

Original Article

Clinical survey for registering treatment decision criteria in advanced non-small-cell lung cancer radiotherapy and determination of the dose–response relationship for 1-year survival

Ioanna Chalimou¹, Helena Lind², Georgios C. Sakellaropoulos¹, Bengt K. Lind³, Nikos Papanikolaou⁴, Georgios C. Nikiforidis¹, Panayiotis Mavroidis^{3,4}

¹Laboratory of Medical Physics, Medical School, University of Patras, Patras, Greece, ²Department of Oncology – Pathology, Clinical Cancer Epidemiology, Karolinska Institutet, Stockholm, Sweden, ³Division of Medical Radiation Physics, Karolinska Institutet and University of Stockholm, Stockholm, Sweden, ⁴Division of Medical Physics, Department of Radiation Oncology, University of Texas Health Sciences Center, San Antonio, TX, USA

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Abstract

Purpose: Recent studies have suggested significant variations in radiotherapy schedules used to treat advanced non-small-cell lung cancer (NSCLC), both between different centers in one country as well as between countries. In this study, different treatment methodologies have been explored using management plans proposed by radiation oncologists regarding general questions and theoretical case histories for patients with advanced NSCLC.

Materials and methods: The survey was conducted by sending a questionnaire to 24 radiotherapy centers in Europe. The questionnaire was composed of two sections. The first section concerned reasons for giving radiotherapy, parameters that influence the choice of total dose and fractionation for radiotherapy and kind of equipment used. The second section concerned the management of five theoretical patients (A–E) regarding the selection of the radiotherapy technique and the aim of treatment (radical or palliative). Furthermore, 19 trials comparing different regimens of palliative radiotherapy in patients with NSCLC were reviewed. There were marked differences in the doses of the investigated radiotherapy schemes, the patient characteristics and the assessed outcome measures.

Results: 70% of the responders answered that the most important factors for deciding what dose and fractionation scheme to use were: metastases, performance status (PS) of the patient, lung function and size of the primary tumour. The most common reasons for giving the treatment were symptom relief, prolongation of life and, in some cases, possibly cure. More than 95% of the responders stated that they would give radiotherapy in each of these cases. The total doses proposed were 20 Gy in five fractions or 30 Gy in ten fractions in 2 weeks for the cases A and D. If the previous two schemes were converted to a fractionation scheme delivering 2 Gy per fraction, the equivalent doses would be 23 and 33 Gy, respectively. For the cases B, C and E, the proposed fractionation schemes were 2 Gy daily to 60–68 Gy in

Correspondence to: Panayiotis Mavroidis, Division of Medical Physics, Department of Radiation Oncology, University of Texas Health Sciences Center at San Antonio, 7979 Wurzbach Rd, MC 7889, San Antonio TX 78229-4427, USA. Tel: +1 210-450-1027. Fax: +1 210-450-1076. E-mail: mavroidis@uthscsa.edu

6 weeks or 2 Gy daily to 68 Gy in 7 weeks. For the case E, 20% of the responders suggested Stereotactic Body Radiotherapy (SBRT) giving 21 Gy three times a week with a day apart to 63 Gy. The total dose and number of fractions of radiotherapy are related to the perceived aims and expectations of treatment. Those aiming at extending life would give significantly higher total doses in a larger number of fractions, whereas those aiming at relieving symptoms would give significantly lower total doses. There is evidence for an increase in survival, in patients who are given higher radiotherapy doses, especially in those patients with better PS.

Conclusions: This survey demonstrates a range of treatment strategies for advanced and inoperable NSCLC within Europe. There are a number of factors that influence the perceived aims of treatment and treatment planning. These factors should be taken into account when evaluating the effectiveness of different irradiation techniques, especially in the determination of radiobiological parameters and dose–response relations. The majority of patients should be treated with short courses of palliative radiotherapy, of one or two fractions. The use of high-dose palliative regimens using many fractions or SBRT should be considered for selected patients with good PS.

