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30 Gy single dose stereotactic body radiation therapy (SBRT): Report on outcome in a large series of patients with lung oligometastatic disease

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ABSTRACT

Objectives: To evaluate the local control (LC) and long term adverse effects in a series of patients with lung metastases who received 30 Gy in single dose with stereotactic technique.
Materials and Methods: Between December 2008 and April 2016, a total of 166 lung metastases in 129 patients affected by oligometastatic disease were treated at our Institution with stereotactic body radiotherapy (SBRT). Mainly, the primary tumors were non small-cell lung cancer and colorectal cancer (45.2% and 28.8%, respectively). Prognostic factors were also assessed.
Results: The median follow-up was 38 months. Local progression occurred in 24 (14.4%) lesions in 21 patients. Intra-thoracic progression (new lung lesions or thoracic lymph node metastases) occurred in 59 (45.7%) patients. Forty-five (34.8%) patients had distant progression after a median time of 14 months. The 3- and 5-years local relapse-free survival (LPFS) were 80.1% and 79.2% (median not reached), respectively. One-hundred forty-eight patients were evaluated for late toxicity (follow-up > 6 months): 51 (34.4%) patients had grade ≤2 fibrosis, 11 (7.4%) patients experienced grade 3 fibrosis. Two (1.3%) cases of rib fracture occurred. One case of toxic death (grade 5) has been reported. Median OS was 39 months. At the univariate analysis, lesion diameter ≤18 mm correlated significantly with a longer LPFS ($p = 0.001$). At the multivariate analysis, lesion diameter < 18 mm was predictive for longer LPFS ($p = 0.006$). Also, oligometastases from primary colorectal cancer was a significant predictive factor for worse LPFS ($p = 0.041$) and progression-free survival ($p = 0.04$).
Conclusions: To our knowledge, the current study represents the largest series on the use of SBRT 30 Gy single dose for lung metastases. Our results confirm the effectiveness and safety of this schedule administered in selected oligometastatic patients. Further prospective series could better validate these results.

1. Introduction

Lung is one of the most common sites of metastases for solid tumors. Local management of lung lesions mainly includes surgery and radiotherapy. Surgical resection is a well-established technique [1]. In the last decade, stereotactic body radiotherapy (SBRT) was demonstrated to be an effective technique in the definitive treatment of lung malignancies showing good compliance by the patients and good tolerance [2].

Effectiveness of SBRT for lung metastases in terms of local control (LC) is in most cases comparable to surgical series. The rate of LC at 3-years for lung metastases is 94% and 90% for SBRT and metastasectomy, respectively [3,4]. Moreover, data suggest that SBRT and surgery for lung metastases have favorable results in terms of 5-years survival outcomes (49% vs. 41%) [5,6].

Recently, SBRT is emerging as a suitable and effective treatment in the oligometastatic state (1–5 metastases). For this category of patients, a good local control of the active sites of disease could lead to improvement of disease-free survival (DFS) and eventually overall survival (OS). A recent prospective phase II randomized trial [7] showed

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that oligometastatic NSCLC patients treated with local definitive therapies, including SBRT, had an improved survival when compared to patients treated with systemic therapy alone (3.9 months for chemotherapy alone vs. 11.9 months after chemotherapy associated to local therapy). After many years of clinical experience using SBRT in the treatment of lung tumors, the optimal dose and fractionation are still unknown. Apparently, a higher biological dose to the tumor has been found to improve local control rates and survival [8]. Furthermore, the dose–response relationship seems not to differ in terms of local control after SBRT between primary NSCLC and secondary lung lesions [9]. Some evidence [10–15] showed that the single-dose SBRT could be an attractive regimen due to its feasibility, high patient's convenience, low costs, limited toxicity, and the easier association to subsequent systemic therapy.

The aim of the current study was to evaluate local control and long-term adverse effects in a series of patients with oligometastatic disease who received 30 Gy in single dose to the lung metastases with stereotactic technique. Also, outcomes in terms of survival, patterns of failure and prognostic factors were assessed.

2. Materials and methods

Between 2008 and 2016, 166 lung lesions in 129 patients with oligometastatic lung disease treated with 30 Gy delivered in single fraction with stereotactic technique were retrospectively analyzed. According to our internal protocol, patients were discussed in a multidisciplinary team (including thoracic surgeon, oncologist, radiation oncologist, pneumologist, radiologist and pathologist).

