Metabolic responses in non-small cell lung cancer after hypofractionated stereotactic radiotherapy
PET and Hypofractionated Radiotherapy

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Abstract. – *Background:* The aim of our study was to evaluate the pattern of local failure after Stereotactic Body Radiotherapy (SBRT) of Non Small Cell Lung Cancer (NSCLC) lesions relating to different type of 18F-FDG Positron Emission Tomography (PET) response.

Methods: Thirteen NSCLC patients for a total of 15 lesions (primary early or locally advanced and metastases) underwent PET before and 6 months after SBRT.

Maximum Standard Uptake Value (SUV_{max}) <2.5 was considered as cut off for complete response (CR) while lesion reduction $\geq$ 50% with residual value above 2.5 for partial response (PR).

Results: With a median follow up of 30 months pre- and post-SBRT mean SUV max values were 8.2 (range 14.2-3.7) and 2.4 (range 12.9-0), respectively.

No "in field recurrence" was observed while 3 cases of "out field recurrence" occurred as regional nodes progression at 7.8 and 14 months after treatment.

Three years overall survival, local control and distant metastases free survival were respectively 66.7%, 63.3% and 44.4%.

Actuarial 75% and 53.3% 3-year local control, 60% and 40% 3-years distant metastases free survival were observed for complete and partial PET response, respectively, after SBRT. Thereafter, 60% and 50% 3-year overall survival were observed for complete and partial response.

Conclusions: Clinical results were significantly better for "responder" than "non responder" and for "complete" than "partial response" group.

Moreover, our data seem to confirm that a significant subset of patients maintain a low metabolic activity without developing local relapse on longer follow up.

Introduction

^{18}F-FDG Positron Emission Tomography (PET) scanning has improved the individualized diagnostic and therapeutic management of cancer patients'.

Molecular Nuclear Imaging requires the use of integrated PET and Computerised Tomography (CT) scanners offering combined information about molecular and morphological tumour characteristics.

PET imaging is based on the increased glucose uptake due to the glucose receptor over expression and high hexokinase activity of tumour compared to normal cells[1,2].

Nowadays, this technique has a well established role for both staging of early Non Small Cell Lung Cancer (NSCLC) and for detection of mediastinal and distant metastases of lung or other primary cancer due to the major overall sensitivity (96%) and specificity (78%) rather than to conventional imaging[3,4].

Furthermore, there is an increasing role to differentiate changes caused by the treatment (inflammatory reaction, fibrosis and parenchyma atelectasis) of surrounding normal tissues from tumour local relapse[5].

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In the last few decades radical radiotherapy has proved its emerging role as curative treatment either for early (non-operable for medical co-morbidities) or for locally advanced NSCLC.

Hypo-fractionated stereotactic body radiotherapy (SBRT) enables to deliver few fractions highly focusing radiation dose to extra-cranial tumours while sparing surrounding normal tissues through a deeply gradient to the periphery.

At first this treatment technique involved the use of special localization and immobilization devices such as stereotactic body-frame to reduce set up margins and keep the planning target volume (PTV) as small as possible without decreasing the risk of "geographical missing".

In the last few years these systems have been replaced step by step by the implementation of Image Guided Radiotherapy (IGRT) Systems using X ray source for cone beam CT (CBCT) volumetric acquisition and online correction before treatment.

The main characteristic is a much shortened treatment course (1-5 fractions) and a higher biological effectiveness after large single dose on tumour response rather than conventional programs.

Together with diagnosis, staging and detection of recurrence, an emerging role of PET-CT is the assessment of cancer response after therapy.

Many data show that a 50-80% reduction of the Maximum Standard Uptake Value (SUV_{max}) or even more after primary treatment is strongly predictive of complete pathologic response and survival with sensitivity, specificity and accuracy of 90%, 100% and 96%, respectively, while focal increased uptake is associated with doubled risk of death[6-8].

Thus PET-CT might be useful to provide prognostic information after completion of neo-adjuvant radiation or chemotherapy.

In this study we retrospectively report our caseload about response evaluation after SBRT of early, locally advanced, or metastatic NSCLC, using SUV reduction as predictive factor of tumour response.

