The Breast 26 (2016) 11–17

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Stereotactic body radiation therapy: A promising chance for oligometastatic breast cancer

Marta Scorsetti [a], Davide Franceschini [a, *], Fiorenza De Rose [a], Tiziana Comito [a], Elisa Villa [a], Cristina Iftode [a], Pierina Navarria [a], Giuseppe Roberto D'Agostino [a], Giovanna Masci [b], Rosalba Torrisi [b], Alberto Testori [c], Corrado Tinterri [c], Armando Santoro [b]

[a] Radiosurgery and Radiotherapy Department, Istituto Clinico Humanitas Cancer Center and Research Hospital, Rozzano, Milan, Italy
[b] Oncology and Haematology Department, Istituto Clinico Humanitas Cancer Center and Research Hospital, Rozzano, Milan, Italy
[c] Senology Unit, Istituto Clinico Humanitas Cancer Center and Research Hospital, Rozzano, Milan, Italy

ARTICLE INFO

Article history:
Received 6 October 2015
Received in revised form
26 November 2015
Accepted 12 December 2015
Available online 3 January 2016

Keywords:
Breast cancer
Liver
Lung
RapidArc
Stereotactic body radiation therapy

ABSTRACT

Background: Multidisciplinary management of oligometastatic breast cancer with local therapy could improve disease control. The aim of our study is the assessment of safety and efficacy of Stereotactic Body Radiation Therapy (SBRT) in selected subset of patients.

Patients and methods: Oligometastastic patients from breast cancer were treated with SBRT for 1–3 lung and liver lesions, in an observational study. Inclusion criteria were: age >18 years, ECOG 0-2, diagnosis of breast cancer, no extrapulmonary and/or extrahepatic disease, other metastatic sites stable or responding after chemotherapy were allowed, no life threatening conditions, less than 5 lung and liver lesions (with maximum diameter <5 cm), chemotherapy completed at least 3 weeks before treatment, written informed consent. Prescription dose ranged between 48 and 75 Gy in 3 or 4 consecutive fractions. Primary end-point was local control (LC). Secondary end-points were toxicity, overall survival (OS) and progression-free survival (PFS).

Results: From April 2010 to June 2014, 33 patients for a total number of 43 lesions were irradiated. Median follow up was 24 months (range 3–59). Actuarial LC rates were 98% at 1 year and 90% at 2 and 3 years. Complete response, partial response and progressive disease were detected in 25 (53.2%), 16 (34%), and 6 (12.8%) lesions, respectively. Median OS was 48 months. Actuarial OS rates at 1 and 2 years were 93% and 66% respectively. Median PFS was 11 months, with a PFS rate at 1 and 2 years of 48% and 27%, respectively. At univariate analysis DFI >12 months, hormonal receptor positivity, medical therapies after SBRT showed a significant impact on OS. Treatment was well tolerated, with no G3-4 toxicities.

Conclusions: SBRT is a safe and feasible alternative treatment of liver and lung oligometastases from breast cancer, in selected patients not amenable to surgery, with good local control and survival rate.

Introduction

Approximately 30–40% of breast cancer patients develop distant metastases during the course of their disease [1]. Metastatic breast cancer (MBC) is generally regarded as an incurable disease. Median survival for MBC is variably reported but generally short, e.g., 8–24 months [2], 18–24 months [3], or as long as 2–4 years [4]. Gold standard approach to metastatic breast cancer involves the use of systemic therapies. However, curative potential of medical approach is virtually null, with just 1–2% of patients in complete remission after chemotherapy maintaining long term disease control [5–7].

The definition MBC includes very different conditions. Metastases can be present at first diagnosis or metastatic disease may occur very late and often with a large number of metastases. However, according to the spectrum hypothesis, described by Hellmann many years ago [8], there is also a disease state intermediate between locoregionally confined and widely metastatic

* Corresponding author. Radiosurgery and Radiotherapy Department, Istituto Clinico Humanitas Cancer Center and Research Hospital, Via Manzoni 56, 20089, Rozzano, Milan, Italy. Tel.: +39 0282247428.
E-mail address: davide.franceschini@humanitas.it (D. Franceschini).

http://dx.doi.org/10.1016/j.breast.2015.12.002
0960-9776/

cancer. In this situation metastases are limited in number and location, likely still confined and without the features needed for a widespread diffusion. This state is what we call oligometastatic disease. Moving from these considerations, there is a diffuse and growing interest towards local ablative treatments to all known metastases in oligometastatic patients, in order to achieve a long term disease control and potentially cure. Literature data are providing evidence that selected patients may remain disease-free over more than a decade if treated with aggressive combined-modality therapy, including both systemic and local approach [9].

Among ablative local therapies, stereotactic body radiotherapy (SBRT) is emerging as effective and safe treatment when surgery is not allowed or refused. Published studies on SBRT for metastatic disease included very different scenarios, that can be important determinants of outcome, as, for instance, some histological types or disease sites are possibly more responsive to radical treatment than others [10]. When results are analyzed according to tumor type, patients with breast cancer have a much better survival as compared to other cancers. When specific disease sites are considered [9,11], the 2-year local control rate is about 80% for lung metastases, with a corresponding 2-year survival of 50%, and a 5% rate of grade $\geq$3 toxicities. The 2-year local control rate varies between 57 and 92% for liver metastases, and radiation-induced liver damage is exceptional.

