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Critical Normal Structures Doses for Non Small Cell Lung Cancer using 3-D Conformal Radiotherapy

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Abstract

Purpose: In this prospective study, we have aimed to analyze the levels of doses and toxicities of critical normal structures in the treatment of non-small cell lung cancer (NSCLC) with 3-D Conformal Radiotherapy.

Material and Method: We have evaluated 24 patients with biopsy proven inoperable NSCLC stages III, treated with Conformal Radiotherapy. After CT- simulation, GTV, CTV, PTV and critical normal structures (lungs, esophagus, heart, and spinal cord) were contoured by the physician and radiologist and then dose volumes were calculated. Chemoradiotherapy was used in these patients after induction treatment. Induction chemotherapy was administrated: Docetaxe l75 mg/m² + Cisplatin 75 mg/m² from day 1 for each 21 days, total 3 cycles. After induction therapy concomitant Docetaxel 25 mg/m² + Cisplatin 25 mg/m² were administrated weekly for 5 to 6 weeks and radiotherapy was delivered with linear accelerator, 64 – 66 Gy/32 – 33 fr/200 cGy/d. The study endpoints were critical normal structures doses, early and late toxicities, and local control.

Results: DVH: Lungs V20 is 32%. Heart Dmean doses are 1892 cGy (Dmin 22 cGy - Dmax. 4084 cGy). Esophagus Dmean doses are 2700 cGy (Dmin. 912 cGy - Dmax. 4513 cGy) and Spinal cord Dmean is 1201 cGy (Dmin. 115 cGy - Dmax. 2139 cGy).

Acute toxicities; 18 patients (75%) have grade I-II esophagitis, 6 patients (25%) have grade III esohagitis, 7 patients (29%) have grade III-IV pneumonia and 4 patients (16,6 %) have grade I-II pneumonia. No late toxicity has been observed in esophagus, heart and even lungs. Median follow-up was 13 months and local control rate was 41.6%.

Conclusion: This study confirms that 3-D Conformal Radiotherapy is an effective treatment with NSCLC. But patients in the study have large tumors or tumors near critical locations, so critical normal structures doses were high compared with literature.

Keywords: 3-D Conformal Radiotherapy; Non small cell lung cancer; Dose to critical normal structures; toxicities

Introduction

Lung cancer is the most common cancer in the world. For patients with inoperable, locoregionally advanced non-small cell lung cancer (NSCLC), the prognosis is poor. Management of NSCLC remains one of the major challenges for radiotherapy. Despite various efforts during the past few decades, local control and overall survival after radiotherapy remains poor. More than one-third of patients with NSCLC have locally advanced, or surgically unrespectable disease on diagnosis. Since the primary tumor and lymph node metastases spread in close proximity to critical normal structures the prescription dose has been limited 60-70 Gy [1,2]. Different strategies to improve outcome of patients with advanced NSCLC after radiotherapy have been studied including modified fractionation, integration of chemotherapy, molecular targeting and escalation of radiation dose [3,4,5]. Radiation dose escalation is based on the clinical observation of the relationship between total radiation dose to the tumor, local control and survival. In several clinical trials dose escalation using three-dimensional conformal radiotherapy appeared feasible, leading to favorable outcomes [6,7,8]. However, lung, esophagus, medulla spinals and heart toxicity in particular remain a major obstacle for dose escalation as well as for intensified chemoradiotherapy in advanced NSCLC [9,10]. Consequently reducing the radiation dose surrounding normal tissues without compromising tumor coverage is the ideal.

In our study, clinic effectiveness and normal organ toxicities of 3-D conformal radiotherapy for stage III NSCLC was reported and the relationship between dose and volume was analyzed..

Patients and Methods

Patient's characteristics

A total of 24 patients with stage III were selected for this study; we used CT thorax scans of 24 patients that were treated for lung cancer in our institute. Karnofsky performance status (KPS) has been between 70 and 100. The median age was 58 years (range 42-78). All patients had received previous induction chemotherapy. Taxotere 75 mg/m² and Cisplatin 75 mg/m² were administrated, from day 1 for each 21 days, total 3 cycles. After induction therapy concomitant Taxotere 25 mg/m² and Cisplatin 25 mg/m² were administrated weekly during the radiotherapy. The disease characteristics are listed in Table 1.

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Radiotherapy treatment planning and dose calculation algorithms

Patients were placed in supine position with arms above their head and were immobilized using a wing, device to improve the reproducibility of the setup. Each patients was scanned by using 5 mm slice spaced Computed Tomography.