Keywords: clinical survey; non-small-cell lung cancer; 1-year survival; palliative treatment; radiotherapy protocol

INTRODUCTION

At the time of diagnosis, most pulmonary tumours are either locally advanced or have metastasised and treatment with curative intent will be possible in only half of the patients. Therefore, the majority of the patients with lung cancer will require relief from the symptoms caused by their disease.¹ The objectives of palliative treatment are independent of life prolongation, although this may be a secondary benefit. Assessment of the accomplishments of palliative treatment may be more difficult than it is for curative treatment where tumour-free survival can be measured. However, scales for pain assessment have only recently been developed.² Relief from problems such as cessation of nausea, bleeding or cough may be satisfying to both the patient and physician.³

Carcinoma of the lung is one of the most insidious neoplasms. Signs and symptoms may arise from locoregional tumour growth (invasion to adjacent structures), from distant metastases (e.g., haematogenous dissemination) or from secondary effects of the tumours (e.g., paraneoplastic syndromes). Cough is a major symptom in 75% of the patients and is severe in 40%. Haemoptysis occurs in almost 60% of the cases, being the initial symptom in 4% of them.

Other symptoms found in ~40% of the patients are dyspnoea and chest pain resulting from the involvement of the pleura, chest wall or mediastinal structures. Non-specific initial symptoms such as weight loss, weakness, anorexia and malaise may occur in 10–15% of the patients. Less common are febrile respiratory episodes.

The three most important prognostic factors affecting survival are stage, performance status (PS) of the patient and weight loss. The treatment of lung cancer depends on the cancer's specific cell type, its spread and the patient's PS. The treatments that are usually applied include surgery, radiation therapy and chemotherapy. Operable candidates, such as clinically staged IA, IB, IIA and IIB non-small-cell lung cancer (NSCLC) should undergo radical resection. Patients with stages IIIB and IV disease are treated primarily non-operatively. Although multimodality therapy with concurrent chemoradiation is routinely recommended for stage IIIA disease, it is recommended that it is performed within a clinical trial.^{4–6}

A Cochrane review identified one acceptable phase III trial, the continuous hyperfractionated accelerated radiotherapy (CHART) study, which showed an increase in 5-year survival from 7% to 12% for a scheme of 54 Gy in 36 fractions

in 12 days. 60% of the patients had stage II disease.^{7,8} Attempts to improve these results focus on dose escalation above 60 Gy. There are groups exploring doses from 77.4 to 94.5 Gy, having established evidence that lower doses appear to be safe. Increasing the radiation dose has often required an increase in the overall treatment time. Current estimates suggest that tumour repopulation during treatment necessitates an extra 0.2–0.4 Gy for each additional treatment day. CHART was designed to overcome this repopulation by shortening the overall treatment time to 12 days. In Northern Britain, fraction sizes of 2.75–3 Gy delivered to small volumes have been standard for radical treatments for over 50 years, allowing for 3–4-week treatments rather than the 6–7 weeks used elsewhere. Such fractionation schemes are now being explored in dose escalation trials and presently in a current European Organization for Research and Treatment of Cancer chemoradiotherapy trial.⁹ Both a large meta-analysis and two subsequent randomised studies have shown a small survival benefit of 2–3% at 5 years for full dose platinum-based combination chemotherapy before radical radiotherapy.⁸ Trials of increased radiation dose without altered fractionation have not shown any benefit to date.¹⁰ A meta-analysis of 2128 patients treated in nine randomised trials of post-operative radiotherapy in NSCLC reported a 7% decrease in survival at 2 years.^{9,10}

Palliative care is defined by the World Health Organization as the active total care of patients whose disease is not responsive to curative treatment. On the other hand, advanced NSCLC treatment refers to the treatment of an advanced stage NSCLC, which can also be curative. The goals of the treatment in the palliative care phase are mainly to optimise the patient's remaining time by controlling symptoms and enhancing quality of life. Treatments such as radiotherapy, chemotherapy, molecular targeted therapy and hormonal therapy can help in achieving these goals. About 34–50% of the patients receiving radiotherapy are of palliative intent. Palliative radiotherapy is commonly used in lung cancer to offer relief from symptoms that are produced from the primary tumour such as haemoptysis, dyspnoea, cough, chest pain, malaise or to reduce symptoms

from metastasis such as pain from bone metastases and neurological symptoms by brain metastases.

