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Clinical Investigation: Thoracic Cancer

Total Gross Tumor Volume Is an Independent Prognostic Factor in Patients Treated With Selective Nodal Irradiation for Stage I to III Small Cell Lung Cancer

Bart Reymen, MD,* Judith Van Loon, MD, PhD,* Angela van Baardwijk, MD, PhD,* Rinus Wanders, MD,* Jacques Borger, MD, PhD,* Anne-Marie C. Dingemans, MD, PhD,[†] Gerben Bootsma, MD, PhD,[‡] Cordula Pitz, MD, PhD,[§] Ragnar Lunde, MD,^{||} Wiel Geraedts, MD,[¶] Philippe Lambin, MD, PhD,* and Dirk De Ruyscher, MD, PhD*,[#]

**Department of Radiation Oncology (MAASTRO clinic) and [†]Department of Pulmonology, GROW — School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands; [‡]Department of Pulmonology, Atrium Medical Centre, Heerlen, The Netherlands; [§]Department of Pulmonology, Laurentius Hospital, Roermond, The Netherlands; ^{||}Department of Pulmonology, St Jansgasthuis, Weert, The Netherlands; [¶]Department of Pulmonology, Orbis Medical Centre, Sittard, The Netherlands; and [#]University Hospital Leuven/ KU Leuven, Leuven, Belgium*

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Summary

In this series of 119 patients with stage I to III small cell lung cancer who were treated with accelerated concurrent chemoradiation using selective nodal irradiation based on positron emission tomography, less than 2% of patients experienced elective nodal failure. In multivariate analysis, total gross tumor volume appears to be the most important prognostic factor for survival.

Purpose: In non-small cell lung cancer, gross tumor volume (GTV) influences survival more than other risk factors. This could also apply to small cell lung cancer.

Methods and Materials: Analysis of our prospective database with stage I to III SCLC patients referred for concurrent chemo radiation therapy. Standard treatment was 45 Gy in 1.5-Gy fractions twice daily concurrently with carboplatin-etoposide, followed by prophylactic cranial irradiation (PCI) in case of non-progression. Only fluorodeoxyglucose (FDG)-positron emission tomography (PET)-positive or pathologically proven nodal sites were included in the target volume. Total GTV consisted of post chemotherapy tumor volume and pre chemotherapy nodal volume. Survival was calculated from diagnosis (Kaplan-Meier).

Results: A total of 119 patients were included between May 2004 and June 2009. Median total GTV was 93 ± 152 cc (7.5-895 cc). Isolated elective nodal failure occurred in 2 patients (1.7%). Median follow-up was 38 months, median overall survival 20 months (95% confidence interval = 17.8-22.1 months), and 2-year survival 38.4%. In multivariate analysis, only total GTV ($P=.026$) and performance status ($P=.016$) significantly influenced survival.

Conclusions: In this series of stage I to III small cell lung cancer patients treated with FDG-PET-based selective nodal irradiation total GTV is an independent risk factor for survival. © 2013 Elsevier Inc.

Reprint requests to: Bart Reymen, MD, 6229 ET Maastricht, The Netherlands. Tel: +31 (0)88 44 55 666; Fax: +31 (0)88 44 55 667; E-mail: bart.reymen@maastro.nl

Conflict of interest: none.

Introduction

Classic prognostic factors for survival in small cell lung cancer (SCLC) include stage, age, level of lactate dehydrogenase (LDH), time between start of any treatment to the end of radiation therapy (SER), male sex, N3 nodal status, and WHO performance score (WHO-PS) (1).

Clinicians intuitively accept that larger tumors are less likely to remain controlled. Gross tumor volume (GTV) is a fairly recent concept, which could not be investigated in the pre-computed tomography (CT) era. Indeed, in the International Union Against Cancer (UICC) TNM classification, only the T-stage may include the 2-dimensional (2D) diameter of the primary tumor, but size of nodes or total GTV are not present (2).

