Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 1, pp. 138–142, 2006
Copyright © 2006 Elsevier Inc.
Printed in the USA. All rights reserved
0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.11.049

CLINICAL INVESTIGATION **Lung**

SPANISH PATTERNS OF CARE FOR 3D RADIOTHERAPY IN NON–SMALL-CELL LUNG CANCER

Francesc Casas, Ph.D.,* Núria Viñolas, Ph.D.,† Alberto Sanchez-Reyes, Ph.D.,‡ Sandra Jorcano, M.D.,§ Isabel Planas, M.D.,§ Jordi Marruecos, M.D.,§ Francisco Pino, M.D.,§ Antoni Herreros, M.D.,§ and Albert Biete, Ph.D.§

*Radiation Oncology Department, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; †Medical Oncology Department, Hospital Clínic i Universitari, Barcelona, Spain; ‡Unitat de Radiofísica (CROC), Clínica Platón, Barcelona, Spain; and §Radiation Oncology Department, Hospital Clínic i Universitari, Barcelona, Spain

Purpose: Curative radiotherapy for non-small-cell lung cancer is a difficult challenge, despite the use of conformal radiotherapy. Optimal three-dimensional delineation of treatment volumes is essential for improvement of local control and for limiting of tissue toxicity.

Material and Methods: A planning course on clinical practice of lung cancer was held in Barcelona. A questionnaire was given concerning (*1*) patient positioning, (*2*) planning-computed tomography scan, (*3*) accounting for tumor mobility, (*4*) investigative-procedure respiration-gated radiotherapy and breath-holding maneuvers, (*5*) generation of target volumes, (*6*) treatment planning, and (*7*) treatment delivery. This questionnaire was made to determine the Spanish application of European recommendations.

Results: On the negative side, 1 hospital did not use three-dimensional tools, less than 50% used immobilization devices, and 55.6% used computed tomography slices of greater than 5 mm. On the positive side, 70.4% did not use standard margins for gross target volume derived from a computed tomography scan, 92.6% agreed with the inclusion of Naruke anatomic criteria of 1 cm or more in gross target volume planning, and 75% used V20 to estimate the risk of pneumonitis.

Conclusions: This study is the first validation of European recommendations for treatment planning and execution of radiotherapy in lung cancer. The main conclusion is the need to improve the negative aspects determined.
© 2006 Elsevier Inc.

Lung cancer, External radiotherapy, 3D planning.

INTRODUCTION

Radical radiotherapy for non–small-cell lung cancer (NSCLC) continues to be a clinical challenge because of the limitation of both local control and survival. Nonetheless, randomized studies that used hyperfractionation (1) or radiochemotherapy (2) have shown an increase in survival, albeit with a greater toxicity in surrounding tissue (3). This toxicity may be caused by the planning and administration of two-dimensional (2D) radiotherapy (RT), which has been used since the late 1980s. This 2D technique seems to have limitations, such as errors in target-volume coverage, which may be found in up to 15% of the patients (4).

Recent advances in both imaging and treatment delivery have led to significant improvements in techniques for conformal radiotherapy of lung cancer (LC) (5). Thus, the use of three-dimensional (3D) planning is essential to adequately define the target volume required to improve local control and, at the same time, limit normal-tissue toxicity.

Nonetheless, generalized use of these technical advances has been slow, as demonstrated in different studies (6, 7). However, guidelines for unification of the criteria for the planning and radiotherapeutic treatment of NSCLC have recently been presented in the United States (8) and Europe (9).

During the course of clinical practice in the treatment of LC, held in Barcelona in April 2004, aimed at Spanish radiation oncologists with experience in this field, we developed a survey that focused on analysis of the patterns of planning treatment, on the basis of on available European recommendations. A questionnaire was given to Spanish radiation oncologists to evaluate clinical practice and compare the data obtained with that from other countries.

Reprint requests to: Francesc Casas, Ph.D., Radiation Oncology Department, Hospital Clínic i Universitari, Villarroel 170, 08036 Barcelona, Spain. Tel: (+34) 93-227-5580; Fax: (+34) 93-227-5542; E-mail: fcasas@clinic.ub.es

This work was supported in part by Instituto de Salud Carlos III, Red Temática del Cáncer C03/10.