We designed this study to evaluate safety and efficacy of lung and liver stereotactic radiation therapy for inoperable oligometastatic breast cancer patients.

Material and methods

This observational study was approved by the local ethical committee. From April 2010 until June 2014 oligometastatic patients with liver or lung metastases from breast cancer were treated with SBRT in our institution. Inclusion criteria were: age >18 years, ECOG 0-2, diagnosis of breast cancer, no extrapulmonary and/or extrahepatic disease, other metastatic sites stable or responding after chemotherapy were allowed, no life threatening conditions, less than 5 lung and liver lesions (with maximum diameter <5 cm), chemotherapy completed at least 3 weeks before treatment, written informed consent for the treatment. Systemic therapies other than chemotherapy were allowed during RT (i.e hormonal therapies and/or immunotherapy). Patients were excluded from these analysis if pregnant. All patients gave written informed consent for treatment.

Primary end point was local control (LC), secondary end points were toxicity, progression free survival (PFS) and overall survival (OS).

All patients were staged with thorax and abdomen CT and PET/CT to confirm the oligometastatic state. Abdominal MRI was required in patients with liver metastases.

All patients were immobilized with a thermoplastic body mask.

For liver metastases a Styrofoam block for abdominal compression was added to minimize respiratory organ motion. A contrast-free and 3 phases contrast-enhanced computed tomography (CT) scan were acquired for all patients. If respiratory excursion was larger than 5 mm a 4-dimensional CT (4D-CT) imaging was performed. Planning CT images were co-registered (with deformable registration methods) with magnetic resonance imaging (MRI) and positron emission tomography (from CT-PET) to better identify the gross tumor volume (GTV). The clinical target volume (CTV) was defined as equal to the GTV. In all patients who underwent 4D-CT scan, an internal target volume (ITV) was defined as the envelope of all GTVs in the different respiratory phases. Dose plans were optimized on the average CT; this contributes to mitigate the residual organ motion not blocked by the abdominal compression. The planning target volume (PTV) was generated from either the GTV or the ITV by adding an overall isotropic margin of 5 mm from ITV. In case of lung metastases, no abdominal compression was applied; as per institutional policy in these cases, 4D-planning was always required and CT images were co-registered with PET. GTV was identified on all phases to generate the ITV. The PTV was generated from the ITV by adding an overall isotropic margin of 7 mm.

All patients were treated with a volumetric modulated arc technique (VMAT). All SBRT/VMAT plans were optimized by inverse planning to ensure maximal dose conformity and rapid dose falloff toward critical structures. SBRT/VMAT was delivered with 6- or 10-MV photons, using modulated dynamic arcs. Dose was prescribed as the mean dose to PTV ensuring that more than 98% of PTV would receive 95% of prescribed dose. Normal tissues tolerances used for planning are showed in Table 1.

Patients positioning was checked daily with CB-CT. No respiratory motion management device, apart from abdominal compression, was required during treatment delivery.

During treatment patients were evaluated the first and the last day of RT, or more frequently if required; patients were evaluated again 4 weeks after the end of treatment for acute toxicity. Toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.0.

Thereafter, patients were followed up two months after the end of treatment and then every three months for the first year, every four months during the second year and then every six months. Contrast-enhanced CT scan imaging was performed within 2 months after SBRT/VMAT and then for every follow up visit. FDG-PET/CT was performed at 6 months after RT.

Response assessment was evaluated using the RECIST criteria (version 1.1).

Survival and time to LC were calculated from the date of start of the SBRT treatment. Patients were observed for LC, even if new distant lesions developed. Kaplan–Meier method was used to generate the actuarial LC, OS and PFS curves. Log rank test was used for group comparison. All calculations were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois). Univariate analysis was used to correlate morphologic and clinical factors to LC, OS and PFS and statistical significance was accepted for p-values of <0.05.

Results

Thirty-three patients with a total number of 47 lesions were irradiated. All but three patients received chemotherapy for metastatic disease before SBRT. Median number of chemotherapy lines before SBRT was 2 (range 1–4). Hormonal therapy was administered in 7 patients at time of SBRT. After SBRT 15 patients continued

Table 1
Normal tissue tolerances used for planning, in brackets the more relaxed constraints for the fractionation schemes with 4–8 fractions.

Normal tissue	Constraints
Healthy liver	>700 cm^3 < 15 Gy
Spinal cord	$D^3_{0.1cm}$ < 18 (20) Gy
Kidneys	V_{15Gy} < 35%
Stomach	D^3_{1cm} < 21 (36) Gy
Duodenum	D^3_{1cm} < 21 (36) Gy
Small bowel	D^3_{1cm} < 21 (36) Gy
Large bowel	D^3_{1cm} < 21 (36) Gy
Lungs	Mean < 4 Gy V_{20Gy} < 10%
Heart	D^3_{1cm} < 30 Gy
Oesophagus	$D^3_{0.1cm}$ < 30 Gy