In prognostic models concerning non-small cell lung cancer (NSCLC), GTV, together with the number of nodal stations, outweigh TNM stage (3,4). Therefore we investigated the value of total GTV, defined as the volume of the primary tumor and the involved lymph nodes on a planning positron emission tomography (PET)-CT as a potential stratification factor in SCLC. Furthermore, we updated our results of selective nodal irradiation (SNI) based on PET-CT (5).

Methods

Patient population

Since 2003, patients treated at Maastricht Clinic are collected in a prospective database.

We analyzed all patients with stage I to III SCLC referred for concurrent chemoradiation therapy from May 2004 until June 2009.

Patients had pathologically proven SCLC stage I to III according to UICC TNM classification version 6, excluding T4 disease due to malignant pleural or pericardial effusion (6). WHO-PS of 0 to 2 and adequate pulmonary function (forced expiratory volume at 1 second [FEV₁], carbonic oxygen diffusion capacity [DLCO] both $\geq 30\%$), hematological, hepatic, and renal function were required. Patients with N3 disease (including contralateral supraclavicular and/or contralateral mediastinal nodes) were also treated radically.

Staging

All patients were staged by whole-body ¹⁸F-fluorodeoxyglucose (FDG)-PET scan (not in treatment position) and CT or magnetic resonance imaging (MRI) of the brain.

Chemotherapy

Standard chemotherapy in the region of the Integraal Kankercentrum Limburg consisted of carboplatin on day 1 and etoposide (120 mg/m²) on days 1 to 3 for 5 cycles, repeated every 21 days. Carboplatin dose was based on the target AUC (5 mg/ml/h) $\times$ (glomerular filtration rate [GFR] + 25). GFR was calculated using the Cockcroft-Gault formula. Standard dose-reduction rules applied.

Radiation therapy

Apart from the staging PET scan, a dedicated FDG-PET-CT scan in treatment position (supine, arms raised) was used for treatment planning in almost all patients 5 to 7 days before start of radiation therapy. From April 2006 onward (81 patients, 68%), respiration-

correlated CT (RCCT) images were acquired. When a planning PET was not available, the diagnostic PET was fused with the planning CT.

Patients were scanned from the cricoid to the second lumbar vertebra with 3 mm-slices. Automated rigid registration based on mutual information of PET and CT images was followed by fusion using the Focal software (Computerized Medical Software [CMS], St Louis, MS). Contouring was done on the mid-ventilation images of the RC-CT. Treatment planning was performed on the XiO system (CMS), using a convolution and from May 2007 onwards a superposition algorithm. The GTV of the primary tumor was the post chemotherapy volume defined on the planning PET-CT while for the lymph nodes, the pre chemotherapy extension was reconstructed to avoid previously involved nodal sites being left out of the planned target volume (PTV). Window settings were W = 1700, L = -300 (lung) and W = 600, L = 40 (mediastinum). The nuclear medicine physician's pre chemotherapy PET report was used to locate tumor sites. PET-negative enlarged lymph nodes were not delineated. In case of confluent central masses, the part adjacent to the lung was considered the primary tumor, whereas the mediastinal extension was considered as nodal volume and delineated accordingly. The border between the 2 volumes was left up to the treating physician. GTV was expanded with 5 mm to create a clinical target volume (CTV), excluding vessels and esophagus. No elective nodal regions were delineated. CTV-to-PTV margin was 5 mm for the lymph nodes and 10 mm for the tumor.

Dose constraints for the organs at risk were: mean lung dose (MLD) of 19 Gy $\pm$ 1 Gy (volume of both lungs minus GTV). The esophagus had no dose constraint. Three-dimensional (3D) conformal radiation therapy plans were constructed following the International Commission on Radiation Units and Measurements (ICRU) 50 guidelines using 6 or 10 MV photons. The prescribed dose was 45 Gy in 30 fractions administered in 1.5-Gy fractions twice daily over 3 weeks with a minimal inter-fraction interval of 8 hours. Radiation therapy was started as soon as possible after the first chemotherapy to limit the "start of any therapy to the end of radiation therapy (SER)" time (7). No gating or breath hold was used, and treatment verification was done with routine (daily) electronic portal imaging dosimetry (8).