Our purpose was to observe pattern of local failure over time in the irradiated area correlated to the different type of PET response after SBRT.

Patients and Methods

Patients Characteristics

According to an internal protocol, patients with the following criteria were considered eligible for stereotactic treatment: early NSCLC non operable for medical co-morbidities; lung metastases (≤3 nodules) or single mediastinal adenopathy from primary NSCLC without radiological evidence of progressive disease after systemic therapy; isolated local recurrence after surgery.

Almost the total of patients (10/13) underwent to prior chemotherapy and in most cases radiation treatment was delivered as consolidation with curative intent.

All patients had been informed by written consent; in all patients' histological confirmation of primary cancer (either biopsy or cytology) and clinical staging according to Tumour Nodal Metastases (TNM) Classification and American Joint Committee on Cancer Stage (AJCC – Sixth Edition) were obtained.

There were no restrictions for enrolment relating to location of lesions.

Patients were classified using Eastern Cooperative Oncology Group (ECOG Scale) for Performance Status and Charles Morbidity Index for co-morbidities evaluation.

The workup included complete history and physical examination, complete blood count, bronchoscopy and pulmonary function testing including spirometry, volumes and diffusing capacity (DLCO).

In our protocol, baseline forced expiratory volume at first second (FEV_1) ≤ 1 litre was considered as cut-off value for stereotactic treatment eligibility.

Radiological staging before treatment included computed tomography (CT) of the chest and upper abdomen and PET scanning.

Follow-up was performed at 4 weeks post-treatment with blood exams and chest X-ray, at 12 weeks with CT scan and at 24 weeks with PET; thereafter, every 4 months, alternating total abdomen ultrasound and CT scanning.

According to data in literature we considered SUV_{max} value <2,5 as cut off for complete response (CR) and SUV_{max} reduction ≥50% with residual value above 2,5 to define partial response (PR).

Therefore, no response (SD) and progression disease (PD) were defined, respectively, as persistence of SUV pre-treatment value or reduction <50% and as SUV_{max} increased levels.

The biologically equivalent dose (BED) was used to compare different fractionation schedules (considering a / value of 10 Gy for tumour and 3 Gy for normal tissues); so we distinguished lesions treated with BED ≥ 70 Gy_{10} and those with BED = 50.7 $Gy_{10.}$

Finally, we distinguished "in field recurrence" (IFR) for relapse occurred inside and "out field recurrence" (OFR) for those outside the treated volume but in the regional tumour spread area (e.g. regional nodes or lung recurrences).

Treatment

At the beginning stereotactic treatments were performed by Stereotactic Body Frame (Elekta Oncology, Norcross, GA, USA) which uses a rigid frame and a vacuum pillow for patients positioning and immobilization plus an abdominal compression device, when required, to reduce respiratory target motion especially in cranio-caudal directions.

In this subset of patients, clinical set up was performed by two orthogonal MV set up fields (0-90°/270°) and offline correction (Frame 2D IGRT).

Afterwards, together with the advent of three dimensional IGRT (DHX Varian Medical System Inc., Palo Alto, CA, USA) with an on board imaging (OBI) system, according to our internal protocol, we continued to perform stereotactic treatments "frameless" for fixed (e.g. mediastinal adenophaty) and "frame based" for mobile targets (e.g. medium or lower lobe lesions).

Frameless set up involved the use of a vacuum pillow plus wing board system as positioning device and set up errors were minimized using volumetric CBCT for online corrections.

All patients underwent treatment planning contrast-enhanced CT 3 mm slice thickness for tumour target volume visualization and isocenter localization.

Gross tumour volume (GTV) was identified using pulmonary windowing for lung lesions or mediastinal windowing for adenopathy.

Clinical target volume (CTV) was defined as GTV plus 2 mm expansion in all directions for microscopic tumour spread and further 5 mm in anterior-posterior (AP) and right-left direction (LL), 1 cm in cranio-caudal direction (CC) to define internal target volume (ITV).

Planning was conducted on the Pinnacle 3D 8.0m Version Planning System (Philips Healthcare, Best, Netherlands).

