulinė terapija. Viena specialistų grupė atliko dviejų dimencijų spindulinio gydymo planavimą pagal „auksinį standartą". Kita nepriklausoma specialistų grupė apibrėžė to paties ligonio klinikinį taikinio tūrį trijų dimencijų planavimo sistemoje. Abu planai buvo „uždėti" vienas ant kito ir įvertintas taikinio dozės dydžio adekvatumas. Apskaičuota maksimali pasiekiama suminė dozė išlaikant normalių audinių pažeidimo tikimybės parametrus tame pačiame lygmenyje bei vertinamas tikslumo pagerėjimas.

Rezultatai. Planuojant dviejų dimencijų metodika, maksimali pasiekiama dozė į taikinį vidutiniškai yra 52 Gy (su 3 Gy 1 standartiniu nuokrypiu). Dauguma šių planų klinikinio tūrio dozės dydis buvo nepakankamas, nes 95 proc. paskirtoji izodozė apėmė tik 57–63 proc. klinikinio taikinio tūrio. Minimali dozė į taikinį buvo maža – 5–10 proc. nuo paskirtos dozės. Trijų dimencijų konforminė radioterapija įgalina padidinti skiriamą dozę į klinikinį taikinio tūrį su elektyvinių limfmazgių apšvita iki 68–72 Gy ir į klinikinį taikinio turį be elektyvinių limfmazgių apšvitos iki 78–90 Gy. Klinikinio taikinio tūrio dozės dydžio tikslumas buvo priimtinas visiems ligoniams; 95 proc. izodozės paviršius apimtas mažiausiai 95 proc. klinikinio taikinio tūrio.

Išvada. Daugumai plaučių vėžiu sergančių ligonių trijų dimencijų konforminis radioterapijos planavimas įgalina padidinti suminę dozę į taikinį, o normaliems audiniams išlaikyti toleruojamą dozę. Gydant plaučių navikus, tik derinant šiuolaikinę modernią radiodiagnostiką, planavimą ir apšvitos metodiką, galima adekvačiai ir homogeniškai apimti klinikinio taikinio tūrį terapiškai pagrįsta doze.

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