Received July 25, 2005, and in revised form Oct 13, 2005. Accepted Nov 23, 2005.

METHODS AND MATERIALS

A 7-issue, self-adapted questionnaire was developed from the summary of the recommendations for high-precision radiotherapy in LC from European literature–based recommendations (9). The European recommendations were modified from a statement form to that of a question form. Responders were asked to complete the questionnaires regarding these treatment techniques and to return the questionnaires before the beginning of the course. Response to the questionnaire was voluntary and the participants were informed that the aim of the survey was to determine the rate of compliance with the European recommendations on 3D planning in NSCLC in Spain.

The first issue in the questionnaire was related to patient positioning, specifically to the devices for arm support used, as well as the devices for patient immobilization.

The second issue had 4 questions on planning of computed tomography (CT) scans: (*1*) What kind of CT scan do you use? (*2*) Where do you preferably locate the treatment isocenter? (*3*) Do you use i.v. contrast for RT planning? (*4*) How thin are your CT slices?

The third issue concerned tumor mobility and was subdivided into 5 questions: (*1*) Do you use fluoroscopy for characterizing tumor mobility for 3D radiotherapy planning? (*2*) Do you apply standard margins for gross tumor volumes (GTVs) derived from a single rapid CT scan? (*3*) What margins do you add to any contoured mediastinal node to account for nodal mobility? (*4*) What margins do you use to derive a PTV from the GTV? (*5*) Do you apply any setup-correction protocol in the treatment unit?

The fourth issue was related to the use of investigative-procedure respiration-gated RT and breath-holding maneuvers.

The fifth issue was on the generation of volumes and had 5 questions: (*1*) What CT window setting do you use for contouring tumors in lung parenchyma? (*2*) What CT window settings do you use for contouring mediastinal nodes? (*3*) Taking the Naruke scheme for nodal stations into account, which short-axis node diameter do you include in radiotherapy planning? (*4*) Do you use elective nodal irradiation for any patient with localized NSCLC (Stages I–II), or does it depend on whether chemotherapy is or has been administered? (*5*) Do you use 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans to generate target volumes?

The sixth issue referred to treatment planning and was divided into 4 questions: (*1*) Do you use 3D radiotherapy in all cases (100%) of localized LC? (*2*) What margins are required for microscopic tumor extension in radiotherapy planning of NSCLC? (*3*) Do you use the V20 (volume of both lungs minus the planning target volume (PTV), which receives a dose of 20 Gy) to estimate the risk of radiation pneumonitis? (*4*) Do you contour the esophagus in your planning to reduce the incidence of toxicity?

The seventh and last issue included 2 questions on treatment implementation: (*1*) What setup-verification method do you use? (*2*) Which beam energies do you prefer in LC treatment?

RESULTS

The course was attended by 46 specialists (44 radiation and 2 medical oncologists) from 31 hospitals in 25 Spanish cities. A total of 28 questionnaires from these 44 radiation oncologists were completed. One hospital had 3D tools that were not yet used in LC planning. The radiation oncologist from this center answered some of the items on the questionnaire, but others he preferred not to answer. More than 1 answer was possible in a few of the questions. Below we provide subject-to-subject answers.

Patient positioning

Arm support devices were used on 46.4% of the cases, and only immobilization devices to immobilize the lower extremities were used on 7.1%. Both were implemented on 17.9% of cases, and none of these tools were used in 28.6% of the patients (Table 1).

Planning CT scan

In 63% of the cases, radiation oncologists used the spiral CT scan, and in 37% of the cases, they used single-slice CT scan. Treatment isocenters were located on simulator setup by 63% of the radiation oncologists, whereas 37% did so with CT scan. Intravenous contrast for RT planning was never used by 81.5%, was always used by 11.1%, and was sometimes used by 7.4%. CT slices of 5 mm or more were used by 55.6% of the specialists used, whereas 44.4% implemented slices of less than 5 mm (Table 2).