Treatment was always delivered using a 6MV energy and a micro-multileaf collimator either by a static technique with 5-7 non coplanar, non opposing fixed beams or by a dynamic technique using conformal arc.

The arc interval in the transverse plane varied from a minimum of 180 to a maximum of 360

degree and the beam aperture was drawn to encompass just the planning target volume without margins.

Treatments dose was prescribed to the isodose line covering the PTV obtaining a heterogeneity tumour target dose up to 115%.

PET Imaging

All patients were studied with PET before and 24 weeks after SBRT.

Patients must be fasting for at least 6 hours before intravenous injection with 0.10 mCi/kg of ^{18}F-FDG and imaging was started 60 min after injection. Blood glucose levels should be below 180 mg/dl. Diabetic patients were appropriately treated with hypoglycemic agents and/or insulin.

The patients were studied on a 8-slice dual modality PET-CT (Discovery GE).

PET emission images were obtained from the base of the brain to the mid-thigh region on all patients at a scan time of 4 min per bed position (15 cm). CT imaging with conventional settings for mA and kVp was obtained over the same anatomic areas and used for attenuation correction of the PET emission image data.

All PET-CT studies included the area of the body from the base of the brain to the mid-thigh region. The degree of metabolic uptake in both the tumour site and the surrounding normal tissues was quantified using SUV. The SUV_{max} for the target lesions and reference tissues was obtained using a three-dimensional voxel region of interest placed simultaneously on the three orthogonal projections. To ensure that changes in tumour SUV_{max} were not caused by a generalized and unrelated increase or decrease in tissue FDG uptake, the tumour FDG uptake was normalized to FDG uptake of several reference tissues. Ratios of tumour SUV_{max} to the SUV_{max} of the reference tissues lung, blood, and liver were calculated.

Statistical Methods

The primary endpoints of the study were overall survival and local recurrence.

The secondary end-point was distant metastases free survival.

The Kaplan-Meier method was used to estimate survival, local recurrence and distant metastases rate [9].

Differences in survival and in local and distant progression-free survival were assessed by the log-rank test.

Overall survival was defined as the interval between diagnosis and death or last follow-up.

Local and distant recurrences were defined as the interval of time between the start of treatments and documented disease progression after SBRT.

In this analysis, patients dying in the absence of a disease progression were censored at the time of death and were classified as progression-free.

All analyses were conducted with SPSS version 13.0, 2004 (SPSS Inc., Chicago, IL, USA).

Results

Between December 2006 and January 2010, 13 patients (9 males and 4 females), for a total of 15 NSCLC lesions, were enrolled into the protocol.

Median age was 66 years (range 52 to 79 years); ECOG ≤1 and Charles Index ≤ 2.

Patient characteristics are summarized in Table I.

Of this total number 7 were primary lung lesions (3 stage IB; 1 stage IIB; 1 stage IIIA; 1 stage IIIB; 1 stage IV), 2 metastatic lung nodules (stage IV), 2 mediastinal adenopathy (stage IIIA N2), and 4 were local recurrence after primary surgery.

All patients but three with early NSCLC underwent to prior chemotherapy and then were enrolled to radical radiation treatment with curative intent.

Thirteen lesions were centrally located (2 mediastinal and 11 lung) while 2 were peripherally sited.

Clinical set up was performed by 2D frame based IGRT in 5 cases, while in the remaining 10 cases it was performed by frame or frameless 3D IGRT; 9 lesions were treated through a dynamic technique whereas in 4 lesions a static technique was used.

Seven lesions received BED major than $70Gy_{10}$, while the remaining 8 lesions received a dose ranging between 50 to $70Gy_{10}$.

Based on our protocol, all patients underwent PET-CT staging before treatment and 24 weeks after SBRT for tumour response evaluation.

Pre- and post-SBRT mean SUV_{max} values were 8.2 (range 14.2-3.7) and 2.4 (range 12.9-0), respectively.

These data are shown in Table II.

According to PET response criteria, 8 lesions underwent CR and 5 lesions PR, while 2 lesions had only a minimal SUV decrease and were classified as SD.

Table I. Patients and tumor characteristics.