After the end of chemoradiation, patients with a WHO-PS ≤ 2 were offered prophylactic cranial irradiation (PCI) to a dose of 25 Gy in 10 fractions in case of clinical nonprogression.

Follow-up

The radiation oncologist checked patients weekly during radiation therapy, and at 2 to 4 weeks after the end of treatment. Patients were followed until acute side effects subsided to grade 1. Afterward the pulmonologist performed 3-monthly follow-up during the first year, 6-monthly from years 2 to 5 and yearly thereafter. Toxicity was recorded following CTCAE, version 3.0. A chest CT-scan or x-ray was acquired at each visit until progression. Overall survival was evaluated using the "Gemeentelijke Basis Administratie" (GBA) database (5, 9).

Statistical analysis

Endpoints were patterns of failure, overall survival (OS), and progression-free survival (PFS). In-field failure was defined as recurrence in which more than 50% of the tumor volume was included in the original CTV. Out-of-field failure was defined as

a recurrence for most part extending outside the original CTV. Elective nodal failure (ENF) was defined as out-of-field nodal recurrence in hilar, mediastinal or supraclavicular lymph nodes. Isolated ENF or local tumor failure was defined as ENF or local tumor failure without other sites of recurrence. Survival was calculated using SPSS, version 17.0, (Kaplan-Meier) from diagnosis until death.

Factors included in multivariate survival analysis were stage, age, level of LDH at diagnosis, SER, male sex, N3-status, WHO-PS, and GTV (1). Total GTV comprised the total volume of nodes (pre chemotherapy) and tumor (post chemotherapy) defined on the planning PET-CT scan.

Median survival is expressed with the 95% confidence interval (CI), other results as mean $\pm$ standard deviation (SD) and their range. Cox regression multivariate analysis was performed. A *P* value of less than .05 was considered significant.

Results

Patient characteristics

From April 2004 until June 2009, 119 patients with stage I to III SCLC were referred to Maastricht Clinic for concurrent chemoradiation therapy.

Patient characteristics are summarized in Table 1.

Patients were 41 to 85 years of age, with a median age of 66 $\pm$ 8.8 years. All but 2 patients received carboplatin-etoposide. Both of these patients received carboplatin-paclitaxel instead: 1 patient because of synchronous ovarian cancer, and the other because of intolerance to etoposide.

Two patients (1.6%) did not receive the planned dose of 45 Gy because of neutropenic sepsis; 1 patient died after 4 fractions (6 Gy), and 1 patient was hospitalized after 39 Gy.

The median interval between the pathologic diagnosis of SCLC and start of treatment was 15 $\pm$ 9.8 days (0-47 days). The median interval between the first day of chemotherapy and start of radiation therapy was 20 $\pm$ 13 days (range, -5 to 82 days). The overall treatment time (OTT) of RT was 21 $\pm$ 2.7 days (1-32 days) with a median SER of 39 $\pm$ 13.4 days (8-100 days).

In all, 105 patients (88%) received PCI. Reasons for not receiving PCI were progression (5/14, brain in 4/5), death (5/14), refusal (2/14), WHO>2 (1/14), and miscommunication (1/14).

Patterns of failure

One patient was lost to follow-up after 22 months. Median follow-up is 38 $\pm$ 17 months (22-84 months). A total of 76 patients (64%) had disease progression at the time of analysis. Table 2 lists the frequency and patterns of relapse.

Eighteen patients (15%) developed local tumor recurrence, which was out-of-field in 4 of 14 patients. One patient had a geographical miss; in retrospect, the CTV of the primary tumor had not been included in the PTV.

Distant metastases developed in 65 patients (55%). In 14 patients (12%), isolated brain metastases were the first site.

Thirty-nine patients had a nodal recurrence (32%), mostly in-field (26%).