Accounting for tumor mobility

Fluoroscopy was not used for characterization of tumor mobility by 77.8% of the radiation oncologists in 3D radiotherapy planning. In regard to the application of margins to GTV (gross palpable or visible/demonstrable extent and location of malignant growth) to obtain the CTV (a tissue volume that contains a demonstrable GTV, subclinical microscopic malignant disease, or both), 70.4% did not use a standard margin, whereas 29.6% did. Moreover, 48.1% added a margin of 1 cm to any contoured mediastinal node to determine nodal mobility, whereas 26% added 0.5 cm, 18.5% added more than 1 cm, and 7.4% did not add any margin.

With respect to "accounting for tumor mobility," 33.4% of radiation oncologists added a margin greater than 1.5 cm to derive PTV from GTV. A 1-cm margin was added by 29.6%, a 1.5-cm margin was added by 25.9%, and a 0.5-cm margin was added by 11.1% (Table 3). Only 3.7% applied any setup correction protocols to correct for reproducibility.

Investigative-procedure respiration-gated RT and breath-holding maneuvers

Procedures involving respiration-gated RT and breath holding were not implemented in any of the participating centers.

Table 1. Patient positioning

Arm support	13 of 28	46.4%
Immobilization lower extremities	2 of 28	7.1%
Both	5 of 28	17.9%
None	8 of 28	28.6%

Table 2. CT scan

1. Spiral CT	17 of 27	63%
Single-slice CT scan	10 of 27	37%
2. Isocenter localization		
Simulator	17 of 27	63%
CT Scan	10 of 27	37%
3. Intravenous contrast		
Never	22 of 27	81.5%
Always	3 of 27	11.1%
Sometimes	2 of 27	7.4%
4. Thickness of CT slices		
≥5 mm	15 of 27	55.6%
<5 mm	12 of 27	44.4%

Abbreviation: CT = computed tomography.

Generating target volumes

For generation of target volumes, 88.9% of the specialists used a pulmonary or parenchyma CT window for to contour tumors (not nodes) in lung parenchyma, whereas 11.1% used only a mediastinal CT window. To contour mediastinal nodes, 96.3% of the specialists used a mediastinal CT window. For GTV radiotherapy planning, taking the Naruke scheme for nodal stations into account, 92.6% used a node size with a short-axis diameter of 1 cm or more, whereas 7.4% used a diameter greater than 1.5 cm.

Most of the specialists, 85.7%, never used elective nodal irradiation in NSCLC Stages I to II, irrespective of the administration of chemotherapy. FDG-PET scans were not used by 89.3% of the specialists to generate target volumes. (Table 4).

Treatment planning

With respect to the question as to whether they used 3D radiotherapy planning in all localized LC cases(100%), 75% of the specialists answered always, 21.4% answered only in radical treatments, and a 3.6% answered never.

With regard to margins, 64.3% of the radiation oncologists required a margin greater than 5 mm for microscopic tumor extension, whereas 35.7% used only 5 mm.

In LC planning, 75% of the specialists used the V20 to estimate the risk of radiation pneumonitis, and 60.7% used the contour of esophagus to reduce the incidence of toxicity at this level (Table 5).

Treatment implementation

With regard to setup verification, 78.6% used only digital reconstruction radiographs (DRRs), where as 10.7% (3 of 28) also had electronic-portal imaging devices (EPID).

Several answers were given by the specialists on the level of beam energies used in LC treatment: 53.6% used 18 MV, 46.2% used 6 MV, 17.9% used 15 MV, and 3.6% used ^{60}Co, 10 MV, or 23 MV (Table 6).

Table 3. Tumor mobility

1. Fluoroscopy use		
No	21 of 27	77.8%
Yes	6 of 27	22.2%
2. Margins added to GTV		
Nonstandard margin	19 of 27	70.4%
Standard margin	8 of 27	29.6%
3. Margins added to GTV		
1 cm	13 of 27	48.1%
0.5 cm	7 of 27	26%
>1 cm	5 of 27	18.5%
No margin	2 of 27	7.4%
4. Margins to PTV from GTV		
0.5 cm	3 of 27	11.1%
1 cm	8 of 27	28.6%
1.5 cm	7 of 27	25.9%
>1.5 cm	9 of 27	33.4%

Abbreviations: GTV = gross tumor volume; PTV = planning target volume.