Patients' selection were based on the following inclusion criteria: 1) performance status ECOG (Eastern Cooperative Oncology Group Criteria) ≤2; 2) patients with oligorecurrent/oligometastatic state (≤5 synchronous or metachronous metastases at the time of treatment) and controlled primary/extrathoracic disease; 3) no other active sites of distant metastasis; 4) no candidate to surgery because of advanced age, comorbidities or refusal for invasive surgery.

Patient could have received systemic therapy (ST) previous to the SBRT both as adjuvant treatment after initial surgery or as therapy for the metastatic disease. SBRT was administered at least 1 month after the last cycle of ST. In case of further oligoprogression, patients were evaluated to receive a new course of SBRT and/or ST. When systemic spread was observed patients were evaluated to receive ST or best supportive care (BSC) based on physicians' evaluation.

Lesions adherent to critical mediastinal OARs or ≤1.5 cm from mediastinum were not included in the study to avoid excessive toxicity. The treated metastases were located in the lung parenchyma and the exact sites are reported in Table 1.

Pre-treatment evaluation included clinical examination, total body computed tomography (CT) scan, pulmonary function tests, and 18-fluorodeoxyglucose-positron emission tomography (FDG-PET/CT).

The current study was carried out according to the Declaration of Helsinki (1964) and the Internal Review Board has approved the study. Written inform consent was obtained by all patients.

2.1. Treatment

Details of SBRT planning and delivery at our Institution have been extensively described in previous publications [16,17]. Briefly, all patients underwent a 4-dimensional (4D) pre-treatment planning CT. The maximum intensity projection was reconstructed using software (Advantage 4D, General Electrics Company, Waukesha, WI) from the 10-phase 4D-CT images and was used to delineate the internal target volume (ITV) from the gross tumor volume (GTV). Planning CT images were matched with diagnostic PET/CT images for the GTV delineation. The planning treatment volume (PTV) was determined by adding 4–5 mm in all directions to the ITV.

The prescribed dose to the PTV was 30 Gy in single dose (biological equivalent dose 10 [BED10] = 120 Gy) at the 95% isodose with normalization to the maximal dose.

Position before treatment was verified using an in-room cone-beam (Kilo-Voltage) CT scan. The treatment was delivered with a Varian Linear Accelerator with 6-MV photons, using 7–9 static non-opposing coplanar fields.

Table 1
Patients' characteristics (n Patients = 129).

Mean age (years)	69
Range (years)	24–89
Gender	
Male	77 (59.5)
Female	52 (40.5)
Primary tumor	
NSCLC	51 (39.5)
CRC	41 (31.7)
Breast	8 (6.3)
Kidney	5 (3.9)
Uterus	5 (3.9)
Others	19 (14.7)
No. of lung lesions (per patient)	
1	99 (76.7)
2	23 (17.8)
3-5	7 (5.5)
Timing of SBRT (per metastasis)	
Synchronous	98 (75.9)
I° recurrence	27 (20.9)
II° recurrence	4 (3.2)
Systemic therapy	
Pre SBRT	50 (38.7)
Post SBRT	52 (40.3)
Mean lesion size (mm/cc)	13/3.46
Range lesion size (mm/cc)	2-50/0.03–47.48
PTV volume (per metastasis)	
≤10 cc	105 (63.2)
10-16 cc	27 (16.2)
16-20 cc	6 (3.6)
20-50 cc	24 (14.5)
> 50 cc	4 (2.5)
Localization of lesions	
SRD	35 (21)
ML	18 (10.8)
IRD	36 (21.7)
SLL	36 (21.7)
ILL	41 (24.8)

NSCLC: non-small cell lung cancer, CRC: colorectal cancer, SRD: superior right lobe, ML: middle lobe, IRD: inferior right lobe, SLL: superior left lobe, ILL: inferior left lobe.

2.2. Follow-up and statistics

The first follow-up was performed 6 weeks after treatment with a Chest-CT scan. The following follow-up was performed using a CT scan with contrast medium or an FDG/PET-CT every three months for the first two years after RT and every six months afterwards. Treatment-related adverse effects were assessed at each follow-up according to CTCAE v 4.0.

Local recurrence was diagnosed based on the dynamic enlargement of the local tumor on follow-up CTs that continued for at least 6 months and on the metabolic values indicated by the FDG-PET routinely used.

LPFS was defined as the time to occurrence of in-field or marginal regrowth of the disease; PFS was defined as the time to local/distant progression; MFS was defined as any site of distant progression (including the ipsilateral lung); OS was defined as the time to the death or last follow-up. Survivals were estimated using the reverse Kaplan–Meier method. Prognostic factors such as age, sex, primary tumor, previous systemic therapy, synchronous or metachronous oligometastatic