In 2 patients (1.7%), an isolated ENF occurred. Sixteen months after treatment for a tumor with a single PET-positive node in region 6, 1 patient had a nodal recurrence in regions 2L and 1L, which was re-treated with concurrent chemoradiation therapy. The

Table 1 Patient characteristics

Characteristic	No. (%) of patients*
Sex	
Male	69 (58)
Female	50 (42)
Age (y)	
Median	66 ($\pm$ 8.8)
Range	41-85
WHO-PS	
0	38 (32)
1	64 (54)
2	17 (14)
UICC Stage	
IA	1 (1)
IB	3 (3)
IIA	5 (4)
IIB	6 (5)
IIIA	24 (20)
IIIB	80 (67)
GTV (cc)	
Median	93 ($\pm$ 152)
Range	7.5-895
N3 subdivision	
Supraclavicular nodes	29 (24)
Contralateral supraclavicular	15 (13)
Contralateral hilar nodes	10 (8)
Chemotherapy	
Carboplatin-etoposide	117
Carboplatin-Taxol	2
SER	
Median	39 ($\pm$ 13)
Range	8-100
>30 d	102 (86)
LDH	
Normal	86
Elevated (> upper limit of normal)	33
Delivered dose of radiation therapy (Gy)	
Median	45 ($\pm$ 3.6)
Range	6-45

Abbreviations: WHO-PS: World Health Organisation-Performance Status; Gy = Gray; GTV = gross tumor volume; LDH = lactate dehydrogenase; SER = start of any treatment to the end of radiation therapy; UICC = Union Internationale Contre Cancer.

* Values in parentheses are percentages, except for age, which is standard deviation.

other patient had had PET-positive nodes in the left hilum and region 5. The recurrence occurred after 31 months in region 4R. This node was not pathologically validated, because the patient was diagnosed simultaneously with an inoperable pelvic recurrence of ovarian cancer, which was uncontrolled and was only treated palliatively.

Survival

At a median follow-up of 38 $\pm$ 17 months (22-84) the median actuarial OS was 20 $\pm$ 1 months (95% confidence interval [CI] = 17.9-22.1 months) with a 2-year OS of 39% and a 3-year

Table 2 Patterns of relapse

Recurrence	No. (%) of patients
None	43 (36)
Local tumor failure	18 (15)
Local failure + regional/distant failure	16 (13)
Isolated local tumor failure	2 (2)
In-field tumor failure	13 (11)
Regional nodal failure	39 (32)
Nodal + local/distant failure	33 (27)
Isolated nodal failure	6 (5)
Isolated elective nodal failure	2 (2)
Distant failure	65 (55)
Distant + local/regional failure	28 (24)
Isolated distant failure	37 (31)
Isolated brain recurrence	14 (12)

Numbers between parentheses are percentages. Location of relapses were assessed with CT.

OS of 25% (Fig. 1). Median actuarial PFS was 14 ± 0.7 months (95% CI = 12.5-15.4 months), with a 2-year PFS of 32%.

Factors associated with survival

On univariate analysis factors influencing survival were GTV ($P=.008$) and WHO-PS ($P=.023$). Contralateral hilar or supraclavicular nodes did not have a significant impact on OS ($P=.314$).

Multivariate analysis was performed considering GTV a continuous variable.

The only factors showing a significant influence on OS were total GTV ($P=.016$, hazard ratio of 1.002 per cubic centimeter [cc]) and WHO-PS (0/1 vs 2) ($P=.026$). A threshold GTV could not be established. Stage (I/II vs III), N-status (N3 vs other), SER (≤ 30 days vs >30 days), sex (male vs female), age (<70 years vs ≥ 70 years) and LDH (normal vs elevated) did not gain significance. Table 3 shows the results of the univariate and multivariate analysis.

Fig. 1. Overall survival, Kaplan-Meier curve. Actuarial overall survival of 119 patients.