The practice of palliative radiotherapy is guided by basic ethical principles and available clinical evidence. It requires sophisticated assessment to balance the potential benefits and side effects to the patients with respect to patient's autonomy and expectations, and consideration of logistical factors. The present study aims at investigating the factors that dominate the decision of clinicians in different radiotherapy centers regarding the treatment of selected cases. Furthermore, it determined the dose–response relationship for 1-year survival after radiotherapy based on reported dosimetric and treatment outcome data from different clinical trials.

MATERIALS AND METHODS

Questionnaire

Palliative radiotherapy to the chest is often used in patients with lung cancer, but the radiotherapy regimens used in practice are most often based on historical rather than research results. A study-specific questionnaire was composed and consisted of two main sections. The first section concerned reasons for starting radiotherapy, as well as the parameters that influence the choice of total dose and fractionation for radiotherapy and the kind of equipment that is used (Table 1). The second section presented five case histories and asked the responders about the management of these theoretical patients regarding the radiotherapy techniques proposed and the aim of treatment (curative or palliative; Table 2). The questionnaire was sent to 24 radiotherapy centers in Europe (located in Sweden, Greece and United Kingdom) and it was answered by the Radiation Oncologists of those centers. The objective of this study was to make an inventory of how patients with NSCLC are treated in three European countries with special attention to why, how and with what equipment is treatment provided.

1-year survival

A review of the relevant literature was performed aiming at finding the most effective and least toxic regimens of palliative radiotherapy

for NSCLC and to investigate whether higher doses increase 1-year survival. The trials that were selected were controlled trials comparing different regimens of palliative radiotherapy in patients with NSCLC. In the trials that were

reviewed, there were important differences in the doses of radiotherapy applied, the patient characteristics and the outcome measures. Data from a total of 19 trials were selected.^{11–29} The equivalent dose for fractionation 2 Gy per fraction was calculated. The number of patients and the number of responders was also used and the Poisson model was used to estimate the dose versus 1-year-survival curve.

Table 1. Questionnaire

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1. Do you treat patients with lung cancer?
If not, thank you very much.
If you treat patients with lung cancer, please continue to the next question.
 2. Which parameters influence your choice of total dose and fractionation for radiotherapy for NSCLC?
Size of the primary tumor
Location of the tumor
Age of the patient
Performance status of the patient
Distant metastases
Metastases to loco regional lymph nodes
Symptoms
Lung function
Previous chemotherapy or other treatment
Histology
Sex
Other parameters (e.g., participation in a relevant clinical trial)
 3. What kind of equipment would you normally use when treating lung cancer patients?
 4. Which is the main reason for initiating the treatment?
Symptom relief
Prolongation of life
Better quality of life
Cure
Other reasons (e.g., prophylactic radiotherapy for brain metastases)
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The Poisson model

Assuming N_0 clonogenic cells and a probability of cell survival, $S(D)$, at a dose D , the response probability using Poisson statistics, $P(D)$ is given by

$$P(D) = \exp(-N_0 S(D)) \\ = \exp(-e^{\gamma} - (D/D_{50}) \cdot (\gamma - \ln \ln 2)) \quad (1)$$

D_{50} is the dose, which gives a 50% response and γ is the maximum normalised dose–response gradient. Parameters D_{50} and γ are specific for every organ and type of clinical endpoint and they are derived from clinical data.³⁰