CT scan based treatment plans were designed on the treatment planning system XiO 4.3. (CMS-Germany). The objective of the treatment planning procedure was to achieve dose conformance around the PTV and minimize dose in the critical structures. Target volumes and normal organs (esophagus, spinal cord, heart - atriums and ventricles and both lungs) were delineated out on each slice by radiotherapist and radiologist.

All the treatments were delivered with 6 or 15 MV photon; patients were scheduled to receive 64-66 Gy/32-33 fraction/2.0Gy/day. Faz I 46 Gy was given for primary tumor and involved lymph nodes and then Faz II treatment reduced volume (spinal cord was spared). The gross tumor volume (GTV) of the primary tumor and the nodes was delineated based on CT data. The clinical target volume (CTV) was defined as the GTV plus 0.5 cm magrin. Also 15 mm isotropic 3D margin was added for the PTV.

All the treatments planning were normalized to the ICRU reference point (Figure1,2,3).

Evaluation

Toxicity was graded based on the Radiation Therapy Oncology Group (RTOG) criteria for esophageal and pulmonary or cardiac toxicity. Physical examination, KPS, CT, Echocardiography or PET scans for tumor response were monitored at 4 weeks after treatment and then every 3 months for first years, and every 4 to 6 months thereafter. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG); Radiation pneumonitis grade I- mildly symptomatic, but does not require steroids , grade II- moderately symptomatic, and requires steroids, grade III- severely symptomatic, requiring supplemental O_2, grade IV- Life threatening, requiring assisted ventilation, grade V- Causing death. RTOG - Acute esophagitis grade I- mild dysphagia or odynophagia; may require topical anesthetic, non-narcotic agents, or soft diet, grade II- moderate dysphagia or odynophagia; may require narcotic agents or puree/liquid diet, grade III- severe dysphagia or odynophagia with dehydration or weight loss (>15%) requiring

Characteristics	No of patients	%
Age		
Median (range)	58 (42-78)	
<65	18	75
>65	6	25
Gender		
Male	22	91.6
Female	2	8.3
Stage		
IIIA	10	41.6
IIIB	14	58.3
T stage		
T1	4	16.6
T2	7	29.1
T3	9	37.5
T4	4	16.6
N stage		
N1	3	12.5
N2	10	41.6
N3	11	45.8
Histology		
Adenocarcinoma	4	16.6
Squamous cell	19	79.1
Large cell carcinoma	1	4.1
Karnofsky Performance Status (KPS)		
70-80	9	37.5
90-100	15	62.5

Table 1: Patients Characteristics.

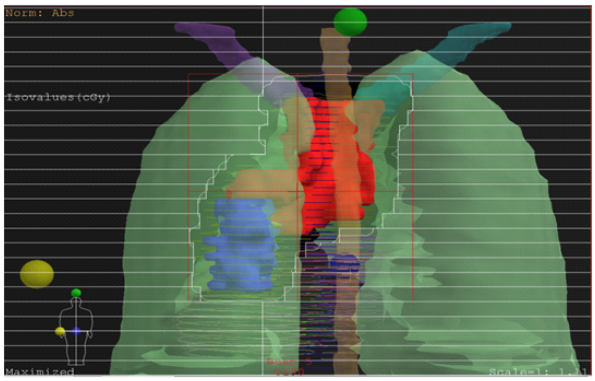

Figure 1: Three dimensional treatment planning for a patient with lung cancer.

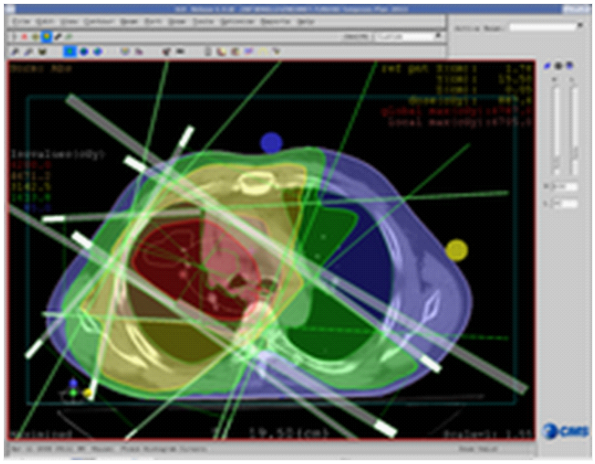

Figure 2: The dose distrubitions for 3-D CRT.