Table 4. Generating target volumes

1. For contouring tumors		
Lung parenchyma CT window	24 of 27	88.9%
Mediastinal CT window	3 of 27	11.1%
2. For contouring nodes		
Mediastinal CT window	26 of 27	96.3%
Lung parenchyma CT window	1 of 27	3.7%
3. Node size to include in the GTV		
≥1 cm	25 of 27	92.6%
>1.5 cm	2 of 27	7.4%
4. Elective nodal irradiation		
Never	24 of 28	85.7%
Always	4 of 28	14.3%
5. FDG-PET use		
Never	25 of 28	89.3%
Always	3 of 28	10.7%

Abbreviations: CT = computed tomography; FDG-PET = 18F-fluorodeoxyglucose-positron emission tomography; GTV = gross tumor volume.

DISCUSSION

The great variability in the technical aspects of radiation treatment in LC is well known, and numerous surveys on treatment decision making have been undertaken in differ-

Table 5. Treatment planning

1. Use of 3D planning in all lung cancer		
Always	21 of 28	75%
Only in radical treatments	6 of 28	21.4%
Never	1 of 28	3.8%
2. Margin +B8 size to generate CTV		
>5 mm	18 of 28	84.3%
5 mm	10 of 28	36.7%
3. V20 use		
Always	21 of 28	75%
Never	7 of 28	25%
4. Esophagus contour		
Always	17 of 28	60.7%
Never	11 of 28	39.3%

Abbreviation: CTV = clinical target volume.

Table 6. Treatment complementation

1. Setup verification		
DRRs		
Always	22 of 27	78.6%
Never	5 of 27	21.4%
EPID		
Yes	3 of 27	10.7%
No	24 of 27	89.3%
2. Beam energies		
18 Mv	15 of 28	53.6%
6 MV	13 of 28	42.6%
15 MV	5 of 28	17.0%
10 MV	1 of 28	3.6%
23 MV	1 of 28	3.6%
^{60}Co	1 of 28	3.6%

Abbreviations: DRRs = digital reconstruction radiographs; EPID = electronic-portal imaging device.

ent countries (10, 11). This lack of general guidelines to homogenize our practice led to the Patterns of Care Lung Study on American (8) and European guidelines (9) to establish the patterns of care of LC in RT departments. The European guideline is particularly of practical use and is a consensus based on the recommendations in the literature to achieve a greater therapeutic index (greater effectiveness with lower associated morbidity) in irradiation of LC.

In April 2004, a practical course on planning in LC was carried out in Barcelona and was attended by 44 radiation oncologists (from 25 different Spanish cities) dedicated specifically to radiotherapy of these tumors. We wanted to determine the treatment-planning patterns used by these specialists and, although the sample did not include all the Spanish radiation oncologists, it was representative of 14 of the 17 autonomous communities in Spain. A questionnaire based on the European recommendations was adapted and completed before the course for later analysis.

Spain was one of the first European countries to apply the properties of X-rays to different benign and malignant diseases (later known as radiation oncology). However, subsequent military events led to a marked social and scientific slow down that, among many things, produced a considerable technological delay (12). In 2003, a survey of all the Spanish divisions of radiation oncology was performed by the Spanish Association of Radiotherapy and Oncology (AERO) to determine the status of this specialty and its needs (13). The primary goals of this survey were to quantify the basic structural features and the clinical, teaching, and research activity of all radiation oncology divisions in the nation. Eighty-four centers were analyzed, with a total of 157 megavoltage units, 67 of which were cobalt units, and 90 accelerators. The conclusion of this study was that the Spanish radiation-therapy equipment was old and that Spanish public health-care system should invest more resources in radiation therapy.

In this first analysis of the recommendations of the European guidelines, the results of the Spanish implementation of these guidelines may be grouped as positive or negative findings according to whether they agree with the recommendations. First, the wide usage of 3D technology for the planning of LC treatment by the Spanish radiation oncologists consulted was of note.