RESULTS

Questionnaire

Seventeen centres replied to the questionnaire, which accounted for 70%. All the responders

Table 2. Clinical case scenarios

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- A. 80-year-old man, smoker with ECOG performance status 3, haemoptysis, dyspnoea, weight loss, malaise and anorexia diagnosed with squamous NSCLC stage IV. CT scan reveals occlusion of the right bronchus.
 - B. 50-year-old man, smoker with ECOG performance status 2, dyspnoea and cough diagnosed with anaplastic NSCLC stage IIIB. CT scan shows a central mass of 3 cm diameter.
 - C. 57-year-old woman with ECOG performance status 1 and productive and severe cough diagnosed with adenocarcinoma NSCLC stage IIIA. CT scan reveals occlusion of the left main bronchus by a mass of 5 cm diameter.
 - D. 70-year-old woman with ECOG performance status 4, haemoptysis and superior vena cava syndrome diagnosed with NSCLC stage IV. CT scan reveals occlusion of the left main bronchus.
 - E. 55-year-old man with ECOG performance status 1, chest pain, dyspnoea and Forced Expiratory Volume ratio (FOV1%) = 60% diagnosed with NSCLC stage IIB adenocarcinoma. CT scan reveals peripheral mass of 4 cm diameter. No information on concurrent diseases.
- What would you recommend for the patient cases A–E regarding the following factors?
- Total dose
 - Number of fractions
 - Overall treatment time
 - Additional treatment
 - Number of fields
 - Energy
 - Fixation
 - Gating
 - Other recommendations
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Abbreviations: CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

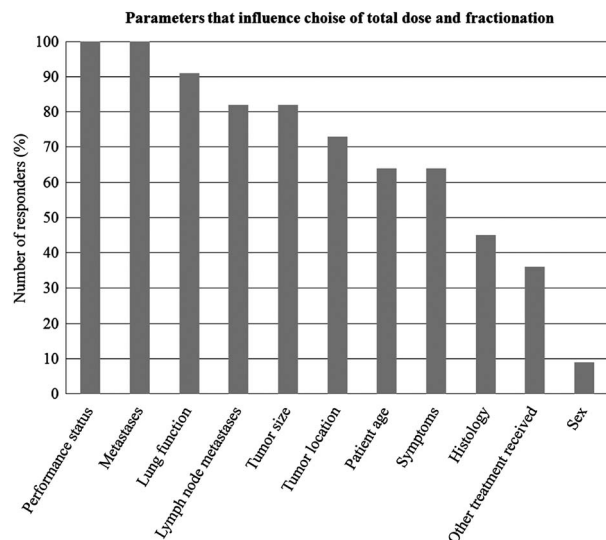


Figure 1. Summary of the statistics derived from the clinical survey regarding the parameters that influence the choice of total dose and fractionation for NSCLC radiotherapy. Abbreviation: NSCLC, non-small-cell lung cancer.

replied that they treat patients with lung cancer and that these centres are available not only for curative but also for palliative treatment. As it is shown in Figure 1, the responders suggested that distant metastases (100%), patients' PS (100%), lung function (75%), size of the primary tumour (69%) and metastases to locoregional lymph nodes (69%) are among the factors that influence the choice of total dose and fractionation schedule. Less important factors are location of the tumour (56%), age of the patient (56%), previous chemotherapy or other treatment, histology of the tumour and sex of the patient. The equipment that is used when treating lung cancer patients is megavoltage linear accelerator. The treatment procedure is facilitated by using three-dimensional conformal radiotherapy, multileaf collimator and electronic portal imaging devices. In Figure 2, it is indicated that the most common reasons for starting the treatment is not only possible cure, but also symptom relief and better quality of life. Other reason for initiating the treatment is prophylactic radiotherapy for brain metastases, in order to reduce the possibility of brain metastases from the primary lung tumour. Tables 3 and 4 show a summary of other treatment recommendations and the range of dose and number of fractions proposed for each case, respectively. Regarding the different patient