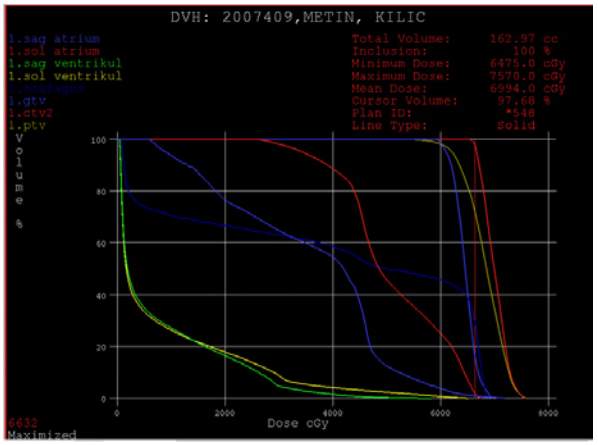

Figure 3: Dose Volume Histogram (DVH).

	Heart Dmean (cGy)	Heart V30 (%)	Left atr. Dmean.(cGy)	Right atr. Dmean (cGy)	Left vent. Dmean (cGy)	Right. vent. D-mean (cGy)
Mean	1892	25	2988	1770	1542	1237
Min.	22	18	26	3	0	1
Max.	4084	57	5850	6128	4629	3925

Table 2: Heart Dose Parameters.

	Pneumonitis n (%)	Esophagitis n (%)	Cardiac Toxicities n (%)
Grade 1	-	8 (33%)	-
Grade 2	4 (16.6%)	10 (41.6%)	-
Grade 3	7 (29%)	6 (25%)	-
Grade 4	-	-	-

Table 3: Radiation Toxicities

nasogastric feeding tube, I V fluids, or hyperalimentation, grade IV - complete obstruction, ulceration, perforation, or fistula.

Statistical analysis

Normal tissue doses for lung, heart, esophagus, and spinal cord was calculated.

Data were analyzed using the software from Statistical Package for Social Science (SPSS 12).

Results

Median follow up was 13 months. After induction chemotherapy leading to a partial response in 9 patients (37.5%), 1 patient (4%) had minimal response. There is no progression of the tumor. After one month of the radiotherapy, 10 patients (41.6%) were complete tumor responsive.

Considering dose Volume Histograms (Figure 3).

The median of Lungs V20 is 32% (range 28%-36%) and V30 is 28% (range 25%-32%).

Heart doses; Dmean for heart is 1892 cGy (Dmin 22 cGy - Dmax. 4084 cGy) and V30 is 25% (range 18% - 57%) calculated.

For Right atrium doses; Dmean is 1770 cGy (Dmin. 3 cGy – Dmax. 6128 cGy), Left atrium doses is Dmean 2988 cGy (Dmin. 26 cGy - Dmax. 5850 cGy), Right ventricular Dmean is 1237 cGy (Dmin. 1 cGy – Dmax. 3925 cGy), Left ventricul Dmean is 1542 cGy (Dmin. 0 – Dmax. 4629). Heart doses were shown in Table 2.

Esophagus Dmean doses is 2700 cGy (Dmin. 912 cGy – Dmax. 4513 cGy) and Spinal cord Dmean is 1201 cGy (Dmin. 115 cGy – Dmax. 2139 cGy).

Treatment related toxicity is summarized in Table 3. There were no treatment related deaths. Seven patients required steroid treatment and oxygen administration for grade III radiation pneumonitis which is determined by Thorax CT.

Discussion

In this study 3-D Conformal Radiotherapy techniques for the treatment of advanced stage NSCLC were analyzed. We focused on the question of whether it is possible to protect normal structures with this technique.

Conventional radiotherapy alone resulted in a median survival of 10 months and a 5 year survival of 5% [11]. To improve local control and survival, led the investigators to pursue additional strategies, including concurrent cisplatin-based chemotherapy with RT, new chemotherapeutic agents combined with RT or conformal RT.

Concurrent chemoradiation has become the standard of care since 2001. It is important to note that toxicity is significantly greater with concurrent chemotherapy.

In RTOG 9410, the locoregional failure after concurrent chemoradiotherapy was still around 34% to 43%. To improve the local control rate, Lee et al. [12] and Socinski et al. [13] conducted a phase I/II dose escalation clinical trial using high-dose 3DCRT (60 to 74 Gy) for inoperable stage IIIA/IIIB NSCLC with induction chemotherapy followed by concurrent chemoradiotherapy. They reported a 3 year survival rate of 36% and a 13% locoregional relapse rate as the only site of failure. For patients who finished radiotherapy, the 3 year survival rate was 45%. No grade III or above lung toxicities were reported; 8% of the patients developed grade III/IV esophagitis. In our study, our patient was given concurrent chemoradiotherapy with cisplatin and docetaxel. Acute toxicities with grade III pneumonitis were seen in 7 (29%) patients and grade III esophagitis was seen in 6 (25%) patients. Because of patients in the study have large tumors or tumors near critical locations, so critical normal structures doses were high compared with literature.