Table 3 Impact of prognostic factors on overall survival (OS)

Factor	Univariate analysis	Multivariate analysis	
		<i>P</i> value	Hazard ratio
Total GTV	0.008	.016	1.002 (per cc)
WHO-PS	0.028	.026	0.512
Stage	0.284	.631	NS
Age	0.976	.364	NS
Gender	0.810	.668	NS
LDH	0.103	.529	NS
N-status	0.236	.359	NS
SER	0.468	.362	NS

Abbreviations: GTV = gross tumor volume; LDH = lactate dehydrogenase; N-status = nodal status (N3 vs N0-2); SER = interval between start of any treatment and the end of radiation therapy; WHO-PS = World Health Organisation-Performance Status.

Toxicity

Esophagitis grade 3 (necessitating hospitalization and/or feeding tube) was the most frequent severe reaction, occurring in 22 patients (19%) but subsiding to grade 1 or less in all but 1 patient 3 months after radiation therapy. Eight patients (7%) developed grade 3 dyspnea during or shortly after radiation therapy, which was still present after 3 months in 1 patient with severe chronic obstructive pulmonary disease (COPD; DLCO, 32%) and grade 2 dyspnea already at baseline.

Cough reached grade 3 in 3 patients during treatment (2.5%). In 1 patient, this was due to a severe pneumonia requiring IV antibiotics. In all patients, this subsided to grade 2 or less at 3 months after radiation therapy.

At baseline, 46% of patients presented without dyspnea, whereas 3 months after treatment, 72% had no dyspnea.

Discussion

In the past years, the interest of researchers in selective nodal irradiation in SCLC has grown. Already starting from the late 1980s, smaller radiation ports were used in trials to decrease the acute toxicity of emerging combined modality treatments (10). However, omission of elective nodal irradiation was pioneered by De Ruysscher et al, whose first attempt of CT-based SNI yielded an elective nodal failure rate of 11%, probably due to the low sensitivity and specificity of CT in mediastinal nodes of SCLC (11).

Based on the higher accuracy of PET scans in detecting malignant mediastinal nodes, a subsequent trial on PET-based SNI in 60 patients with stage I to III SCLC reported isolated nodal failure in only 3% of patients, comparable to results in NSCLC (5, 11, 12). Shirvani et al confirmed this in their retrospective analysis of 60 patients treated with PET-based intensity modulated radiation therapy (IMRT) concurrently with platinum-based chemotherapy, reporting an isolated elective nodal failure (ENF) rate of 2% (13). Our present series is a continuation of the work by Van Loon et al, expanding her series of 59 patients (60 patients, excluding 1 patient referred for sequential chemo radiation in that series) with the next consecutive 60 patients treated following the same methods. We deliberately kept our follow-up at a minimum of 22 months to ensure robust survival data. Indeed, the effects of

a change in treatment regimen on local control will start affecting overall survival only after an average of 2 years (14, 15).

Isolated ENF occurred in only 2 patients, which is remarkably similar to the frequency noted in the Shirvani et al article and which strengthens the case for PET-based irradiation of SCLC (13).

We defined an isolated elective nodal failure as a nodal relapse occurring in an area that would have been included in the elective CTV in absence of other sites of disease as this represents in our view a potential missed cure by omitting elective nodal irradiation (ENI).

An often-heard criticism of SNI is the fact that there is still a high number of ENF detected along with distant metastases (16). In this case the question arises as to whether prevention of the nodal recurrence would have prevented the metastases. Fifteen patients with out-of-field ENF were diagnosed simultaneously with distant metastases. Ten of these patients had simultaneous in-field relapses. This means that 5 patients (4.2%) had a combination of ENF and distant metastases, diagnosed at a median of 14 months. Whether these metastases would have been prevented by ENI is a question that can be answered only by a large randomised trial. However, because of the small numbers at risk and the high incidence of distant relapse, a significant survival benefit of ENI, keeping the rest of the treatment (RT dose and chemotherapy) constant, would be difficult to establish.