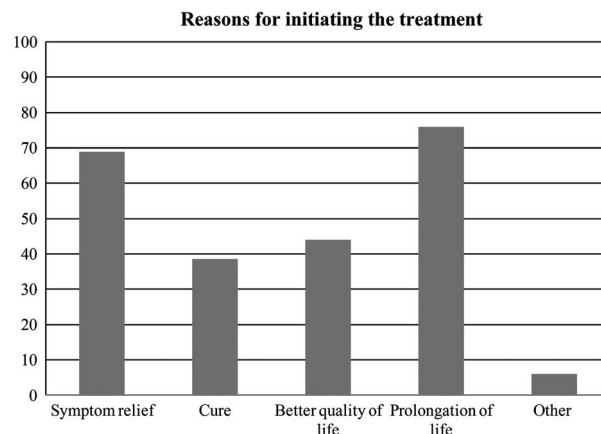


Figure 2. Summary of the statistics derived from the clinical survey regarding the reasons for initiating radiotherapy treatment.

Table 3. Other treatments that were recommended to be applied in addition to radiotherapy

Treatment modality	A	B	C	D	E
None (%)	65	6	6	53	24
Chemotherapy (%)	–	88	82	12	47
Surgery (%)	–	–	12	–	6
Other (%)	35	6	–	35	23

cases (scenarios) examined, the following results were obtained.

Patient A

Most of the responders from all the countries proposed that this patient should be treated by palliative radiotherapy and considered the patient incurable, although the majority of the groups thought that the primary aim of treatment should be to relieve symptoms. There was a relationship between the total dose and number of fractions and the aim of treatment, for example, those who felt that life could not be extended by treatment chose a lower dose and fewer fractions than those who felt that treatment could extend life. There were differences in the proposed total dose, number of fractions and overall treatment time, which ranged from 8 Gy in one fraction (equivalent dose for fractionation 2 Gy per fraction, $D_{eq} = 12$ Gy) to 39 Gy in 13 fractions in 13 days ($D_{eq} = 42$ Gy). The most common total doses proposed from the majority of the responders were 20 Gy in five fractions in 1 week ($D_{eq} = 23$ Gy) and 30 Gy in ten fractions in 2 weeks ($D_{eq} = 33$ Gy). One Swedish center would not

Table 4. Range of dose and number of fractions proposed for each case

Fractionation parameters	A	B	C	D	E
Dose (Gy)	8–39	40–68	55–68	16–40	16–40
Number of fractions	1–13	4–34	20–34	2–15	2–15

give radiotherapy to this theoretical patient. The majority of the responders from all the participating countries proposed that the treatment technique, which should be applied to this patient should consist of two opposed fields and only two responders from Sweden proposed three or four fields. The suggested beam energy was 6 MV or 18 MV and the fixation method proposed was vacuum pillows and support for knees. None of the responders suggested gating for this patient. Other recommendations for this theoretical patient were palliative care and drugs in order to relieve symptoms.

Patient B

All the responders considered radiotherapy with curative intent for this patient. The range of total dose and number of fractions proposed was wide and ranged from 55 Gy in 20 fractions in 4 weeks ($D_{eq} = 58$ Gy) to 68 Gy in 34 fractions in 7 weeks ($D_{eq} = 68$ Gy). The most common dose proposed from the majority of the responders was 60 Gy in 30 fractions in 6 weeks ($D_{eq} = 60$ Gy). Two Swedish centers suggested stereotactic body radiotherapy with 40 Gy in four fractions in 4 days ($D_{eq} = 67$ Gy). Nearly all the responders proposed that this patient should be treated by simulated radiotherapy fields, which ranged from three to seven fields and the beam energy suggested ranged from 6 to 15 MV. All the radiotherapy centers recommended chemotherapy as additional treatment.