The most commonly used chemoradiation combination includes cisplatin, carboplatin, docetaxel and paclitaxel. The reported grade III to IV esophagitis and pneumonitis rates approach 26% to 46% and 17% to 22%, respectively, when chemotherapy is used concurrently with RT [14,15].

3DCRT has several significant advantages: tumor and normal tissue delineation, image segmentation and display, accurate dose calculation, and the ability to manipulate beam geometry. The importance of improved target delineation cannot be overemphasized. Once patients are immobilized and given a CT scan in the treatment position, the radiation oncologist can delineate the tumor and adjacent tissues in three dimensions, choose beam angles to maximize tumor coverage and/or minimize normal tissues treated [16].

The International Commission on Radiation Units Report No.50 guidelines [17] for defining targets has been applied to the treatment of lung cancer. The GTV is the primary tumor and any grossly involved lymph nodes. The clinical tumor volume is the anatomically defined area thought to harbor micrometastasis (hilar or mediastinal lymph nodes or a margin around the grossly visible disease). The PTV accounts for physiologic organ motion during treatment and the inaccuracies of daily setup in fractionated therapy. In our study, the gross tumor volume (GTV) of the primary tumor and the nodes was delineated based on CT data. The clinical target volume (CTV) was defined as the GTV+0.5 cm margin. Also 15 mm isotropic 3D margin was added for the PTV. Faz I; treated volume is GTV +2 cm, and Faz II; treated volume is GTV +1 cm.

It is extremely important not to exceed the maximum doses tolerated by sensitive and intrathoracic structures such as the lung, spinal cord, and heart. Dose-volume histograms (DVHs) for all normal organs in the chest are evaluated for dose and volume of irradiation. DVH analysis still is being developed, but preliminary results indicate that it can predict the development of complications such as pneumonitis and lead to improved and more objective treatment planning [18,19].

The objective of our treatment planning procedure was to achieve dose conformance around the PTV and minimize dose in the critical structures. Target volumes and normal organs (esophagus, spinal cord, heart - atriums and ventricles and both lungs) were delineated out on each slice.

All the treatments were delivered with 6 or 15 MV photons. All the treatments planning were normalized to the ICRU reference point.

Radiation-induced toxic effects in normal tissue are related to both dose and volume. In addition, the spatial arrangement of the functional subunits in the normal tissue is also critical.

The most important complications of radiotherapy in lung cancer are toxicity of the lung and esophagus.

Radiation-induced pneumonitis usually occurs after completion of radiotherapy, peaks at 2 months, and is stabilized or resolved around 6 to 12 months. It can be treated with corticosteroids such as prednisone 20 to 60 mg/day. Lung fibrosis occurs a few months after radiation and becomes chronic. Emerging clinical data based on 3DCRT in lung cancer have shown that mean lung dose (MLD), V5, V13, V20, and V30 are correlated with radiation lung injury. Graham recommended a cut-point of V20 Gy at 40% with radiotherapy alone, at which 36% of patients developed grade II and above pneumonitis. He also reported that a total MLD of 20 Gy and above is associated with 24% grade II and above pneumonitis. In this study; MLD was 1762 cGy and associted with 24.9% grade II and above pneuomonitis.

Yorke et al. [20] reported that grade III and above pneumonitis correlated well with the MLD and V20. At MLD of 20 Gy, about 28% patients developed grade III and above pneumonitis.

Our data showed that 7 patients who have grade III-IV pneumonia required steroid treatment and oxygen administration and 4 patients have grade I-II pneumonia. DVH analysis indicated that for lungs V20 is 32% (range 28% - 36%), V30 is 28% (range 25% - 32%), which correlated with radiation lung injury.

The radiotherapy of thoracic malignancies often exposes the esophagus to high levels of ionizing radiation. After 2 to 3 weeks of conventionally fractionated radiotherapy, patients often complain of dysphagia and/or odynophagia that usually worsen toward the end of radiotherapy and peaks at the first week after completion of radiotherapy. This acute reaction to radiation can cause significant morbidity from dehydration and weight loss that can lead to treatment interruptions. The late reactions of the esophagus to radiation generally involve fibrosis of the organ that can lead to strictures. Patients may experience various degrees of dysphagia and may require endoscopic dilation. As with the acute reaction, rare cases may involve perforation or fistula formation.