With respect to positive findings, 70.4% of the oncologists had not used standard margins of GTV derived from a CT scan, and 92.6% agreed with inclusion of the Naruke anatomic criteria of greater than a 1-cm margin in GTV planning. Moreover, a large proportion used the appropriate CT window setting for contouring lung tumors or mediastinal nodes. Seventy-five percent used V20 to estimate the risk of radiation pneumonitis, and 78.6% used DRRs for setup verification.

On the other hand, negative issues included the fact that 2 hospitals did not use 3D tools, less than 50% used immobilization devices, 53.6% used CT slices greater than 5 mm, the isocenter was located preferably on simulator setup, and none of the hospitals used respiratory-gated RT.

Some responses to the questionnaire could not be considered either positive or negative. The first referred to elective nodal irradiation. Although the European guidelines indicate that insufficient evidence is available to support its use in any patient with localized NSCLC (Stages I–III), whether or not chemotherapy is administered, other authors, such as Martel *et al.* (14) and Rosenzweig *et al.* (15) consider this type of irradiation controversial and suggest that 3D planning may be important in the irradiation of a few, near, mediastinal nodes and should be taken into account (16).

The question as to the ideal photon energy to be implemented in the treatment of patients with LC, many of whom have emphysema-like symptoms and a wide thoracic cavity, should be commented upon. According to the questionnaire, Spanish radiation oncologists use 6 different photon energies, from cobalt to 23-MV accelerator. Many centers use more than 1 energy, and just over half prefer 18 MV. However, the European guidelines indicate that the use of beam energies above 10 MV appears to be inappropriate because the lack of lateral scattering in the low-density lung may degrade the target coverage. Given this fact, the calculation algorithms used in the common planning software (pencil beam) do not sufficiently take this effect into account (17). Other reports indicate that these limitations in use of high energies are only truly significant in small tumors, especially with a PTV of less than 100 cm^3 (18), or even in patients with anteroposterior separations greater than 20 cm, the dose delivered to the chest wall with 6-MV X-rays may exceed the dose to the prescription point at midline by 10% or more. The resulting superficial high doses can cause significant acute and late skin reactions or radiation pneumonitis if lung tissue is involved. Increasing the beam energy to 18 MV results in a more uniform central axis dose and significantly reduces doses to superficial structures. For opposed fields, the difference in penumbra degradation of the 6-MV and 18-MV photon beams is clinically insignificant compared with daily setup errors and patient movement (19), which are taken into account in PTV. This beam energy should probably be individualized for each patient according to anthropometric and tumoral characteristics.

The positive findings are more related to scientific than

technologic methodology, which demonstrated a high knowledge of the literature among the Spanish radiation oncologists. The interest in the course may reflect the greater scientific training of specialists in this field. However, we infer that these positive findings may univocally reflect the median level of the Spanish radiation oncologists in the treatment of LC. In any case, it may be a reference of the measurement of quality to consider. On the other hand, the negative results include the lack of immobilization methods and the limitation in the use of CT, the latter of which is almost always assigned by the radiodiagnostic department and is correlated with the difficulty in making both slices of less than 0.5 cm and the availability of time to localize the isocenter of the CT field. Furthermore, they reflect limitations in the technology and the infrastructure of the Spanish public health-care system, as well as in the respective autonomous communities in Spain. This observation is supported by the previously mentioned report on the infrastructure of radiotherapy in Spain (13) and other similar studies (20).

The negative aspects brought to light by the results of this questionnaire will be improved simply by their diffusion among the oncologic community, and they should also be taken into account in public health-care planning of resources in clinical oncology as a whole. Moreover, these negative aspects may also be improved with the development of continuous formation by the organization of the more courses in this field.

Because the European guidelines are based on recommendations reported in the literature and, to date, no other similar studies have been conducted, European or otherwise, to this end, our questionnaire may be used as a reference questionnaire for future analysis of radiotherapy planning in LC.

CONCLUSION

This study is the first validation of the European recommendations for treatment planning and execution of RT in LC in a specific European country (Spain). Despite the positive findings that demonstrate the good scientific and technical level of Spanish specialists in radiotherapy in LC, the main conclusion is the need to improve the negative issues observed that may reflect the limitations of financial support for radiation oncology by the Spanish health-care policies and those of the respective autonomous communities.