Total no. patients	13
Total no. lesions	15
Age (yrs): median (range)	66 (52-79)
Gender, no. (%):	
Male	9 (69%)
Female	4 (31%)
ECOG PS*, no. (%):	
0	6 (46%)
1	7 (54%)
Charles Index, no. (%):	
0	3 (23%)
1	7 (54%)
2	3 (23%)
Type of lesions, no. (%) and stage (AJCC, 6th edition)	
Primary lung lesions	7 (47%)
Stage IB	3
Stage IIB	1
Stage IIIA	1
Stage IIIB	1
Stage IV	1
Metastatic lung nodules	2 (13%)
Mediastinal nodes	2 (13%)
Local recurrence	4 (27%)
Tumour histology, no. (%):	
Adenocarcinoma	8 (53%)
Squamous cell carcinoma	7 (47%)
Tumour location, no. (%):	
Centrally	13 (87%)
Peripherally	2 (13%)
Chemotherapy, no. (%):	
Yes	10 (77%)
No	3 (23%)

*ECOG PS: Eastern cooperative oncology group performance status.

With a median follow up of 30 months (range 12-60 months) the 3-year overall survival was 66.7%; the 3-year local control and distant metastases free survival were 63.3% and 44.4%, respectively (Figures 1 and 2).

No IFR were observed while 3 cases of OFR occurred as regional nodes progression at paratracheal levels (2R and 4R) at 7.8 and 14 months after SBRT. On the other side, 8 patients underwent systemic progression disease.

Table II. Pre- and post-SBRT SUV_{max}.

	Mean SUV_{max}	Range
Pre-SBRT	8.2	3.4-14.2
Post-SBRT	2.4	0-12.9

SBRT: Stereotactic body radiotherapy; SUV_{max}: Standard uptake value.
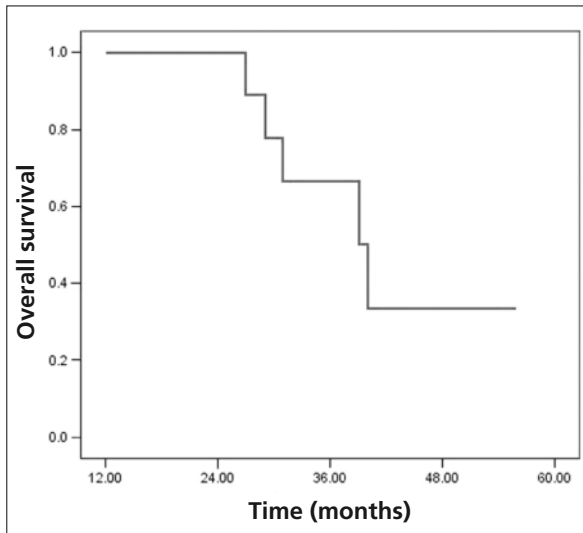
Figure 1. Overall survival.

Furthermore, local relapses, distant metastases free survival and overall survival were analysed by PET response.

Actuarial 75% and 53.3% 3-year local control, 60% and 40% 3-year distant metastases free survival were observed for complete and partial PET response, respectively, after SBRT; thereafter, 60% and 50% 3-year overall survival was observed for complete and partial response (Figures 3 and 4).