The clinical and dosimetric predictors of acute and late esophagitis have become particularly important in the era of radiation dose escalation and concurrent chemoradiotherapy. Emami et al. [21] have reported that TD5/5, TD50/5 values in two-dimensional radiotherapy for stricture and perforation of the esophagus are 60 and 72 Gy in one-third of volume, respectively. Emerging clinical data based on 3DCRT indicated that, in general, the tolerance of the esophagus is around 60 Gy; however, the volume (particularly the length of circumference involvement) is very crucial. Singh et al. [22] reported that the threshold maximal esophageal point dose for grade 3-5 esophagitis was 58 Gy when concurrent chemoradiotherapy was given. The esophageal surface area receiving ≥55 Gy, the esophageal volume receiving ≥60 Gy (V60), and the use of concurrent chemotherapy were the most statistically significant predictive factors for acute esophagitis [23]. For late toxicity, the length of the 100% of the circumference receiving ≥50 Gy (V50) percentage of surface area treated with ≥50 Gy, and maximal percentage of circumference ≥60 Gy are predictive for all grades of late toxicity [24]. It should be noted that acute esophagitis (grade II/III) is correlated significantly with V40 to V70 [25]. In clinical practice, it is hard to avoid esophagitis totally when the target volume is close to the esophagus. Attention should be paid to minimize grade III and above toxicity.

In our study mean esophagus doses was 2700 cGy (range 912 - 4513) associated with 74% grade 1-2 toxicity, and 25% grade 3 toxicity.

Owing to the reduction of field than extensive field radiotherapy, there is a decreased chance of esophagitis, pneumonitis and lung fibrosis [26].

Information on radiation injuries following whole heart radiation come mostly from patients with Hodgkin's disease whereas partial volume information is mainly derived from patients treated post-operatively for breast cancer [27,28]. Early-stage breast cancer and Hodgkin's lymphoma have shown that, if the heart receives <30 Gy, cardiac complications are likely to be minimal. Emami et al, having reviewed available literature on normal tissue tolerance, suggest whole heart tolerance dose (TD) 5/5 of 40 Gy and 60 Gy for 1/3 of the volume [21]. TD 50/5 values are mostly speculative and have been extrapolated from TD 5/5 data but estimations show TD 50/5 70 Gy for one third of the heart and 50 Gy for whole heart [29]. However, it is often asymptomatic and of little clinical significance. A retrospective study from Velindre Hospital in Cardiff has also quantified doses of radiotherapy received by the heart during chemoradiation as well as assessing the effect on myocardial function. Mean cardiac doses and volume of heart receiving >70% of total dose were calculated from DVHs in 15 patients treated with chemoradiation in whom pre and post radiotherapy multiple gated acquisition scans were available. The median ejection fraction pre-treatment was 63% and the median drop was 11% of baseline function, which was statistically significant. Median radiation doses with and without shielding blocks was 27.4 Gy and 35 Gy. This difference was statistically significant. In the two phase technique 63.8% of the volume of heart received 70% or more of the total radiation dose. The use of a 3F technique throughout would have reduced the median cardiac dose to 22.7 Gy [29].

Cardiac toxicity is increasingly important to consider in the treatment of lung cancer, especially as patients also have risk factors of cardiac disease. Improvement of radiotherapy techniques used to treat lung cancer is necessary. Conformal planning should routinely be used in this group of patients with careful consideration to long-term toxicity.

In our study; Dmean for heart is 1892 cGy (Dmin 22 cGy - Dmax. 4084 cGy). It is limited by normal tissue tolerance. In order to decrease the volume of irradiated normal tissue, planning target volume may be reduced by minimizing the tumor movement or by using various

techniques like 3-D conformal Radiotherapy, IMRT, or Stereotactic radiotherapy [30,31]. Patients with small tumors or more central lesions may benefit from conformal radiotherapy without high doses and less toxicities for normal tissues.

In this report, doses of various critical organs; lungs, esophagus, heart-left and right atrium and ventricles, spinal cord were listed. The doses of normal tissues were found high when compared to available literature. These results were due to large tumor volumes and we couldn't spare normal tissues. Although the high levels of normal tissues, early and late toxicities were less.

Conclusion

Our results showed that 3-D Conformal Radiotherapy can improve target coverage and reduce the irritated volume of most critical structures (heart, lung, esophagus and spinal cord) especially small tumor volumes. This was our first application of conformal radiotherapy at our clinic, also the volumes of tumors sizes were large, resulting in higher toxicities than other observed values in current literature

However, target coverage for large T3 tumors while sparing crictical normal tissues is difficult, and toxicities for normal tissues will be high in advanced disease.

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