REFERENCES

1. Saunders MI, Dische S, Barret A, *et al.* Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: A randomized multicenter trial. *Lancet* 1997;350:161–165.
2. Furuse K, Fukuoka M, Kawahara M. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small cell lung cancer. *J Clin Oncol* 1999; 17:2692–2699.
3. Turrisi AT III, Kim K, Blum R, *et al.* Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:267–271.
4. Rosenman JG, Halle JS, Socinski MA. High-dose conformal radiotherapy for treatment of stage IIIA/B non-small-cell lung cancer: Technical issues and results of a phase I/II trial. *Int J Radiat Oncol Biol Phys* 2002;54:348–356.
5. Armstrong JG, Burman C, Leibel S, *et al.* Three-dimensional conformal radiation therapy may improve the therapeutic ratio of high dose radiation therapy for lung cancer. *Int J Radiat Oncol Biol Phys* 1993;26:685–689.
6. McNee SG, Rampling R, Dale AJ, *et al.* An audit of 3D treatment planning facilities and practice in the UK. *Clin Oncol* 1998;10:18–23.
7. Tai P, Yu E, Battista J, *et al.* Radiation treatment of lung cancer: Patterns of practice in Canada. *Radiother Oncol* 2004; 71:167–174.
8. Movsas B, Moughan J, Komaki R, *et al.* Radiotherapy patterns of care study in lung carcinoma. *J Clin Oncol* 2003;21:4553–4559.
9. Senan S, DeRuyssscher D, Mirimanof R, *et al.* Literature-based recommendations for treatment planning and execution for high-precision radiotherapy in lung cancer. *Radiother Oncol* 2004;71:139–146.
10. Choy H, Yu S, Cmelak AJ, *et al.* Patterns of practice survey for non small cell lung carcinoma in the US. *Cancer* 2000; 88:1336–1346.
11. Tai P, Yu E, Battista J, *et al.* Radiation treatment of lung cancer–Patterns of practice in Canada. *Radiother Oncol* 2004; 71:164–174.
12. Medina R, Casas F, Calvo FA. Radiation oncology in Spain: Historical notes for the radiology centennial. *Int J Radiat Oncol Biol Phys* 1996;35:1075–1097.
13. Esco R, Palacios A, Pardo J, *et al.* Infrastructure of radiotherapy in Spain: A minimal standard of radiotherapy resources. *Int J Radiat Oncol Biol Phys* 2003;56:319–322.
14. Martel MK, Sahijdak WM, Hayman JA, *et al.* Incidental dose to clinically negative nodes from conformal treatment fields for nonsmall cell lung cancer (Abstr.). *Int J Radiat Oncol Biol Phys* 1999;45 (Suppl. 3):244.
15. Rosenzweig KE, Sim SE, Mychalczak B, *et al.* Elective nodal irradiation in the treatment of non-small-cell lung cancer with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 2001;50:681–685.
16. Jeremic B. Incidental irradiation of nodal regions at risk during limited-field radiotherapy (RT) in dose-escalation studies in nonsmall cell lung cancer (NSCLC): Enough to convert no-elective into elective nodal irradiation (ENI)? *Radiother Oncol* 2004;7:123–125.
17. Fu W, Dai J, Hu Y. The influence of lateral electronic disequilibrium on the radiation treatment planning for lung cancer irradiation. *Biomed Mater Eng* 2004;14:123–126.
18. Haedinger U, Krieger T, Flentje M, *et al.* Influence of calculation model on dose distribution in stereotatic radiotherapy for pulmonary targets. *Int J Radiat Oncol Biol* 2005;2:239–249.
19. White DJ, Zwincker RD, Huang DT. Comparison of dose homogeneity effects due to electron equilibrium loss in lung for 6 MV and 18 MV photons. *Int J Radiat Oncol Biol Phys* 1996;5:1141–1146.
20. Esco R, Pardo J, Palacios A, *et al.* Final report from the Spanish Society of Radiotherapy and Oncology. Infrastructures Commission about Department Standards Recommended Able in Radiation Oncology. Vienna: IAEA C and S Papers Series 2001;7:897–901.