Patient C

All the responders considered this clinical case as curative and they would give the same total dose as in case B. The number of fractions and the overall treatment time would also be the same. The centers suggesting Stereotactic Body Radiotherapy (SBRT) in the previous case proposed 68 Gy in 34 fractions in 7 weeks in this case. All the centers suggested giving additional chemotherapy. Fifty percent of the responders also suggested surgery

if possible. The beam energy, number of fields, fixation and gating recommendations were the same as in the previous cases.

Patient D

The majority of responders from all the countries proposed palliative radiotherapy with a treatment technique that would apply two opposed fields. Only one center proposed multiple fields. There were differences in the total doses and the number of fractions proposed, which ranged from 16 Gy in two fractions in 2 days ($D_{eq} = 24$ Gy) to 40 Gy in 15 fractions in 3 weeks ($D_{eq} = 42$ Gy). The most common scheme proposed was 30 Gy in ten fractions in 2 weeks ($D_{eq} = 33$ Gy). The beam energy proposed for this scenario ranged from 6 to 10 MV. Fifty percent of the responders did not suggest additional treatment, while others proposed steroids, drugs in order to reduce symptoms, vena cava stent to relieve from vena cava syndrome and additional chemotherapy. The suggestions for fixation and gating did not differ from the previous cases.

Patient E

All the responders considered the aim of treatment as curative. The total doses proposed ranged from 55 Gy in 20 fractions in 4 weeks ($D_{eq} = 58$ Gy) to 68 Gy in 34 fractions in 7 weeks ($D_{eq} = 68$ Gy). The most common scheme proposed by 60% of the responders was 68 Gy in 34 fractions in 7 weeks. Furthermore, three of the centers (two Swedish and one Greek) proposed SBRT with 45 Gy in three fractions in 5 days or 21 Gy in three fractions. Other recommendations for the treatment of this patient were chemotherapy or surgery if that was possible. All the centers would use a multiple field technique for this theoretical patient.

1-year survival

All studies reported survival as an important endpoint. Reinfuss et al. reported a statistically

significant survival benefit at 2 years (18% versus 6%) for the 50 Gy in 25 fraction regimen compared with 40 Gy in ten-fraction split-course regimen.²⁰ Prolonged, interrupted and split course treatments have been shown to be less effective than equivalent continuous treatments in NSCLC.^{31,32} Kramer et al. reported a significant improvement in 1-year survival with 30 Gy in 10 fractions compared with 16 Gy in two fractions (19.6% versus 10.9%). On subgroup analysis, this was only significant in patients with PS from 0 to 1 but not in patients with PS from 2 to 4.¹⁴ Bezzak et al. reported a significant improvement in median survival with 20 Gy in five fractions compared with 10 Gy once (6 versus 4.2 months).¹² On post-subgroup analysis, the improvement only persisted for the patients who had PS between 0 and 1 and had localised disease. Senkus-Konefka et al. reported a significant improvement in median survival with 16 Gy in two fractions compared with 20 Gy in five fractions (8.0 versus 5.3 months).²¹ Appold et al. reported that the survival of the patients treated with 60 Gy was significantly better than the survival in the other groups.²⁹ Median survival was 11 months after 60 Gy, 6 months after 40 Gy and 5 months after 25 Gy. The most important prognostic factor was the PS of the patients.