The low loco regional control rate remains worrisome. Fifteen percent of patients experienced a local tumor recurrence, and in-field nodal relapses occurred in 26% of cases. This is in line with the respective 36% and 34% local failure rate reported by Turrisi and Watkins, but contrasts with the 8% (5/60) in-field locoregional relapse rate reported by Shirvani (13, 14, 17).

Comparison of our series with the Shirvani et al paper is difficult in this respect. Their shorter median follow-up time of 26 months inevitably leads to a larger confidence interval in results. Of our patients, 46% had N3 disease versus 37% in their series. Apart from using IMRT opposed to our 3D conformal radiation therapy, they also used radiation therapy schedules different from the Turrisi schedule in 32% of their patients, with total doses ranging up to 63.8 Gy, which could obviously affect loco regional control, as is the subject of 2 ongoing EORTC (CONVERT) and Intergroup (CALGB 30610, RTOG 0538, NCT00632853) trials (13).

As in other series the predominant pattern of recurrence is the development of distant metastases, implying an important role for more effective systemic therapy. During the studied time period, carboplatin held the personal preference of an influential staff member of the university hospital, which was adopted throughout the region. Recently our region has switched to cisplatin instead of carboplatin, although a recent meta-analysis suggests equivalent tumor outcome with either regimen (18).

To our knowledge, this is the first time that total GTV has been shown to affect overall survival in SCLC more than classical factors such as age, gender, LDH, and stage. This result is in line with findings in NSCLC (3, 4). Why age, gender, LDH, or stage were not even significant on univariate analysis is not clear, but might also be attributable to sample size or for some parameters because of their relatively narrow range. We could not define a threshold GTV for stratification. In the present series of patients, 72 cc comes closest to separation into prognostic groups with a *P* value of .06 for overall survival. The inclusion of more patients might solve this problem, but as the definition of GTV in our protocol is still somewhat dual, in this article it is best treated as a continuous variable.

Whether the impact of total GTV represents the sheer number of cells to be eradicated, a higher rate of hypoxia in larger tumor sites, or

a more aggressive phenotype can not be deducted from current data. Another explanation might be the fact most of our patients received 1 cycle of chemotherapy before starting radiation therapy. By using the post chemotherapy GTV for the primary tumor, a smaller volume could thus be a surrogate for response to chemotherapy.

Whichever mechanism underlies the influence of GTV on survival, future trials should take the total GTV into account as a stratification factor.

We confirm the detrimental impact of a poor performance status at diagnosis: patients with WHO-PS of 0-1 had a 2-year OS of 42%, versus those with a WHO-PS of 2 who had an OS of 12%. Only 2 of 17 patients presenting with a WHO-PS of 2 survived for more than 2 years, both being alive, however, at 4 years after diagnosis. The exclusion of patients from radical treatment solely based on a WHO-PS of 2, remains debatable, but this parameter should certainly be incorporated into prognostic models.

There are some drawbacks to this study. This is a monocentric series that was prospectively collected but was retrospectively evaluated for toxicity and tumor status. However, follow-up in our region is performed according to strict guidelines with good compliance. Survival data were collected directly from the central Dutch GBA database, which guarantees accurate results. Prospective trials using PET-CT-based selective nodal irradiation are not expected in the near future. The CONVERT trial uses selective nodal irradiation, but does not require PET-CT scans for treatment planning. By limiting the analysis to patients referred for concurrent chemoradiation, a selection bias toward more fit patients is present. We also recognize that GTV in this series is a mixed parameter composed of pre chemotherapy nodal and post chemotherapy tumor volumes. Nevertheless it provides an estimate of relative disease burden, even though there is a chance that the primary tumor volume can be somewhat influenced by response to the first cycle of chemotherapy.

Despite these limitations, we believe that this study adds to the growing body of evidence supporting the safety and efficacy of selective nodal irradiation for SCLC using FDG PET-CT data. Furthermore, we propose the total GTV as a valuable factor to be investigated for use in future prognostic models.

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