100% of local and distant metastases at 3-years after treatment were observed in the two patients with SD and no patient was alive at 3 years.
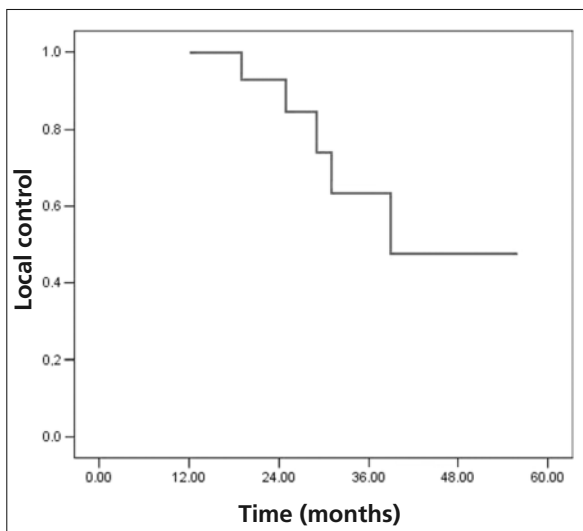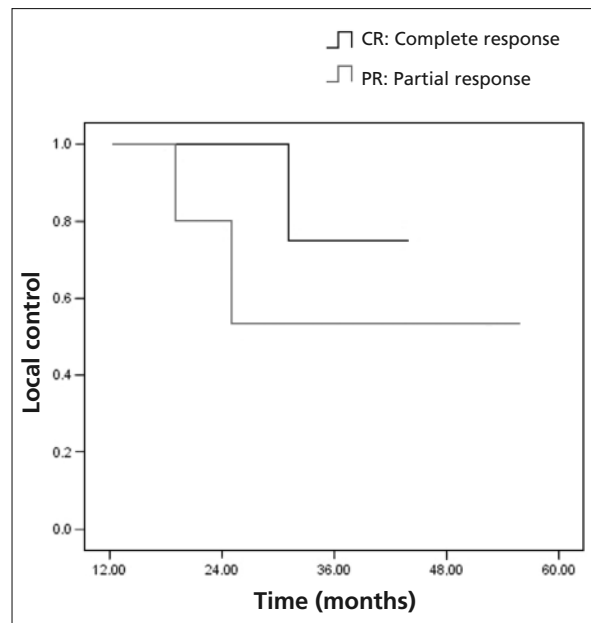

Figure 2. Local control.

Figure 3. Comparison of local control for complete and partial PET response.

Discussion

Nowadays, there is an emerging role of PET for therapeutic monitoring after treatment of various types of cancer.

At first, metabolic changes, subsequent to biological radiation tumour effect, seem to occur
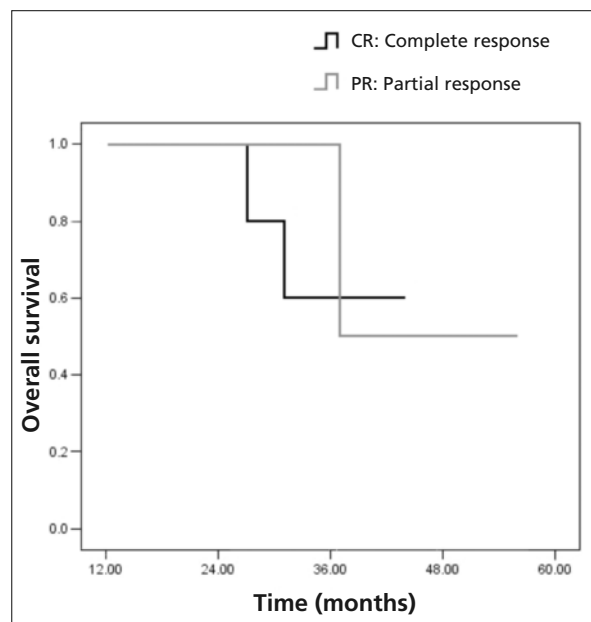

Figure 4. Comparison of overall survival for complete and partial PET response.

much earlier than morphological downsizing detectable by CT scan, so that functional imaging might be very useful for an early response evaluation.

In this regard, Choi et al[10] data showed an inverse relationship between tumour control probability based on pathological response (pTCP) and residual metabolic activity (MRglc) only 2 weeks after conventional preoperative radiotherapy or radiochemotherapy in locally advanced NSCLC.

By now, many reports suggest the use of this diagnostic technique after radical radiotherapy in NSCLC showing superiority to CT scan for therapeutic response assessment.

Moreover, PET complete response after radical radiotherapy or radio-chemotherapy seems to be highly predictive of freedom from local recurrence, distant metastases and survival.

In a prospective clinical trial on 73 primary NSCLC medically or surgically unresectable, Mac Manus et al[11] observed a significant correlation between early CT scan or PET response after conventional radiotherapy or radio-chemotherapy and survival.

On the following multivariate analysis also evaluating Performance Status, Stage and weight loss, only PET response (no CT response) resulted to be a significant prognostic factor for long term survival.