Figure 3 shows the experimental data of the probability for 1-year survival against dose as they were registered in the above clinical trials. Furthermore, the Poisson model was used to determine the corresponding dose-response

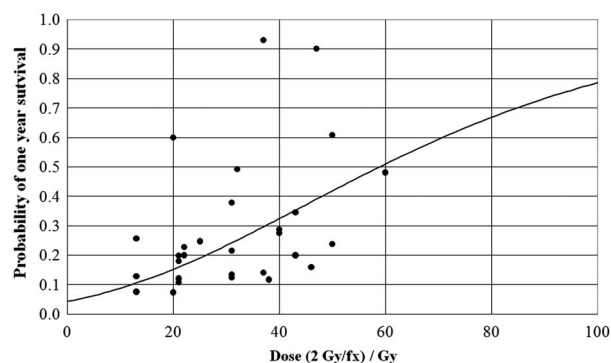


Figure 3. This diagram illustrates the probability of 1-year survival according to the dose. Dots represent the data for the trials selected and the line represents the dose-response curve derived using Poisson model.

curve. It can be observed that with the exception of some outliers, the spread of the experimental points around the dose-response curve is not large. This spread could be even smaller if the three-dimensional dose distribution could be used instead of the prescribed dose. It should be noted that even without radiotherapy (dose equals to zero) there is a small proportion of the patients that is expected to survive for 1 year.

DISCUSSION

Palliative radiotherapy is mainly indicated for offering relief from various local symptoms in cancer patients as those presented in Table 5. Its effectiveness has been confirmed by cumulative clinical evidence. Unfortunately, palliative radiotherapy may sometimes have significant side effects for the patient such as acute complications, hospitalisation, multiple visits to the radiotherapy unit with associated discomfort in transport. Poor PS, short predicted life expectancy, perception of slow onset of therapeutic effects and overly

Table 5. Indications for palliative radiotherapy

Pain relief
Metastatic bone pain
Painful lymphadenopathy
Pain due to soft tissue infiltration by cancers
Neuropathic pain due to nerve compression and infiltration
Rescue of neurological deficit
Spinal cord compression
Brain metastases
Relief of pressure symptoms
Thoracic tumours
Superior vena cava obstruction (SVC0)
Upper airway obstruction
Dysphagia
Collapse of lung
Reduction of intracranial pressure due to brain metastases
Retroperitoneal tumours
Relief of hydronephrosis
Pelvic tumours
Relief of hydronephrosis
Urinary retention
Intestinal obstruction
Decrease infection and ulceration of metastatic or primary skin tumours
Haemostasis
Bleeding rectal or gynaecological cancers
Bleeding skin cancers
Prophylaxis of impending symptoms
Durable control of advanced locoregional disease beyond cure.

burdensome of palliative radiotherapy often preclude palliative radiotherapy as a tool for symptom relief in terminal cancer patients.

Questionnaire

The first part of this study illustrates the wide range of practices in the management of advanced and inoperable NSCLC among European radiotherapists and has attempted to explore some of the reasons for these variations. Case histories may not reliably reflect the management that would be applied in all the clinical settings. But while this may undoubtedly be true in the case of individual patients, it may be a useful method to explore the type of policy used by the clinicians. This criticism may be particularly applied to the treatment of NSCLC, where important prognostic indicators, such as lung function, were not supplied. However, a similar range of treatment strategies was found in the expert surrogate study of Palmer et al., in which a number of non-tumour, non-patient variables could be shown to influence the proposed therapy as a function of the specialty of doctor (surgeon, radiotherapist or medical oncologist) or country of origin.³³ The study revealed a number of areas of uncertainty. Although the majority of the responders agreed that the treatment would be palliative for the cases A, D and E and radical for the cases B and C, there were differences in the perceived prognosis and aims of treatment. Variation in dose and fractionation could be related to some of these differences, for example those who aimed to prevent symptoms or extend life tended to prescribe higher doses than those who aimed just to relieve symptoms. Those who aimed at a longer survival tended to prescribe higher doses and larger numbers of treatment fractions.

For patient D, there was a generally poor agreement regarding the aims of the treatment and a wide range in the total dose and number of fractions was proposed. This confirms the variation seen in other studies.^{33–35} The perceived aim of radiotherapy was clearly different in those proposing radical radiotherapy giving higher doses and more fractions than in those proposing palliative therapy. Palliative doses were higher than 8 and <40 Gy. On the other hand, curative doses were higher than 55 Gy.

Furthermore, some responders viewed treatment as both curative and palliative and prescribed higher doses and larger number of fractions than those who regarded the treatment as palliative only. There is some evidence that low doses of radiotherapy relieve common symptoms of cancer, for example, a single fraction of 8 Gy can relieve pain from bone metastases and short fractionation regimens relieve symptoms related to lung cancer.

This study suggests that radiation oncologists believe that a higher dose of radiotherapy is needed to prevent or maintain symptom response as opposed to relief of symptoms only in the treatment of metastatic disease. The longer the patients live, the higher is the dose required to achieve this, although more data are required to support this belief. The variation in predicted survival times confirms the findings of other works suggesting that radiation oncologists are poor at predicting survival for patients with advanced and incurable diseases.^{36,37} A significant difference was the suggestion of SBRT from some Swedish and one Greek centers. This difference may be related to cultural differences in attitude towards an advanced disease and its treatment, but may also be related to different local methods or organisation of cancer care or training of radiation oncologists.

1-year survival

The literature review shows that in the majority of the patients, a short course of radiotherapy with only one or two visits for treatment, improves symptoms as effectively as longer courses, without more side effects. For some patients with better PS, a longer course of radiotherapy may give a slightly better chance of living for 1 or 2 years, but with more immediate side effects, especially oesophagitis with accompanying swallowing problems. Patients who have advanced loco regional cancers with good PS and long life expectancy can preferably be treated with protracted fractionated schedules of higher total doses and low dose per fraction to achieve durable local control.³

It seems that in most of the patients, short hypofractionated regimens such as 10 Gy once

or 17 Gy twice are probably as effective at providing palliation as more protracted schedules, and have the advantage of fewer patient visits to hospital and reduced workload for the radiotherapy departments. There is strong evidence for a modest increase in survival (5% at 1 year and 3% at 2 years) in patients with localised disease and better PS given higher dose radiotherapy, as a large, high quality, study indicate.¹⁵ In Reinfuss et al., a large difference in survival was reported, in a group of patients who seemed to have better PS.²⁰ Bezjak et al. showed the improvement in survival seen with the higher dose regimen only persisted in patients who had PS = 0–1 and had localised disease.¹² The Kramer et al. trial also showed that the survival advantage seen with the higher dose regimen only applied to good PS patients.¹⁴ It therefore seems likely that any survival benefit is modest and confined to good PS patients and those with localised disease.

In Figure 3, the small gradient of the dose–response curve indicates that apart from dose there are also other factors (e.g., inter- and intra-patient radiosensitivity variation, PS, stage, chemotherapy) that may have a significant impact on the 1-year survival, which, if taken into account properly, can reduce the spread of the experimental points and lead to a steep dose-dependent dose–response curve. The diagram indicates that if an advanced radiation modality (e.g., intensity-modulated radiation therapy) had been used to increase the dose to the target keeping at the same time the dose to the organs at risk at the same or even lower levels then the proportion of the patients succeeding 1-year survival could have been significantly increased, without any increase in the rate of radiation-related side effects.

CONCLUSION

This survey demonstrates a range of treatment strategies for advanced NSCLC within Europe. Influential factors in this study included the perceived aims of treatment and the estimated prognosis of the patient. Those aiming at extending life would give significantly higher total doses in a larger number of fractions, whereas those aiming at relieving symptoms

would give significantly lower total doses. These factors should be taken into account when evaluating the effectiveness of different radiotherapy regimens.

The dose–response relationship for 1-year survival was established based on clinical data. This relationship indicates that higher doses are associated with an increased rate of 1-year survival. Selected patients with good PS should be considered for treatment with higher dose palliative regimens such as 36 Gy in 12 fractions, if the chance of a modest increase in survival is after informed discussion with the patient, considered to be worthwhile for the extra visits to hospital and the increased risk of toxicity.

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