Nowadays, is very important to evaluate the prognostic factor of NSCLC treatment because radiation therapy with advanced technology might be useful in most clinical scenarios.

Radiobiological historical data of non small lung cancer published by Martel et al[12] showed a clear relationship between dose escalation and tumour local control.

Based on the above data, the role of radiotherapy has focused on dose escalation on involved field volume aimed to improve local tumour control and consequently overall cancer related survival[13-18].

So in the last few decades, together with advanced technology development toward very focusing image guided radiation delivery, hypofractionated radiotherapy has emerged as a new promising treatment modality delivered in a short time using very large single fraction doses.

At this time poor data are available on PET response evaluation, especially regarding SUV course, after hypo-fractionated radiotherapy.

Coon et al[19] reported their experience on 28 patients (primary, recurrent or metastatic lung nodules) underwent PET scan prior and after SBRT (60Gy/3 fractions).

SUV decrease was noticed in 28% of patients with stable disease, 48% with partial response and 94% with complete response.

In a retrospective series by Hoopes et al [20], 4/28 patients (14%) with post-SBRT PET after 22-26 months showed persistence of moderate hyper-metabolic activity (SUV=2.5-5) but no evidence of loco-regional or distant failure on longer follow up.

These data are confirmed in a recent update publication by the Indiana University group.

Authors [21] indicate that almost half patients maintain $SUV_{max} > 3.5$ without evidence of local failure on further follow up and support that moderately elevated SUV_{max} should not be considered as surrogate of local failure.

In this retrospective series we reported our caseload on a heterogeneous patient population consisting on primary NSCLC lesions (mainly locally advanced), local recurrent NSCLC after primary surgery and mediastinal nodes or lung metastases from primary NSCLC.

Our purpose was to focus on SUV_{max} course at a fixed time after SBRT and to observe metabolic behaviour of treated lesions related to further clinical and radiological follow up.

Overall 13 patients for a total of 15 lesions underwent diagnostic PET before and 24 weeks after SBRT.

Thirteen lesions underwent complete or partial PET response (86.6% total response rate).

Two lesions underwent only a minimal reduction of metabolic activity and were classified as stable disease while no case of metabolic increase (defined as progression disease) after SBRT was observed.

In our series 3 patients experienced loco-regional recurrences on longer follow-up consisting on lymph nodes regional progression immediately outside radiotherapy target volume.

No case of failure inside primary target volume was observed.

Then, after careful revision of the prior treatment plan, especially regarding normal structures limiting doses, all patients underwent SBRT re-treatment.

Non responders lesions were those with lowest and highest pre-treatment SUV_{max}.

One patient was affected by a metastatic NSCLC with a high metabolic rate of the primary hilar lesion (SUV_{max} 10.3). The stereotactic treatment was delivered after 4 cycles of prior chemotherapy on a residual metabolic lesion of SUV 3.7.

The other patient was affected by a solitary lung metastasis (SUV_{max} 14.2) undergone to prior 6 cycles of chemotherapy. This lesion was observed to remain roughly unchanged both before chemotherapy regimen and stereotactic treatment (SUV_{max} 12.9).

A possible explanation for this phenomenon might be related to the proliferation index and metabolic statement of cancer cells.

In the first case, selection of resistant tumour clones characterized by a low metabolic activity after primary chemotherapy might be the reason for poor radio-responsiveness.

In the second case, high growth fraction and proliferation rate associated to necrotic or hypoxic areas inside tumour mass could explain high tumour aggressiveness and consequent resistance to radiation damage.

After stratification for PET response, local control and distant metastases free survival at 3 years post-SBRT are significantly better for "responder" than "non responder" and for CR than PR group (75% and 53.3% vs. 60% and 40%); besides these results seem to reflect on 3 years overall survival (60% for CR and 50% for PR).

Moreover, our findings seem to confirm that a significant subset of patients maintain a moderately elevated metabolic activity ($SUV_{max} > 2.5$) without developing local relapse on longer follow up after SBRT.

Therefore, despite the limited number of patients, our results appear to have the same trend of Mac Manus' study.

In addition, according to literature data, stable or progressive SUV lesion increase seem to be related to local treatment failure and poor prognosis.

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